Hoffmann - Rockstroh - Kamps

HIV Medicine 2007

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Flying Publisher

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Preface 2007

As in previous years, all chapters of the 15th edition have been thoroughly revised. Again, the book is freely available on the Internet. That is the way, we firmly believe, that medical textbooks should be handled in the 21st century.

HIV Medicine is available in Spanish, German, Russian, and Portuguese (www.hivmedicine.com/textbook/lang.htm), and translations into further languages are under way. This is clearly a challenge for the future, and the authors of HIV Medicine are ready to take the challenge. As a matter of fact, the 2008 edition is already under way.

The philosophy which governs the publication of HIV Medicine 2006 has been published at www.freemedicalinformation.com.

Christian Hoffmann

Jürgen K. Rockstroh

Bernd Sebastian Kamps

Hamburg, Bonn, Paris – December 2007

Preface 2003

Hardly any field of medicine has ever undergone a similar stormy development to that of the therapy of HIV infection. Little more than 10 years passed, between the discovery of the pathogen and the first effective treatment! However, there is also hardly a field that is subjected to so many fast- and short-lived trends. What today seems to be statute, is tomorrow often already surpassed. Nevertheless, therapeutical freedom must not be confused with freedom of choice. This book presents the medical knowledge that is actual today: from December 2002 to January 2003.

Because HIV medicine changes so fast, HIV Medicine 2003 will be updated every year. Additional chapters about opportunistic infections, malignancies and hepatitis are freely available at our Web site www.HIVMedicine.com.

Under certain conditions, the editors and the authors of this book might agree to remove the copyright on HIV Medicine for all languages except English and German. You could therefore translate the content of HIV Medicine 2003 into any language and publish it under your own name – without paying a license fee. For more details, please see http://hivmedicine.com/textbook/cr.htm.

Christian Hoffmann and Bernd Sebastian Kamps

Hamburg/Kiel and Paris/Cagliari, January 2003

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Content

Part 1

Basics

1. Introduction

Bernd Sebastian Kamps and Christian Hoffmann

The first reports of homosexual patients suffering from previously rare diseases such as pneumocystis pneumonia and Kaposi's sarcoma were published in May 1981 (Centers for Disease Control 1981a, 1981b, 1981c). It soon became clear that the new disease affected other population groups as well, when the first cases were reported in injecting drug users. However, it took almost two years until, in 1983, the human immunodeficiency virus type I (HIV-1) was defined as the primary cause of the acquired immunodeficiency syndrome (Barré-Sinoussi 1983, Broder 1984, Gallo 1984).

Almost 25 years have now elapsed. Twenty-five years, in which HIV infection has changed from a fatal condition to a manageable chronic illness. Twenty-five years, in which the development of antiretroviral therapy (ART) has been one of the dramatic advances in the history of medicine. However, for the vast majority of people living with HIV/AIDS, ART is still light years away – largely inaccessible in resource-poor countries where HIV continues to devastate families, communities and societies, especially the poor and the socially marginalized.

In the following 800 pages, we present a comprehensive overview of the treatment of HIV infection and its complications. As in previous years, all chapters have been thoroughly revised, and most parts of the book were available on the Internet (www.HIVMedicine.com) months before they were printed here. The philosophy that governs the publication of HIV Medicine 2006 has been published at www.freemedicalinformation.com. We firmly believe that that is the way medical textbooks should be handled in the 21st century.

Transmission routes

There are several ways in which someone can become infected with HIV. These transmission routes are well defined (see also Chapter "Post-Exposure Prophylaxis"). HIV infection can be transmitted through:

- unprotected sexual intercourse with an infected partner;
- injection or transfusion of contaminated blood or blood products (infection through artificial insemination, skin grafts and organ transplants is also possible);
- sharing unsterilized injection equipment that has been previously used by someone who is infected;
- maternofetal transmission (during pregnancy, at birth, and through breastfeeding).

Occupational infections of healthcare or laboratory workers may occur; however, a 1995 study estimated that although 600,000 to 800,000 needlestick injuries occurred among healthcare workers every year in the USA, occupational infection was not frequent. The risk of occupational HIV transmission from contaminated needles to healthcare workers was found to be 0.3 % in case series performed prior to the availability of potent ART.

There are sometimes concerns that there may be alternative routes of HIV transmission. It must be explicitly stated that HIV is **NOT** transmitted by mosquitoes, flies, fleas, bees, or wasps. HIV is **NOT** transmitted through casual every day contact. No case of HIV infection has been documented to arise from contact with non-bloody saliva or tears. Since HIV is not transmitted by saliva, it is not possible to contract it through sharing a glass, a fork, a sandwich, or fruit (Friedland 1986, Castro 1988, Friedland 1990). In the opinion of leading experts, exposure of intact skin to HIV-contaminated body fluids (e.g. blood) is not sufficient to transfer the virus.

Sexual intercourse

Unprotected sexual intercourse is the most important transmission route of HIV infection worldwide. Although receptive anal sex is estimated to produce the highest risk of infection, infection after a single insertive contact has also been described. The presence of other sexually transmitted diseases markedly increases the risk of becoming infected with HIV.

The lower the viral load, the less infectious the patient. A prospective study of 415 HIV-discordant couples in Uganda showed that of 90 new infections occurring over a period of up to 30 months, none was from an infected partner with a viral load below 1,500 copies/ml. The risk of infection increased with every log of viral load by a factor of 2.45 (Quinn 2000). It should be noted that the levels of viral load in blood and other body fluids do not always correlate with one another. Thus, individual risk remains difficult to estimate. In addition, HIV-infected patients are not protected from superinfection with new viral strains.

The higher the viral load, the more infectious the patient. This is especially true for patients during acute HIV infection. During acute HIV-1 infection, the virus replicates extensively in the absence of any detectable adaptive immune response, reaching levels of over 100 million copies of HIV-1 RNA/ml (see Chapter “Acute HIV-1 infection”).

Intravenous drug use

Sharing unsterilized injection equipment that has been previously used by someone who is infected is an important route of HIV transmission in many countries with a high prevalence of intravenous drug users. In contrast to the accidental needlestick injury (see also Chapter “Post-Exposure Prophylaxis”), the risk of transmission through sharing injection equipment is far higher: the intravenous drug user ensures the proper positioning of the needle by aspiration of blood.

Maternofetal

In the absence of any intervention, an estimated 15-30 % of mothers with HIV infection will transmit the infection during pregnancy and delivery. In approximately 75 % of these cases, HIV is transmitted during late pregnancy or during delivery. About 10 % of vertical HIV infections occur before the third trimester, and 10-15 % are caused by breastfeeding.

In Western countries, perinatal (vertical) HIV infection has become rare since the introduction of antiretroviral transmission prophylaxis and elective cesarean section. For more details, see Chapter “Pregnancy and HIV”.

Injection or transfusion of contaminated blood products

In most Western countries, administration or transfusion of HIV-contaminated blood or blood products has become a rare event. With current testing methods (for details see also Chapter "HIV Testing"), the risk of acquiring HIV from a unit of transfused blood is about 1:1,000,000. However, while Western European countries, the United States, Australia, Canada, and Japan have strict and mandatory screening of donated blood for HIV, not all countries do.

Natural history

The "natural history" described in the following refers to HIV infection in the absence of HAART.

The acute viral syndrome of "primary" HIV infection (which is defined as the time period from initial infection with HIV to the development of an antibody response) shows symptoms that often resemble those of mononucleosis. These appear within days to weeks following exposure to HIV (see Chapter "Acute HIV-1 Infection"). However, clinical signs and symptoms may not occur in all patients. During acute HIV infection, there is usually a high plasma viremia and frequently a marked decrease in CD4+ T-cells. The CD4+ T-cell count later increases again, normally to levels inferior to the pre-infection values (see Figure 1).

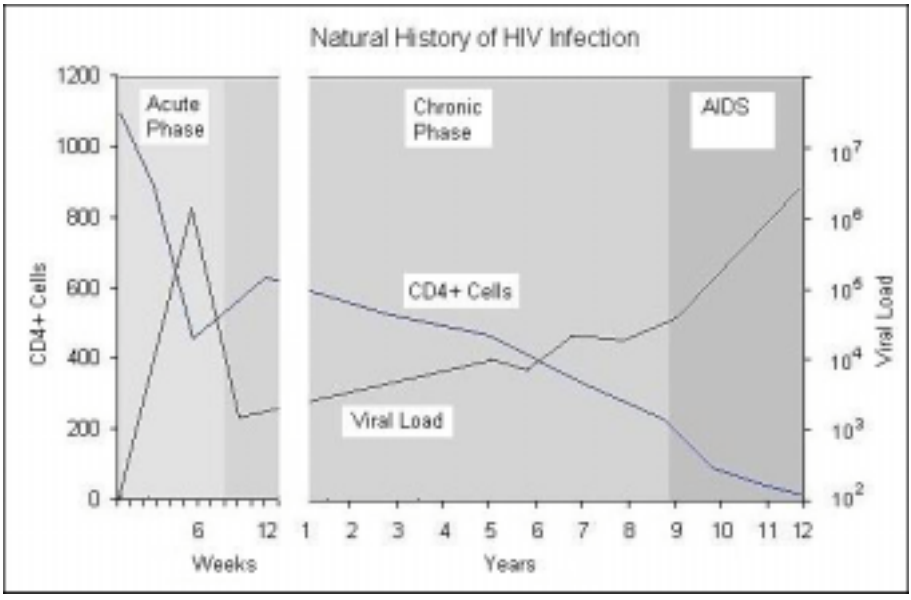

Figure 1: CD4+ T-cell count and viral load during HIV infection.

After the acute infection, equilibrium between viral replication and the host immune response is usually reached, and many infected individuals may have no clinical manifestations of HIV infection for years. Even in the absence of antiretroviral treatment, this period of clinical latency may last 8-10 years or more. However, the

term “latency period” may be misleading, given the incredibly high turnover of the virus and the relentless daily destruction of CD4+ T-cells.

At the end of the “latency period”, a number of symptoms or illnesses may appear which do not fulfill the definition of AIDS. These include slight immunological, dermatological, hematological and neurological signs. Many of them are listed in the Category B of the CDC classification system (see Table 1). Constitutional symptoms, such as fever, weight loss, night sweats, and diarrhea may also develop. In this situation, the level of 200 CD4+ T-cells/µl is an important cut-off, below which the risk of many AIDS-defining illnesses increases, among them several opportunistic infections and certain neoplasms (see Table 1). Above 200 CD4+ T-cells/µl, most AIDS-defining illnesses are rare events (see also Chapter “AIDS”).

However, the course of infection may vary dramatically, and in some cases, the progression to AIDS occurs rapidly. Host factors mainly determine whether or not an HIV-infected individual rapidly develops clinically overt immunodeficiency, or whether this individual belongs to the group of long-term non-progressors, who represent about 5 % of all infected patients (for details, see “Pathogenesis of HIV-1 Infection”).

CDC classification system

The most widely accepted classification system of HIV infection, initially published by the U.S. Centers for Disease Control and Prevention (CDC) in 1986, is based on certain conditions associated with HIV infection (see Table 1). This classification system was intended for use in conducting public health surveillance and it has been a useful epidemiological tool for many years. In 1993, the CDC classification was revised (CDC 1993b). Since then, the clinical definition of AIDS has been expanded in the USA (not in Europe) to include HIV-infected patients with a CD4+ T-cell count of less than 200 cells/µl or less than 14 % of all lymphocytes, even in the absence of the listed conditions.

Thus, the current CDC classification categorizes persons on the basis of clinical conditions and CD4+ T-lymphocyte counts. There are three clinical categories (A, B, C – see Table 1) and three CD4+ T-lymphocyte categories (1, 2, 3 – see Table 2). For example, a patient with oropharyngeal candidiasis and a CD4+ T-cell count of 250/µl would be classified as B2; someone with asymptomatic infection and a CD4+ T-cell count of 550/µl would be in category A1. Categorization of the CD4+ T-cells should be based on the lowest accurate CD4+ T-cell count (“CD4 nadir”) and not on the most recent one.

For children less than 13 years of age, there is a modified and revised classification system for HIV infection (see chapter “Antiretroviral Therapy in Children”). It should also be noted that, besides the CDC classification, the World Health Organization (WHO) has also published a staging system for HIV infection. The WHO classification is an approach for use in resource-limited settings and is widely used in Africa and Asia.

Table 1. Clinical categories of the CDC classification system in HIV-infected persons

Category A	**Category C** - AIDS-defining illnesses**
Asymptomatic HIV infection	Candidiasis of bronchi, trachea, or lungs
Acute (primary) HIV infection with accompanying illness or history of acute HIV infection	Candidiasis, esophageal
Persistent generalized lymphadenopathy	Cervical cancer, invasive*
	Coccidioidomycosis, disseminated or extrapulmonary
Category B	Cryptococcosis, extrapulmonary
Symptomatic conditions* that are not included among conditions listed in clinical Category C. Examples include, but are not limited to:	Cryptosporidiosis, chronic intestinal (greater than 1 month's duration)
Bacillary angiomatosis	Cytomegalovirus disease (other than liver, spleen, or nodes)
Candidiasis, oropharyngeal (thrush)	Cytomegalovirus retinitis (with loss of vision)
Candidiasis, vulvovaginal; persistent, frequent, or poorly responsive to therapy	Encephalopathy, HIV-related
Cervical dysplasia (moderate or severe)/cervical carcinoma in situ	Herpes simplex: chronic ulcer(s) (greater than 1 month's duration); or bronchitis, pneumonitis, or esophagitis
Constitutional symptoms, such as fever (38.5° C) or diarrhea lasting longer than 1 month	Histoplasmosis, disseminated or extrapulmonary
Hairy leukoplakia, oral	Isosporiasis, chronic intestinal (greater than 1 month's duration)
Herpes zoster (shingles), involving at least two distinct episodes or more than one dermatome	Kaposi's sarcoma
Idiopathic thrombocytopenic purpura	Lymphoma, Burkitt's (or equivalent term)
Listeriosis	Lymphoma, immunoblastic (or equivalent)
Pelvic inflammatory disease, particularly if complicated by tubo-ovarian abscess	Lymphoma, primary, of brain
Peripheral neuropathy	Mycobacterium avium complex or M. kansasii, disseminated or extrapulmonary
	Mycobacterium tuberculosis, any site (pulmonary or extrapulmonary)
	Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
	Pneumocystis pneumonia
	Pneumonia, recurrent*
	Progressive multifocal leukoencephalopathy
	Salmonella septicemia, recurrent
	Toxoplasmosis of brain
	Wasting syndrome due to HIV

* These conditions must meet at least one of the following criteria: a) the conditions are attributed to HIV infection or are indicative of a defect in cell-mediated immunity; or b) the conditions are considered by physicians to have a clinical course or to require management that is complicated by HIV infection.

** Once a Category C condition has occurred, the person will remain in Category C.

Table 2. The CD4+ T-lymphocyte categories*
Category 1: >500 CD4+ T-cells/µl
Category 2: 200-499 CD4+ T-cells/µl
Category 3: <200 CD4+ T-cells/µl

*Categorization is based on the lowest accurate CD4+ T-cell count, not the most recent one

Epidemiology

New estimations have recently resulted in substantial changes in estimates of numbers of persons living with HIV worldwide (UNAIDS 2007). The estimated number of persons living with HIV worldwide is now assumed to be 33.2 million, a reduction of 16% compared with the estimate published in 2006 (Table 3).

The prevalence and incidence of HIV/AIDS vary considerably from continent to continent, from country to country, from region to region. Several countries in sub-Saharan Africa report infection rates of 30 %, especially in urban areas. In other countries, HIV prevalence still remains low. However, low national prevalence rates can be misleading. They often disguise serious epidemics that are initially concentrated in certain localities or among specific population groups and that threaten to spill over into the wider population.

The joint United Nations program on HIV/AIDS (UNAIDS) provides by far the best and most comprehensive overview. With maps and regional summaries, it provides the most recent estimates of the epidemic's scope and explores new trends in the epidemic's evolution. It can be found at the Website http://www.unaids.org/. Table 1 provides an overview of the devastating situation of the HIV pandemic.

Table 3: The AIDS epidemic*

	HIV-infected adults and children	HIV prevalence among adults (%)	New infections per day**	Daily deaths from AIDS**
Subsaharian Africa	22.5 million	5.0	4,700	4,400
South and Southeast Asia	4.0 million	0.3	900	740
Eastern Europe and Central Asia	1.6 million	0.9	410	210
Latin America	1.6 million	0.5	270	160
East Asia	800,000	0.1	250	90
North Africa and Middle East	380,000	0.3	100	70
North America	1.3 million	0.6	130	60
Carribean	230,000	1.0	50	30
Western and Central Europe	760,000	0.3	80	30
Australia, New Zealand and Pacific Region	75,000	0.4	40	3
Total	33.2 million	0.8	6900	5800

* Adapted from WHO: AIDS Epidemic Update December 2007, http://hiv.net/link.php?id=227

** Adults and children

Conclusion

HIV cannot be transmitted as easily as the influenza virus. Compared to other viral diseases, the prevention of HIV infection is therefore easier. In rich countries, individuals who don't want to be infected with HIV may protect themselves and avoid HIV infection. The same people will not be able to avoid the influenza virus of the next pandemia.

HIV infection has become a treatable disease – at least in countries that can afford widespread health coverage. The following chapters describe how patients should be managed in these countries.

Outside these havens of material well-being, things have not changed since the early years of the HIV epidemic 25 years ago. Many people live in a world where no medical progress seems to have been made. This is a shameful situation, and future generations will hopefully do better than we did.

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2. Acute HIV-1 Infection

Marcus Altfeld and Bruce D. Walker

Introduction

Acute HIV-1 infection presents in 40 – 90 % of cases as a transient symptomatic illness, associated with high levels of HIV-1 replication and an expansive virus-specific immune response. With 14,000 new cases per day worldwide, it is an important differential diagnosis in cases of fever of unknown origin, maculopapular rash and lymphadenopathy.

The diagnosis of acute infection is missed in the majority of cases, as other viral illnesses ("flu") are often assumed to be the cause of the symptoms, and there are no HIV-1-specific antibodies detectable at this early stage of infection. The diagnosis therefore requires a high degree of clinical suspicion, based on clinical symptoms and history of exposure, in addition to specific laboratory tests (detection of HIV-1 RNA or p24 antigen and negative HIV-1 antibodies) confirming the diagnosis.

An accurate early diagnosis of acute HIV-1 infection is important, as infection of sexual partners can be prevented and patients may benefit from therapy at this early stage of infection (see below).

Immunological and virological events during acute HIV-1 infection

During acute HIV-1 infection, the virus replicates extensively in the absence of any detectable adaptive immune response, reaching levels of over 100 million copies HIV-1 RNA/ml. It is during this initial cycle of viral replication that important pathogenic processes are thought to occur. These include the seeding of virus to a range of tissue reservoirs and the destruction of CD4+ T-lymphocytes, in particular within the lymphoid tissues of the gut. The very high levels of HIV-1 viremia are normally short-lived, indicating that the host is able to generate an immune response that controls viral replication. Over the following weeks, viremia declines by several orders of magnitude before reaching a viral setpoint. This setpoint, following resolution of the acute infection, is a strong predictor of long-term disease progression rates (Mellors 1995).

Several factors can influence viral replication during acute infection and the establishment of a viral setpoint. These include the fitness of the infecting virus, host genetic factors and host immune responses. While antibodies against HIV-1 with neutralizing capacities are rarely detectable during primary HIV-1 infection, a number of studies have demonstrated a crucial role of HIV-1-specific cellular immune responses for the initial control of viral replication during this stage of infection. A massive, oligoclonal expansion of CD8+ T-cell responses has been described during acute HIV-1 infection (Pantaleo 1994), and the appearance of HIV-1-specific CD8+ T cells has been temporally associated with the initial decline of viremia (Koup 1994, Borrow 1994). These CD8+ T-cells have the ability to elimi-

nate HIV-1-infected cells directly by MHC class I-restricted cytolysis or indirectly by producing cytokines, chemokines or other soluble factors, thus curtailing the generation of new viral progeny (Yang 1997). Further evidence for the antiviral activity of HIV-1-specific CTLs during primary HIV-1 infection has been provided by the rapid selection of viral species with CTL epitope mutations that were detected within a few weeks after HIV-1 and SIV infection in humans and rhesus macaques, respectively (Allen 2000, Price 1997).

During acute HIV-1 infection, the number of CD4+ T-cells decline, occasionally to levels that allow the development of opportunistic infections at that time (Gupta 1993, Vento 1993). Even though the CD4+ T-cell count rebounds with the resolution of primary infection, it rarely returns to baseline levels in the absence of antiretroviral therapy. In addition to the decline in CD4+ T-cell counts, qualitative impairments of CD4+ T-cell function are perhaps the most characteristic abnormalities detected in HIV-1 infection. The impairment of HIV-1-specific CD4+ T-cell function occurs very early in acute infection (Rosenberg 1997, Lichterfeld 2004), potentially due to the preferential infection of virus-specific CD4+ T-cells by the virus (Douek 2002). This is followed by a functional impairment of CD4+ T-cell responses to other recall antigens, as well as a reduced responsiveness to novel antigens (Lange 2003). The impairment of HIV-1-specific CD4+ T-helper cell function in acute HIV-1 infection may subsequently result in a functional impairment of HIV-1-specific CD8+ T-cells (Lichterfeld 2004).

In addition to host immune responses, host genetic factors play an important role in both susceptibility and resistance to HIV-1 infection and speed of disease progression following infection. The most important of these is a deletion in the major coreceptor for entry of HIV-1 into CD4+ T-cells, a chemokine receptor called CCR5 (Samson 1996). Homozygotes for this 32 base pair deletion (CCR5delta32) do not express the receptor at the cell-surface and can only be infected with HIV strains that are able to use other coreceptors, such as CXCR4 (Samson 1996, Biti 1997). Heterozygotes for the deletion exhibit significant lower viral setpoints and slower progression to AIDS. In addition to mutations in the chemokine receptor genes, a number of HLA class I alleles have been described to be associated with both, lower viral setpoints and slower disease progression, including HLA-B27 and -B57 (O'Brien 2001, Kaslow 1996). Recent studies demonstrated that individuals expressing HLA-B57 presented significantly less frequently with symptomatic acute HIV-1 infection, mount strong virus-specific T cell responses restricted by these protective alleles, and exhibited a better control of viral replication following acute infection (Altfeld 2003, Altfeld 2006). These data demonstrate that host genetic factors can influence the clinical manifestations of acute HIV-1 infection and have an important impact on subsequent viral setpoints and the speed of disease progression.

Signs and symptoms

After an incubation period of a few days to a few weeks after exposure to HIV, most infected individuals present with an acute flu-like illness. Acute HIV-1 infection is a very heterogeneous syndrome and individuals presenting with more severe symptoms during acute infection and a longer duration of the acute infection syndrome tend to progress more rapidly to AIDS (Vanhems 1998, Pedersen 1989, Keet

1993). The clinical symptoms of acute HIV-1 infection were first described in 1985 as an illness resembling infectious mononucleosis (Cooper 1985). The most common symptoms (see Table 1) are fever, maculopapular rash, oral ulcers, lymphadenopathy, arthralgia, pharyngitis, malaise, weight loss, aseptic meningitis and myalgia (Kahn 1998). In one study (Hecht 2002), fever (80 %) and malaise (68 %) had the highest sensitivity for clinical diagnosis of acute HIV-1 infection, whereas loss of weight (86 %) and oral ulcers (85 %) had the highest specificity. In this study, the symptoms of fever and rash (especially in combination), followed by oral ulcers and pharyngitis had the highest positive predictive value for diagnosis of acute HIV-1 infection. In another study (Daar 2001), fever, rash, myalgia, arthralgia and night sweats were the best predictors for acute HIV-1 infection.

Table 1: Main symptoms of acute HIV-1 infection

Symptom	Frequency	Odds ratio (95% CI)
Fever	80%	5.2 (2.3-11.7)
Rash	51%	4.8 (2.4-9.8)
Oral ulcers	37%	3.1 (1.5-6.6)
Arthralgia	54%	2.6 (1.3-5.1)
Pharyngitis	44%	2.6 (1.3-5.1)
Loss of appetite	54%	2.5 (1.2-4.8)
Weight loss > 2.5 kg	32%	2.8 (1.3-6.0)
Malaise	68%	2.2 (1.1-4.5)
Myalgia	49%	2.1 (1.1-4.2)
Fever and rash	46%	8.3 (3.6-19.3)

From: Hecht FM et al. Use of laboratory tests and clinical symptoms for identification of primary HIV infection. AIDS 2002, 16: 1119-1129

The symptomatic phase of acute HIV-1 infection lasts between 7 – 10 days, and rarely longer than 14 days. The nonspecific nature of the symptoms poses a great challenge to the clinician and underlines the importance of a detailed history of exposure.

Diagnosis

The diagnosis of acute HIV-1 infection is based on the detection of HIV-1 replication in the absence of HIV-1 antibodies, as these are not yet present at this early stage of infection. Different tests are available for diagnosis of acute HIV-1 infection. The most sensitive tests are based on detection of plasma HIV-1 RNA.

In one study (Hecht 2002), all assays for HIV-1 RNA that were tested (branched chain DNA, PCR and GenProbe) had a sensitivity of 100 %, but occasionally (in 2 – 5 % of cases) led to false positive results. False positive results from these tests are usually below 2,000 copies HIV-1 RNA per ml plasma, and therefore far below the high titers of viral load normally seen during acute HIV-1 infection (in our own studies on average 13 x 10^6 copies HIV-1 RNA/ml with a range of 0.25 – 95.5 x 10^6 copies HIV-1 RNA/ml). Repetition of the assay for HIV-1 RNA from the same sample with the same test led to a negative result in all false positive cases. In contrast, detection of p24 antigen has a sensitivity of only 79 % with a specificity of

99.5 – 99.96 %. The diagnosis of acute HVI-1 infection must be subsequently confirmed with a positive HIV-1 antibody test (seroconversion) within the following weeks.

During acute HIV-1 infection, there is frequently a marked decrease of CD4+ T-cell count, which later increases again, but usually does not normalize to the initial levels. In contrast, the CD8+ T-cell count rises initially, which may result in a CD4/CD8 ratio of < 1. Infectious mononucleosis is the most important differential diagnosis. Hepatitis, influenza, toxoplasmosis, syphilis and side effects of medications may also be considered.

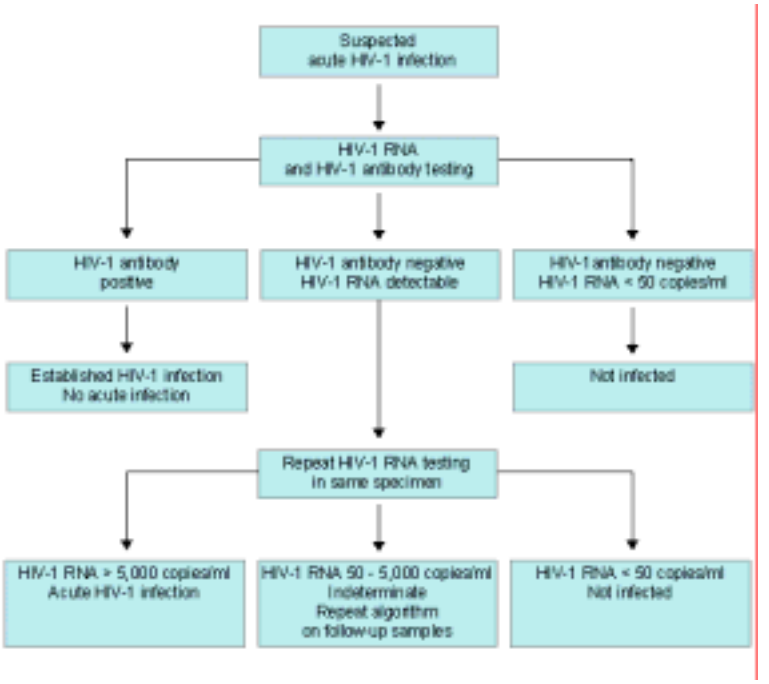

Figure 1: Algorithm for the diagnosis of acute HIV-1 infection

In summary, the most important step in the diagnosis of acute HIV-1 infection is to include it in the differential diagnosis. The clinical suspicion of an acute HIV-1 infection then merely requires performance of an HIV-1 antibody test and possibly repeated testing of HIV-1 viral load, as shown in the algorithm in Figure 1 (adapted from (Hecht 2002).

Treatment

The potential goals of antiretroviral therapy during acute HIV-1 infection are to shorten the symptomatic viral illness, reduce the number of infected cells, preserve HIV-1-specific immune responses and possibly lower the viral set point in the long term. Several studies in recent years have shown that treatment of acute HIV-1 infection allows long-term viral suppression, leads to preservation and even increase of HIV-1-specific T-helper cell responses and allows for the conservation of a very homogeneous virus population, but the clinical relevance of these findings is not known.

First pilot studies in patients treated during primary infection who subsequently went through structured treatment interruptions showed that most patients experienced at least temporal control of viral replication (Rosenberg 2000, Vogel 2006). However, in the majority of individuals in these and other studies, viral load rebounded during longer follow-up, requiring the initiation of therapy (Markowitz 1999, Kaufmann 2004). In a recently published prospective study in HIV-1-infected individuals identified during acute infection that either started HAART for 24 weeks during acute infection (n = 12) or choose to remain untreated (n = 8), viral load at week 48 (24 weeks following termination of HAART in the treatment arm) did not differ between the two groups, despite initial immunological improvements associated with the initiation of HAART during acute infection (Streeck 2006).

In contrast, a second larger retrospective study in 337 subjects that did not initiate treatment during primary infection and 58 subjects that started HAART (13 of whom in acute infection and 45 within the first 6 months of infection) demonstrated CD4+T cell count and viral load benefits in the treatment arm at 24 weeks after treatment discontinuation, and to some extend at 72 weeks (Hecht 2006).

These two recent studies that reached different conclusions regarding the potential benefit of initiation of HAART during acute HIV-1 infection had significant limitations, mainly the lack of randomization for both studies, the small size of the prospective study, and the variation in the duration of treatment and in the treatment regimens in the larger retrospective study (Kinloch-de Loes 2006). These studies further emphasize the need for a randomized controlled study investigating the potential benefit of early initiation of HAART in individuals identified during primary HIV-1 infection. This question regarding the timing of HAART initiation is very relevant, in particular in the context of the results from the recent SMART study suggesting that HAART, once initiated, cannot be routinely or intermittendly discontinued without substaintial risk for the patient (SMART Study Group 2006).

In view of all these unanswered questions, patients with acute HIV-1 infection should be treated in controlled clinical trials (Yeni 2002). If this is not possible, the option of standard first-line treatment should be offered and discussed. It is important during counseling to clearly indicate the lack of definitive data on clinical benefit of early initiation of antiretroviral therapy and to address the risks of antiretroviral therapy and treatment interruptions, including drug toxicity, development of resistance, acute retroviral syndrome during viral rebound and HIV-1 transmission and superinfection during treatment interruptions.

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3. HIV Testing

Wolfgang Preiser and Stephen Korsman

Awareness of one's HIV infection has gained enormous therapeutic relevance. Consequently, a shift in attitude towards HIV testing has taken place over the past decade: while an HIV test was previously often regarded as a threat to civil rights, the carer is now, in the age of HAART, obliged to advise – if necessary, emphatically – HIV testing: Only those aware of being infected can increase their life expectancy through HAART. Sometimes, an HIV test may be in the interest of a third person, e.g. testing of an index patient after a needlestick injury or the screening of pregnant women.

Besides individual diagnostic use, HIV tests are used in large numbers in the screening of blood and organ donors and (often in an anonymous way) for epidemiological surveillance (UNAIDS, 1997a and 2001).

How to test

The diagnosis of an HIV infection is normally made indirectly, i.e. through the demonstration of virus-specific antibodies (Gürtler 1996). These markers of a humoral immune response against the agent are found in virtually 100% of HIV-infected individuals. Their presence equals the diagnosis of chronic active HIV infection. Cases in which infected individuals persistently fail to have detectable antibodies against HIV are exceedingly rare and so far play hardly any role in clinical practice (Connick 2005, Kassutto 2005).

Direct diagnosis of HIV infection is also possible through the demonstration of infectious virus (using cell culture – this is only possible in laboratories of at least biological safety level 3), viral antigen (p24 antigen ELISA) or viral nucleic acid (i.e. viral genome; NAT = nucleic acid testing). To determine the infection status of a patient, direct virus detection is necessary only under certain circumstances, such as a suspected primary or vertically transmitted infection (details below).

Besides qualitative tests ("yes or no" answer) assays for the quantitative detection of virus have become very important: The concentration of viral RNA in plasma, the so-called "viral load", has become an indispensable tool for guiding antiretroviral therapy (Berger 2001). The term "HIV test" (still occasionally but inaccurately called "AIDS test"), however, almost always refers to testing for HIV-specific antibodies as a marker of infection.

HIV antibody diagnosis

Testing for HIV antibodies requires at least two different assays:

1. a screening test and
2. at least one confirmatory test.

To exclude inadvertent mix-ups of samples, a second blood sample from the same patient should generally be tested. Only then should the diagnosis of HIV infection be communicated to the patient in cases of unexpected seropositivity.

Most screening tests are based on the ELISA principle (enzyme linked immuno sorbent assay) or other, closely related test formats (UNAIDS, 1997b). Screening tests must be extremely sensitive to minimize the chance of yielding a false-negative result. This means that they have to be able to also detect low-avidity and low-level antibodies found e.g. early in the course of a primary infection.

If the result of a screening test is reactive (positive), this has to be confirmed by (at least) one confirmatory assay. One should never "diagnose" HIV infection on the basis of a reactive ("positive") screening assay alone!

ELISA screening test

A variety of manual and automated test methods are available. Screening assays are often performed on automated systems, so that large numbers of patient samples can be tested safely and economically. On the other hand, rapid tests are used as screening (and confirmatory) assays in many situations; they are dealt with separately below.

All antibody assays are based on the principle of a specific antigen-antibody reaction. First generation assays employed HIV "whole virus" antigen obtained from cell cultures, those from the second generation onwards recombinant virus proteins or synthetic peptides representing immunodominant epitopes.

In order to avoid a false-negative result with "exotic" virus strains, the antigens used must be able to bind antibodies directed against all potentially occurring virus types (HIV-1, HIV-2), groups (HIV-1-N, HIV-1-O, HIV-1-M) and group M clades or subtypes (HIV-1 C, B, etc.) (UNAIDS/WHO, 1992 and 1997). Conversely, because of cross-reactivity, reliable serological differentiation between infections with different HIV (sub-)types is only possible using specialized assays.

In most ELISA tests, viral antigen is bound to the so-called solid phase (e.g. on the bottom of the wells in a microtitre plate). Upon addition of patient serum containing antibodies directed specifically against these antigens, antigen-antibody binding will occur. A washing step then removes all unbound constituents of the serum, including all antibodies not recognizing the viral antigen.

Antibodies bound to the viral antigen are then detected through addition of an enzyme-labeled "conjugate". This conjugate may be either a second (e.g. goat) antibody directed against human antibody molecules ("antiglobulin" assay) or again viral antigen (often the same antigen that is coated onto the solid phase: "immunometric" or sandwich assay; 3rd generation tests), coupled with an enzyme molecule. "Immunometric" assays detect antibodies of all classes. Again, a washing step removes all unbound conjugate.

Finally a substrate is added. If in the previous step conjugate has been bound, this substrate is converted by the action of the enzyme contained in the conjugate, causing a change of color.; The intensity ("optical density", O.D.) of this color reaction is proportional to the antibody activity in the sample. Positive and negative control specimens must be included in each test run and their O.D. values are often used to calculate the test's cut-off, to distinguish positive from negative values.

Another commonly used method is the MEIA (microparticle enzyme immunoassay). It is based on the same principle as an ELISA; however, the “solid phase” is in

the form of microparticles in liquid suspension. Detection is by means of trapping the particles on a membrane and detecting enzyme activity, as with the ELISA.

A special case is the "competitive" assay: Here, enzyme-labeled HIV antibodies are added to the solid phase together with the patient's sample. These antibodies compete for antigen binding sites with the patient's antibodies. If the patient lacks HIV antibodies, all binding sites will be available to the enzyme-labeled antibody, causing an intense color reaction after addition of the substrate. And vice versa: the more specific antibodies are present in the patient sample, the weaker the color reaction. The intensity of the color reaction is therefore inversely proportional to the antibody activity in the sample. Such "competitive" assays are very specific.

The different formats have different advantages and disadvantages; it is therefore important to know which format a particular assay is based on.

So-called 4th generation tests combine the detection of HIV antibodies with that of viral p24 antigen, in order to detect antigen in the blood sample prior to the formation of antibodies and thus reducing the "diagnostic window" (see below) (Brust 2000). While in many cases useful, this may pose problems for confirmation.

The accuracy of a test is the combination of two factors: its sensitivity and its specificity. Sensitivity denotes the test's ability to correctly identify positive samples as positive, whereas specificity measures its ability to correctly identify negative samples as negative.

ELISA and related screening tests for HIV are extremely sensitive (almost 100 %), which means that even very low HIV antibody activities – e.g. early in the course of a primary infection – are detected. High sensitivity reduces the chance of a "false-negative" test result. Provided such a screening test is used, a negative result six or more months after a potential infection risk means, due to the test's high sensitivity, that the chance of infection is virtually nil (Preiser 2000).

HIV tests entering the European market after 7 December 2003 are subject to European Union legislation on in vitro diagnostic devices and have to carry the CE mark. Amongst the conditions to be fulfilled is that 600 HIV-positive samples, including 200 HIV-2-positive ones, obtained at different stages of HIV infection and disease, all have to be identified correctly as positive.

For screening tests, the emphasis is placed on sensitivity, as any failure to identify a positive sample correctly can have grave consequences. This high sensitivity, however, causes a somewhat lower specificity. This means that the test result may occasionally be a "false-positive". The test result then erroneously indicates the presence of antibodies against HIV. Such false-positive results may be caused by immune stimulation of some sort (acute viral infections, pregnancy, immunizations, autoimmune diseases). Presently available HIV screening tests have a specificity of at least 99.5 %; i.e. among 4,000 HIV-negative samples tested, a maximum of 20 may show a false-reactive test result.

Due to the possibility of non-specific reactivity inherent in any assay, it is preferable to use the term "reactive" – rather than "positive" – screening test result thus avoiding misunderstandings. All reactive screening test results must be confirmed in order to exclude the risk of reporting non-specific reactivity as "positive". Only after confirmatory testing should one talk of a "positive HIV test"!

Laboratory errors are rare but can never be completely excluded (e.g. sample mix-up, contamination with positive material when pipetting, etc.).

Important: a reactive screening test does not mean HIV infection! Only a positive confirmatory test allows the diagnosis of HIV infection, and normally only a confirmed result should be communicated to the patient! It is also important to send a second specimen, particularly when it is an unexpected positive result: for the first sample could have been incorrectly labeled or switched. When a positive result was expected, the subsequent baseline viral load test can replace the second serological test.

Confirmatory assay

For this purpose, some countries such as Germany and the United States, prescribe the use of a Western blot or an immunofluorescence assay (IFT or IFA). In others, such as the United Kingdom, confirmation may be achieved through the use of different tests applied in a defined sequence in the form of an algorithm. This latter approach is by no means inferior to confirmation by Western blot; in fact it is cheaper and more objective (Tamashiro 1993).

The Western blot is a methodology for which HIV is propagated in cell cultures, harvested, purified and denatured (i.e. split into its constituents). The resulting viral proteins are separated according to their molecular weight by electrophoresis and blotted onto a nitrocellulose membrane which is then cut into strips. To perform the test, the membrane is incubated with patient serum. If this contains antibodies against the various viral proteins, they will bind to the areas on the strip onto which the respective antigens have been blotted. This antigen-antibody reaction is revealed using an enzyme-labeled secondary antibody and matching substrate, whereupon the so-called "bands" appear on the test strip.

HIV proteins and corresponding bands on the Western blot are designated "p" (for protein) or "gp" (for glycoprotein), followed by the relative molecular mass in kiloDaltons. They can be divided (using the example of HIV-1 Western blot) into three groups: the env or envelope glycoproteins (gp41, gp120, gp160), the gag or nuclear proteins (p18, p24/25, p55) and the pol or endonuclease-polymerase proteins (p34, p40, p52, p68).

The Western blot is a confirmatory assay that is only carried out if the sample was reactive in the screening assay. Both HIV-1 and HIV-2 Western blots are available commercially. The result of a Western blot may be either positive or negative or (in case of an incomplete pattern of visible bands) equivocal which may reflect borderline or non-specific reactivity.

Criteria for the interpretation of HIV Western blot results differ: The American Red Cross demands at least three bands, one from each group (i.e. one gag, one pol and one env band). The US-American Food and Drug Administration (FDA) demands the p24, the p34 as well as the gp41 or gp120/160 bands (CDC 1989). According to WHO recommendations, however, a Western blot may be judged positive if only two env bands are found. In Germany, the DIN norm 58969 part 41 applies (Deutsches Institut für Normung, 2000): a serum sample is HIV positive if it reacts with at least one viral glycoprotein and one of the other HIV proteins.

Disadvantages of Western blot are its high price, the comparatively demanding test procedure and the unavoidable subjectivity when reading and interpreting the result. For these reasons many countries prefer confirmatory testing using suitable testing algorithms, consisting of a combination of different ELISA or rapid tests with well-evaluated sensitivities and specificities in the relevant setting. The World Health Organization recommends the following strategy for resource-poor settings (WHO 1992):

- Diagnosis in an healthy individual when population prevalence < 10 %: three tests;
- Diagnosis in a healthy individual when population prevalence > 10 %, or in a symptomatic individual independent of prevalence: two tests;
- Screening of blood donations: single immunoassay (unless the blood donor is informed of the result).

It should be noted that when 4th generation assays, detecting both antigen and antibody, are used for screening, confirmatory tests detecting only antibody may be non-reactive in the period before antibody production. During this stage, screening test reactivity can be confirmed as true-positive through viral nucleic acid detection. In practice a follow-up sample obtained several days later will normally resolve the matter.

In addition to the obligatory safeguarding through confirmatory testing e.g. by Western blot, the serological diagnosis of an HIV infection always requires testing of a second, independently obtained blood sample from the patient. If at all possible, the patient should only then be informed about the diagnosis.

Rapid tests

Today a number of rapid HIV tests are available, also referred to as "point-of-care", "bedside" tests or "rapid/simple test devices". These tests are based on one of four immunodiagnostic principles: particle agglutination, immunodot (dipstick), immunofiltration or immune chromatography (Giles 1999, Branson 2003). In most cases whole blood or capillary blood (obtained from a finger tip or an earlobe) can be used, thus sparing the centrifugation of a venous blood sample obtained through venepunction, and test results are normally available within fifteen to thirty minutes.

Many rapid tests contain a "built-in" internal control, e.g. as a control band indicating whether the sample material and, if applicable, the reagents were added correctly. If this "built-in" control fails, the test result must not be accepted (important to avoid false-negative results, when e.g. the sample was not added or insufficient time allowed until reading the result).

Such rapid tests may be useful if the result is needed quickly, for instance in emergency rooms, before emergency operations, after needlestick injuries and to minimize the rate of "unclaimed" test results (if the result is only available after a few days, some of those tested will not return to receive it). Rapid tests, which are easy to perform and require little in terms of equipment, are useful in developing countries (WHO 2004). Rapid tests should fulfill the same basic requirements as ELISA screening tests (WHO/UNAIDS 1998). In developed countries, a rapid test should ideally only be used as first guidance, and the patient retested as soon as possible in

a regular routine laboratory. Problems commonly encountered with rapid tests – besides the need for adequate training of personnel – are the necessity to counsel the patient before testing and to obtain his consent. An HIV test which can be performed by laypersons always carries the potential of misuse (such as compulsory testing of prisoners, etc.).

In the meantime, several HIV rapid tests have been licensed by FDA (Greenwald 2006). Worrying experiences, such as individuals being given the wrong diagnosis, emphasize the need for adequate confirmatory testing and, if necessary, follow-up testing after four weeks (CDC 2004).

In addition, at least some rapid tests have a lower sensitivity than previously assumed: A study in Cape Town found a significant proportion of HIV-infected children with false-negative rapid test results (Claassen 2006). Insufficient sensitivity could also reduce their ability to detect early infections.

Sample types

Serum, EDTA plasma, and occasionally whole blood are used for HIV antibody testing. If sample processing is delayed, it is preferable to remove the plasma or serum from the corpuscular constituents of blood, as haemolysis may lead to test problems.

Immunoglobulins may also be eluted from blood spots blotted onto filter paper and dried (Lillo 1992). Such dried blood spots from routinely obtained Guthrie cards are used for the unlinked anonymous screening of newborn babies (whose antibody prevalence mirrors that of their mothers) (Peckham 1990) and in developing countries with insufficient cold storage and transport facilities. Once completely dry, blood from HIV-infected patients does not constitute an infection risk and is stable over long time periods.

Urine or oral fluid (oral transudate, often incorrectly referred to as "saliva") may also be employed for some assays (Tamashiro 1994, King 2000). The FDA licensed a rapid HIV test marketed by OraSure Technologies for use with oral fluid in 2004. According to available information this assay allows the detection of antibodies against HIV-1 or HIV-2 with a sensitivity of 99.3 % and a specificity of 99.9 %.

Under certain conditions, only such non-blood specimen types make testing possible (non-invasive sampling). However, their sensitivities and specificities are mostly considerably lower. Therefore, blood remains the preferred type of specimen. Whatever type of sample is used, a reactive test result of course requires confirmatory testing.

Test performance

HIV antibody tests are among the best commercially available immunological assays. Sensitivity (high sensitivity → few false-negative results) and specificity (high specificity → few false-positive results) are the two most important parameters. However, in practice it is not so much the sensitivity and specificity of a test that is of interest but rather its predictive value – one does not know the real HIV status of the patient tested and must deduce this from the test result. The positive predictive value (PPV) is the probability with which a patient with a positive test

result is indeed infected; and vice versa, the negative predictive value (NPV) is the likelihood of a patient who tested negative being truly not infected.

Table 1: Two-by-two table.

		Test result:	
		positive	negative
True patient status (determined by reference test)	positive	true-positive	false-negative
	negative	false-positive	true-negative

Table 1 explains the connection between the parameters:

- Sensitivity
  = number true-positive / (number true-positive + number false-negative)
  = probability of a positive test result if the patient is infected
- Specificity
  = number true-negative / (number true-negative + number false-positive)
  = probability of a negative test result if the patient is not infected
- Positive predictive value (PPV)
  = number true-positive / (number true-positive + number false-positive)
  = probability that a patient tested positive is indeed infected
- Negative predictive value (NPV)
  = number true-negative / (number true-negative + number false-negative)
  = probability that a patient tested negative is indeed not infected

Although this may initially not seem plausible, the predictive value of a test not only depends on its sensitivity and specificity, but also on the HIV prevalence (i.e. the pre-test-probability of being positive or negative, respectively) in the population tested.

For example: Using a test with a sensitivity of 100 % and a specificity of 99 % (i.e. 1 false positive in 100), and screening 1,000 patients, one would expect to see the following:

1. in a setting with a high HIV prevalence of 10 % (i.e. 100 per 1,000)
   - 100 true positives per 1,000
   - 10 false positives per 1,000
   - Positive predictive value: 100 true positives/110 total positives = 91 %
2. in a setting with a low HIV prevalence of 0.1 % (i.e. 1 per 1,000)
   - 1 true positive per 1,000
   - 10 false positives per 1,000
   - Positive predictive value: 1 true positive/11 total positives = 9.1 %

In the former scenario, 100 (91 %) of the 110 positive test results are true; in the latter, only 1 (9.1 %) out of 11. Therefore >90 % of patients tested positive in a low-prevalence population will not be infected!

Figure 1 further illustrates this relation. When the prevalence is low, the vast majority of positive (or more aptly, reactive) test results are indeed false positive. In contrast, the overwhelming majority of the positive test results in the high-prevalence group are "true" (which is why, according to WHO, confirmatory testing

may exceptionally be omitted here). These examples stress the importance of adequate confirmatory testing for all positive screening test results!

Unfortunately, this statistical phenomenon is frequently misused for propaganda purposes: Inevitably, e.g. in blood donors with a low HIV prevalence due to diligent donor selection criteria, indeed only a small proportion of those with a reactive screening test result are truly infected. However, because any screening test reactivity must be followed up further by confirmatory testing even before the individual concerned is informed, this phenomenon should not have major consequences: for if the Western blot does not confirm the reactive ELISA result, the patient or blood donor is simply not HIV-"positive"! Nevertheless, this statistical phenomenon is unfortunately often used to "prove" the alleged uselessness of HIV tests.

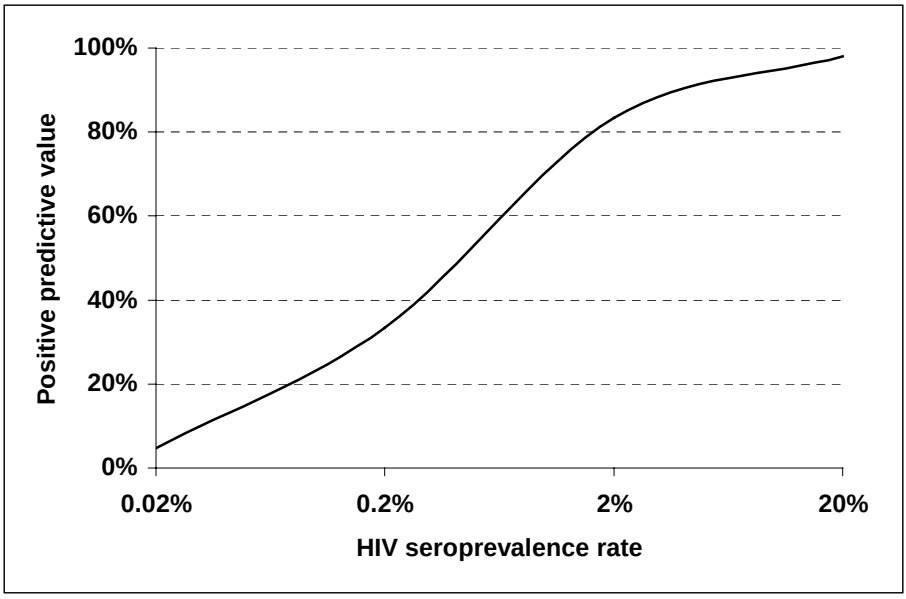

Figure 1: Dependence of the positive predictive value (PPV) on the seroprevalence rate in the population tested, using an antibody test with a constant specificity of 99.6 %.

Problem: The "diagnostic window"

After HIV infection has taken place, it takes several weeks before antibodies become detectable. This phenomenon is called "diagnostic window" and is determined by the time period the body requires to produce detectable levels of antibodies (Busch 1997). The switch from antibody-negative to antibody-positive is called "seroconversion". The screening tests currently used are able to recognize an HIV infection six weeks after primary infection in about 80 % and after the 12th week in almost 100 % of cases; only in very rare cases is an infection recognized only after six months.

4th generation screening assays attempt to shorten the duration of the "diagnostic window" by detecting HIV antibodies and HIV p24 antigen simultaneously (Gürtler 1998, Ly 2001). Although these 4th generation tests become reactive earlier in the

course of an acute primary infection, a second "diagnostic window" phase may occur later on due to methodological reasons, during which the tests may again become non-reactive (Meier 2001).

Early during seroconversion the antibody screening test will be only borderline or weakly reactive. A Western blot carried out for confirmation may at this stage not show any bands at all or an incomplete band pattern, with the p24 band often the first to become visible. The results obtained in such cases are often indistinguishable from those found in uninfected individuals displaying a certain degree of non-specific reactivity; here, too, isolated p24 bands are occasionally seen. This illustrates how important it is to pass important clinical information on to the laboratory carrying out the tests (e.g. "suspected primary infection", "routine screening" etc.)!

Such cases often have to remain unclear for the time being, but are resolved by follow-up testing within a short time. If one is indeed dealing with an early seroconversion, seroreactivity will have increased significantly only a few days later, and within a few weeks a complete band pattern will be found on Western blot. It depends on the individual circumstances whether direct virus detection e.g. by means of PCR is advisable at the outset. Note: antiretroviral post-exposure prophylaxis may make direct virus detection more difficult and potentially delay seroconversion.

The gradual increase of seroreactivity in the course of seroconversion may be utilized for epidemiological studies to measure HIV incidence (i.e. the rate of new infections – in contrast to standard antibody testing that measures HIV prevalence, i.e. established infections), There are several methods in use:

- "Detuned" assays combine highly sensitive with less sensitive antibody tests, to estimate which proportion of positive samples have only recently undergone primary infection (Constantine 2003, Parekh 2005).
- Avidity assays treat specimens with agents that break weaker antigen-antibody bonds, such as those seen in immature antibodies early in infection, and calculate a ratio (avidity index) between such treated and untreated specimen to distinguish between high (old infection) and low avidity (recent infection) (Suligoi 2002, Puchhammer-Stöckl 2005).
- BED IgG capture ELISA ("BED" refers to the use of subtypes B, E, and D in the commercially available assay) captures all IgG molecules and then detects the proportion of HIV-specific antibodies amongst them by detecting the amount of HIV antigen that is bound. Early in infection, the ratio between HIV-specific antibody and other antibody is low, whereas later it is higher (Dobbs, 2004).

It should be noted that these assays are NOT intended for the individual diagnosis of a recent or primary HIV infection, but only for epidemiological studies of HIV incidence in populations.

HIV nucleic acid testing (NAT)

An HIV infection may also be diagnosed through the detection of virus, rather than indirectly through the detection of antibodies. However, virus detection is only necessary in certain situations such as suspected primary infection and to test babies born to HIV-infected mothers.

The detection of viral nucleic acid (i.e. of virus genome) may be achieved by different laboratory techniques, to detect either proviral cDNA in leucocytes (EDTA whole blood) or viral RNA in the cell-free compartment (EDTA plasma or EDTA whole blood).

Various commercial and "in house" methods are available for NAT. These are based on polymerase chain reaction (PCR), branched DNA (b-DNA), nucleic acid sequence-based amplification (NASBA), ligase chain reaction (LCR), or real-time PCR. These assays are generally demanding in terms of laboratory equipment, staff skills etc., require stringent quality control, and are cumbersome, relatively error-prone and expensive.

Qualitative testing for viral genome serves as a marker of infection. It supplements or substitutes antibody testing for the diagnosis of HIV infection in special situations: suspected fresh primary infection, when antibodies are still undetectable during the diagnostic window phase; and newborns of HIV-infected mother, in whom maternal antibodies are still present (see below).

Qualitative testing for viral genome serves as a marker of infection. It supplements antibody testing for the diagnosis of HIV infection in special situations (suspected primary infection: absence of antibodies during the diagnostic window; newborn of infected mother: presence of maternal antibodies – also see below).

The quantitative detection of HIV RNA in plasma ("viral load" testing) is used as a prognostic marker, to monitor antiretroviral therapy and to estimate infectiousness (Berger 2002). "Ultra"-sensitive tests detect as few as 50 copies per millilitre of plasma. Both as a prognostic and as a therapeutic marker, viral load testing is today an indispensable clinical tool. Unfortunately, though, many developing countries cannot afford the currently available assays (Drosten 2006, Fiscus 2006).

The risk of HIV transmission through blood transfusion has decreased enormously through careful selection of donors – to exclude people with potential risk factors for blood-borne viral infections (besides HIV mainly hepatitis B and C) – and through donor screening. Several countries now stipulate HIV NAT in addition to using antibody testing.

It has been suggested to employ NAT for the screening of seronegative patients in high-risk groups (often using pooled samples, i.e. mixing several individual samples together), in order to recognise fresh infections during the "window period" (Pilcher 2004, Pilcher 2005).

Test results

False-positive results obtained after appropriate confirmatory testing are exceptionally rare. A confirmed positive result therefore confirms the presence of HIV-specific antibodies and thus, HIV infection.

A positive test result (i.e. screening and confirmatory tests positive and mistaken sample identity excluded by testing of a second sample) means that the individual tested

- is infected with HIV (i.e. carries the virus that causes AIDS) – except in young children (see below);
- may infect others with HIV unless precautions are taken.

A negative test result means:

- HIV antibodies were not detected in the blood of the individual at the point in time when he or she was tested.

This does not necessarily mean that the person is not infected with HIV. The test could have been performed during the "diagnostic window" period. Antibody-negative people may be highly viraemic, and at this stage are at their most infectious! Beyond the "diagnostic window", meaning later than six months after a possible exposure to HIV, an HIV screening test is rarely "false-negative".

- In case of a (rare) "equivocal" result in the confirmatory assay a follow-up test after a short while is required. Particularly in the case of clinical signs such as fever, lymph node enlargement, rash or neurological symptoms, there may be the suspicion of an acute HIV infection in which seroconversion has only just begun. First antibody reactivities are found, however the full pattern is not yet present.
- In the case of an inconclusive serological result and if an acute primary infection is suspected for clinical and/or anamnestic reasons, direct detection of virus should be attempted by NAT to detect an acute HIV infection

Caution: If, in the case of a suspected fresh primary infection, a quantitative HIV RNA assay is used for virus detection in plasma (because it is often more easily available than PCRs for the detection of proviral DNA in leucocytes), one has to keep in mind that such tests may occasionally lead to false-positive results (Rich 1999). Such false-positive results suggest low levels of HIV RNA (normally not more than 2,000 copies/ml) that are highly unlikely to be found in true acute infection (which normally presents with high "viral load" values). If this phenomenon is not recognized, the patient will be given an erroneous diagnosis of "infected" with all its possibly deleterious consequences.

Special case: Babies born to HIV-infected mothers

Fortunately, the risk of mother-to-child transmission of HIV (MTCT) (see chapter "HIV and pregnancy") has been extremely reduced in developed countries and may be as low as 1 %. Nevertheless, HIV diagnosis is essential in all exposed newborns!

In babies born to HIV-infected mothers, HIV antibodies are normally detectable up to around 12 to 15 months of age, and rarely beyond 18 months. These are passively acquired maternal antibodies transferred transplacentally into the unborn child from around the 30th week of pregnancy onwards. These maternal IgG antibodies confer some physiological immune protection against many infections but in the case of HIV are without protective efficacy. Therefore, most children of HIV-positive mothers, including those not themselves infected (the majority in any setting), will initially have positive HIV antibody test results, albeit with decreasing

reactivities over time, until they become negative after complete elimination of maternal antibodies. In the past one had to wait nine months or longer for a significant fall in the child's antibody level (Newell 1995). If HIV antibodies persist in a vertically exposed child beyond the age of 15 months, the child is usually HIV-infected.

Today, PCR allows a more rapid diagnosis. It is discussed whether the detection of proviral (intracellular) HIV cDNA (from leucocytes) or of (extracellular) HIV RNA (from blood plasma) is more sensitive. In any case, all positive test results must be confirmed immediately on a second sample.

Important: many methods for the detection of HIV nucleic acid may fail in case of unusual HIV-1 subtypes (and with HIV-2) and yield false-negative results (Haas 1996). To exclude this, a maternal sample should also be tested if necessary (e.g. if the mother or her source of infection are from regions with "exotic" subtypes) to ensure the test's ability to detect the viral strain in question. If the mother (before therapy) tests PCR-positive with the same assay, a negative test result on the child may be used; otherwise a suitable method must be chosen in a specialized laboratory or one has to resort to antibody testing alone with its limitations.

In exposed babies, at least two negative HIV PCR results are required in order to exclude HIV infection: the first one between the 1st and the 4th month of life, the second after the 4th month, as only then does it reach its full significance for exclusion of infection (Scarlatti 1991). In addition, PCR should be performed during the first month of life (however not within the first days after delivery, as contamination with maternal virus may occur), as the earliest possible diagnosis of a neonatal infection is important to allow *Pneumocystis* prophylaxis and early antiretroviral therapy in the first months of life. If this first sample tests positive (and is confirmed), this points to an intrauterine infection (less frequent); in case of perinatal transmission during birth (most common scenario), virus will only be detectable in the samples obtained later. Note: breastfeeding carries a significant risk of transmission; what is stated above is only valid if postnatal acquisition of infection is excluded! Even with negative HIV PCR results, the complete elimination of maternal antibodies should be documented at least once in any HIV-exposed child.

Special case: occupational HIV exposure (see also chapter on PEP)

If the index patient is known, he or she should be tested – after relevant counseling and with consent – for HIV and HCV antibodies and for HBsAg. According to the circumstances (e.g. weekend), the use of a rapid assay should be considered (see above). As any delay in instituting HIV post-exposure prophylaxis (HIV PEP) reduces its chances of success (Puro 2004, Panlilio 2005): If there is any doubt, the first one or two doses of HIV PEP (hopefully always readily available as a so-called "starter pack") should be taken and later discontinued once a negative test result becomes available!

If the index patient is seronegative, the chances of him/her – in the absence of any clinical evidence suggesting an acute retroviral syndrome – currently being in the "diagnostic window" phase are remote. It is therefore normally not advisable to employ a method for direct detection of virus (to exclude a fresh primary infection

prior to seroconversion). In case of an unknown index patient the epidemiological situation needs to be taken into account. Important: used injection needles, etc., should not normally be tested for HIV antibodies or HIV genome; effort, cost and particularly the remaining uncertainty (because of the questionable validity of the result) are out of proportion compared to the extremely remote risk of infection with an agent that fortunately has a low stability and tenacity once outside the body.

If the index patient is HIV-positive, all available information (including the current "viral load", results of resistance assays, etc.) must be considered in the decision on the type of HIV PEP (see the relevant chapter).

In the case of an HIV-positive index patient, the injured individual should be tested for HIV antibodies by means of a routine screening assay. Demonstration of initial seronegativity is legally important in order to claim compensation and insurance cover in case of occupational transmission! Further follow-up testing is recommended 6 weeks, 3 months and again 6 months after exposure (Ciesielski 1997). If the index patient is HIV-infected, a further follow-up test of the injured recipient is recommended after 12 months; otherwise this is optional (Ridzon 1997). In addition, an HIV test (and possibly also a test for direct detection of virus) should be done immediately if, at anytime in the months following the incident, the recipient develops illness compatible with an acute retroviral syndrome.

What is relevant in practice?

Testing for HIV continues to be a difficult medical task. Increasingly there are demands for a "re-medicalisation" or "de-stigmatisation" of HIV testing (Manavi 2005, Beckwith 2005; see also www.hiv.net/link.php?id=261). The background is that the requirements for informed patient consent (which may cause embarrassment to the health care provider and takes time and effort) often act as a deterrent so that testing is not done and infected individuals are thus unable to benefit from adequate management. For this reason current CDC recommendations advocate so-called "opt-out" screening for many situations: Here the patient is informed about the planned test but not counselled in detail, and testing is carried out unless the patient explicitly declines (CDC 2006).

Despite all therapeutic progress, a positive test result still has considerable consequences for the concerned individual. Every patient must therefore be informed in advance about an HIV test to be done. The patient's or in the case of minors or adults unable to give consent, parent's or legal carer's consent does not have to be in writing but must be documented in the patient notes.

HIV test results should, if possible, only be communicated by staff knowledgeable about HIV or if newly diagnosed patients can be referred immediately – most will need expert advice and support straight away. A positive HIV test result should never be told by telephone or by e-mail etc., as this does not allow for sufficient counselling or management of the patient's reaction. For the aforesaid reasons rapid tests for home testing are highly problematic (Frith 2007). Such tests may be useful in certain situations but carry the risk of unprofessional usage.

A reactive screening test result on its own must not be revealed to the patient, even if it serves, e.g. after a needlestick injury, as the basis for medical management. Numerous factors may cause a screeening test to become falsely reactive; therefore always wait for the confirmatory assay! Rare inconclusive test results should be discussed with the laboratory and an experienced HIV physician before informing the patient. Even then the result should be confirmed in a second, independently obtained blood sample.

With each HIV test request, one should be aware of the reason behind it. AIDS phobia poses a difficult problem and is not rare – i.e., people who are as firmly as erroneously convinced that they are HIV-infected, often without any appreciable risk. Often they want to be tested at short intervals and by different carers, sometimes insisting on expensive tests such as PCR. Such individuals (who often also suffer from the delusion that positive test results are withheld from them) need psychological and perhaps psychiatric help rather than repeated HIV testing.

Useful Internet sources relating to HIV testing

- World Health Organization WHO: http://www.who.int/ with the following webpages:
- Department of Essential Health Technologies: http://www.who.int/eht/en/
- HIV/AIDS Diagnostics : http://www.who.int/hiv/amds/diagnostics/en/index.html
- Diagnostics and Laboratory Technology: http://www.who.int/diagnostics_laboratory/en/index.html with downloadable reports presenting evaluation results of different commercially available HIV assays.
- The European Commission, Enterprise & Industry, Medical Devices: http://europa.eu.int/comm/enterprise/medical_devices/index.htm with informations about the In Vitro Diagnostic Directive (IVDD)
- Centers for Disease Control and Prevention (CDC), USA, Division of HIV/AIDS Prevention: http://www.cdc.gov/hiv/testing.htm, http://www.cdc.gov/hiv/rapid_testing
- U. S. Food and Drug Administration (FDA), Center for Biologics Evaluation and Research (CBER): Licensed / Approved HIV, HTLV and Hepatitis Tests: http://www.fda.gov/cber/products/testkits.htm

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4. Pathogenesis of HIV-1 Infection

Andrea Rubbert, Georg Behrens and Mario Ostrowski

Since the initial description of the human immunodeficiency virus type I (HIV-1) in 1983 (Barre-Sonoussi 1983, Gallo 1983) and HIV-2 in 1986 (Clavel 1986), these two viruses have been identified for almost 20 years as the primary cause of the acquired immunodeficiency syndrome (AIDS). As HIV-1 is the major cause of AIDS in the world today, our discussion will be primarily limited to HIV-1 infection. Worldwide, the number of HIV-1 infected persons exceeds 40 million, the majority of whom live in the developing countries of Sub-Saharan Africa, Asia and South America.

The introduction of protease inhibitors and non-nucleotide reverse transcriptase inhibitors (NNRTIs) to antiretroviral treatment regimens in 1995 began the era of highly active antiretroviral therapy (HAART), and resulted in dramatic improvements in the mortality and morbidity of HIV disease, as determined by a decreased incidence of opportunistic infections, tumors, and deaths. Despite all the therapeutic advantages achieved during the last decade, including the development of HAART, once an individual has become infected, eradication of the virus still remains impossible.

In addition, new problems relating to the short- and long-term toxicity of drug treatments and the occurrence of resistance mutations in both circulating and transmitted viruses are emerging. In most countries in South East Asia and Africa, the incidence and prevalence of HIV-1 infection continues to increase and surpass that of Europe and North America. However, due to the high costs of drug regimens and the lack of a healthcare infrastructure in these developing countries, the widespread use of HAART is currently still difficult. The further course of the HIV-1 pandemic, therefore, mainly depends on how and to what degree the developing countries with a high HIV-1 prevalence are able to take advantage of the medical progress achieved in Europe and North America, and whether an effective prophylactic vaccine becomes available in the near future.

An understanding of the immunopathogenesis of HIV-1 infection is a major prerequisite for rationally improving therapeutic strategies, developing immunotherapeutics and prophylactic vaccines. As in other virus infections, the individual course of HIV-1 infection depends on both host and viral factors.

The course of infection with HIV-1 in HIV-infected humans may vary dramatically, even if the primary infections arose from the same source (Liu 1997). In some individuals, with a long-term non-progressive HIV-1 infection (i.e., lack of decline in CD4+ T-cell counts, or chronic infection for at least 7 years without the development of AIDS), a defective virion was identified (Kirchhoff 1995). Thus, infection with a defective virus, or one that has a poor capacity to replicate, may prolong the clinical course of HIV-1 infection. However, in most individuals, HIV-1 infection is characterized by a replication-competent virus with a high daily turnover of virions.

Host factors may also determine whether or not an HIV-1-infected individual rapidly develops clinically overt immunodeficiency, or whether this individual belongs to the group of long-term non-progressors, who represent about 5 % of all infected

patients. The identification and characterization of host factors contributing to the course of HIV infection, including immunological defense mechanisms and genetic factors, will be crucial for our understanding of the immunopathogenesis of HIV infection and for the development of immunotherapeutic and prophylactic strategies.

1. The structure of HIV-1

HIV-1 is a retrovirus and belongs to the family of lentiviruses. Infections with lentiviruses typically show a chronic course of disease, a long period of clinical latency, persistent viral replication and involvement of the central nervous system. Visna infections in sheep, simian immunodeficiency virus infections (SIV) in monkeys, or feline immunodeficiency virus infections (FIV) in cats are typical examples of lentivirus infections.

Using electron microscopy, HIV-1 and HIV-2 resemble each other strikingly. However, they differ with regard to the molecular weight of their proteins, as well as having differences in their accessory genes. HIV-2 is genetically more closely related to the SIV found in sootey mangabeys (SIV_{sm}) rather than HIV-1 and it is likely that it was introduced into the human population by monkeys. Both HIV-1 and HIV-2 replicate in CD4+ T-cells and are regarded as pathogenic in infected persons, although the actual immune deficiency may be less severe in HIV-2-infected individuals.

1.1. The morphologic structure of HIV-1

HIV-1 viral particles have a diameter of 100 nm and are surrounded by a lipoprotein membrane. Each viral particle contains 72 glycoprotein complexes, which are integrated into this lipid membrane, and are each composed of trimers of an external glycoprotein gp120 and a transmembrane spanning protein gp41. The bonding between gp120 and gp41 is only loose and therefore gp120 may be shed spontaneously within the local environment. Glycoprotein gp120 may also be detected in the serum as well as within the lymphatic tissue of HIV-infected patients. During the process of budding, the virus may also incorporate different host proteins from the membrane of the host cell into its lipoprotein layer, such as HLA class I and II proteins, or adhesion proteins such as ICAM-1 that may facilitate adhesion to other target cells. The matrix protein p17 is anchored to the inside of the viral lipoprotein membrane. The p24 core antigen contains two copies of HIV-1 RNA. The HIV-1 RNA is part of a protein-nucleic acid complex, which is composed of the nucleoprotein p7 and the reverse transcriptase p66 (RT). The viral particle contains all the enzymatic equipment that is necessary for replication: a reverse transcriptase (RT), an integrase p32 and a protease p11 (overview in: Gelderblom 1993) (Fig. 1).

1.2. The organization of the viral genome

Most replication competent retroviruses depend on three genes: *gag*, *pol* and *env*: **gag** means "**g**roup-**a**nti**g**en", **pol** represents "**pol**ymerase" and **env** is for "**env**elope" (overview in: Wong-Staal 1991) (Fig. 2). The "classical" structural scheme of a retroviral genome is: 5'LTR-gag-pol-env-LTR 3'. The LTR ("**l**ong **t**erminal **r**epeat") regions represent the two end parts of the viral genome, that are connected to

the cellular DNA of the host cell after integration and do not encode for any viral proteins. The *gag* and *env* genes code for the nucleocapsid and the glycoproteins of the viral membrane; the *pol* gene codes for the reverse transcriptase and other enzymes. In addition, HIV-1 contains six genes (*vif*, *vpu*, *vpr*, *tat*, *rev* and *nef*) in its 9kB RNA. *Nef, vif, vpr* and *vpu* were classified as accessory genes in the past, as they are not absolutely required for replication in vitro. The accessory genes, *nef*, *tat* and *rev,* are all produced early in the viral replication cycle.

Tat and *rev* are regulatory proteins that accumulate within the nucleus and bind to defined regions of the viral RNA: TAR (transactivation-response elements), found in the LTR; and RRE (rev response elements), found in the *env* gene, respectively. The *tat* protein is a potent transcriptional activator of the LTR promoter region and is essential for viral replication in almost all in vitro culture systems. Cyclin T1 is a necessary cellular cofactor for *tat* (Wei 1998). *Tat* and *rev* stimulate the transcription of proviral HIV-1 DNA into RNA, promote RNA elongation, enhance the transportation of HIV RNA from the nucleus to the cytoplasm and are essential for translation. *Rev* is also a nuclear export factor that is important for switching from the early expression of regulatory proteins to the structural proteins that are synthesized later.

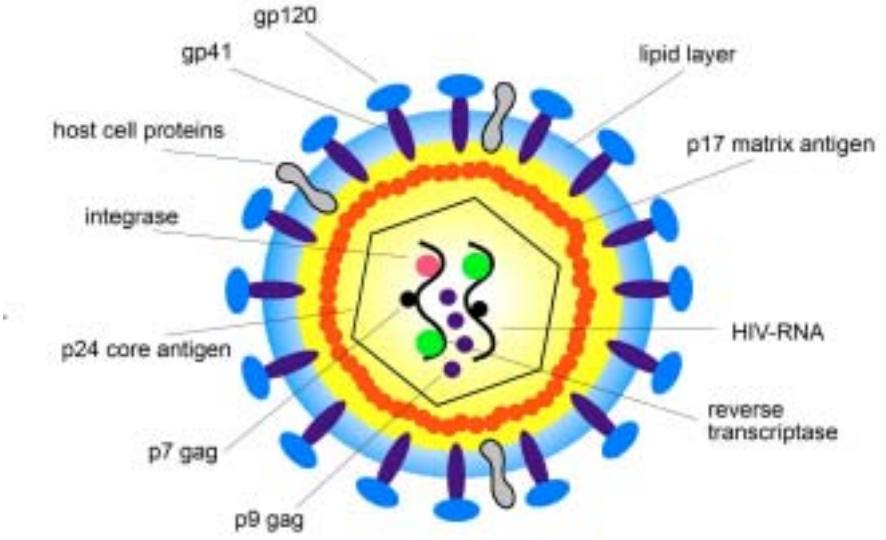


Figure 1: Structure of an HIV virion particle. For detailed explanations see text.

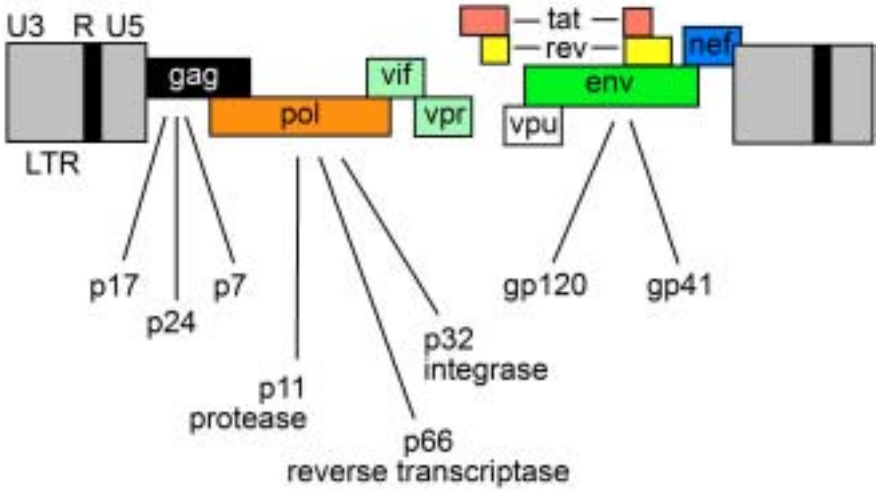


Figure 2: HIV and its genes. For detailed explanations see text.

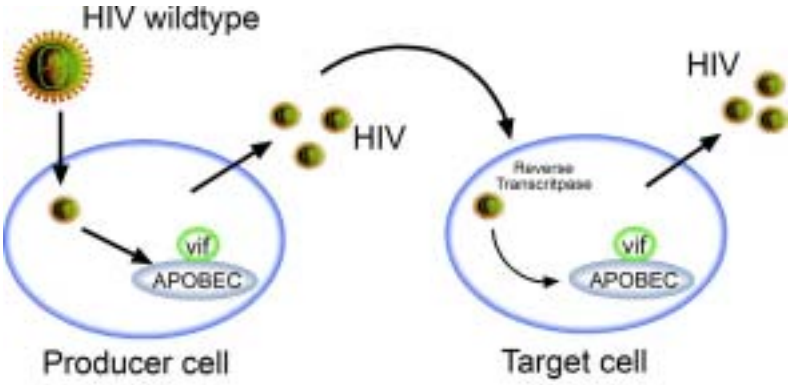
Nef has been shown to have a number of functions. *Nef* may induce downregulation of CD4 (Aiken 1994) and HLA class I molecules (Collins 1998) from the surface of HIV-1-infected cells, which may represent an important escape mechanism for the virus to evade an attack mediated by cytotoxic CD8+ T-cells and to avoid recognition by CD4+ T-cells. *Nef* may also interfere with T-cell activation by binding to various proteins that are involved in intracellular signal transduction pathways (Overview in: Peter 1998). In SIV-infected rhesus macaques, an intact *nef* gene was essential for a high rate of virus production and the progression of disease. HIV-1, with deletions in *nef,* was identified in a cohort of Australian long-term non-progressors. However, more recent reports indicate that some of these patients are now developing signs of disease progression together with a decline of CD4+ T-cells. Thus, although, deletions of the *nef* gene may slow viral replication, they cannot always prevent the development of AIDS.

Vpr seems to be essential for viral replication in non-dividing cells such as macrophages. Vpr may stimulate the HIV-LTR in addition to a variety of cellular and viral promoters. More recently, *vpr* was shown to be important for the transport of the viral pre-integration complex to the nucleus (Overview in: Miller 1997) and may arrest cells in the G2 phase of the cell cycle.

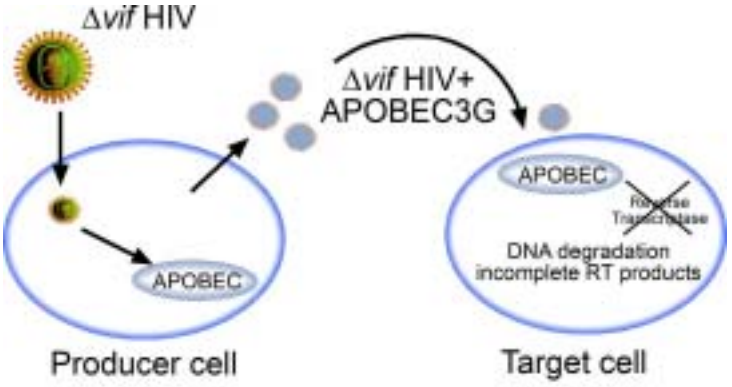
Vpu is important for the virus "budding" process, because mutations in *vpu* are associated with persistence of the viral particles at the host cell surface. *Vpu* is also involved when CD4-gp160 complexes are degraded within the endoplasmic reticulum and therefore allows recycling of gp160 for the formation of new virions (Cullen 1998).

Some recent publications have highlighted a new and important role for vif in supporting viral replication (Mariani 2003). *Vif*-deficient HIV-1 isolates do not replicate in CD4+ T-cells, some T cell lines ("non-permissive cells") or in macrophages. *Vif*-deficient isolates are able to enter a target cell and initiate reverse transcription,

but synthesis of proviral DNA remains incomplete. In vitro fusion of "permissive" and "non-permissive" cells leads to a "non-permissive" phenotype, suggesting that the replication of HIV depends on the presence or absence of a cellular inhibitor. This endogenous inhibitory factor was recently identified as APOBEC3G (Sheehy 2002). APOBEC3G ("apolipoprotein B mRNA editing enzyme catalytic polypeptide-like 3G") belongs to a family of intracellular enzymes that specifically deaminate cytosine to uracil in mRNA or DNA resulting in an accumulation of G-to-A mutations that lead to degradation of viral DNA. By forming a complex with APOBEC3G, *vif* blocks the inhibitory activity of APOBEC3G (Figure 3a).



3a



3b

Figure 3: HIV wild-type infection: vif interacts with APOBEC3G, binds to APOBEC3G and prevents its incorporation in newly formed viruses (Fig 3a). Vif-deleted HIV isolates fail to inhibit intracellular APOBEC3G, which is then incorporated into new viruses and interferes with reverse transcription in the target cell.

Of interest, the antiviral activity of APOBEC3G is highly conserved among various species, whereas the blockade of APOBEC3G by *vif* is highly specific for HIV. HIV-1 *vif* does not complex to murine or rhesus APOBEC3G. In the absence of *vif,* APOBEC3G is incorporated into newly formed viral particles and in subsequently infected target cells, synthesis of proviral DNA is blocked (Figure 3b). In contrast, in the presence of *vif*, APOBEC3G is complexed, degraded and not incorporated in newly formed virions. APOBEC3G is expressed in lymphocytes and macrophages representing the primary target cells of HIV infection.

Currently, there are still a lot of open questions regarding the regulation of intracellular APOBEC3G: for example, whether there is a critical amount of intracellular APOBEC3G that restricts HIV infection in the presence of *vif,* or whether genetic polymorphisms of APOBEC3G exist that may potentially affect the course of disease. It has been shown that dendritic cells upregulate APOBEC3G upon maturation (Pion 2006). In addition, the enzymatic function of intracellular APOBEC3G in lymphocytes may depend on the cellular activation status (Chiu 2005). Meanwhile, the epitopes by which vif and APOBEC3G interact with each other have been characterized and the pathway of intracellular degradation of the APOBEC3G-*vif* complex explored. Of note, specific inhibitors that block the interaction of *vif* and APOBEC3G or that interfere with the intracellular degradation of APOBEC3G could represent promising future treatments. In principle, blockade of cellular structures will likely be associated with a minimal risk that the development of resistance might compromise the efficacy of an antiviral agent. Therefore, targeting *vif* and APOBEC3G represents an interesting therapeutic approach.

2. The HIV replication cycle

2.1. HIV entry

CD4 as a primary receptor for HIV

CD4 is a 58 kDa monomeric glycoprotein that can be detected on the cell surface of about 60 % of T-lymphocytes, on T-cell precursors within the bone marrow and thymus, and on monocytes and macrophages, eosinophils, dendritic cells and microglial cells of the central nervous system. The extracellular domain of the CD4 on T-cells is composed of 370 amino acids; the hydrophobic transmembrane domain and the cytoplasmic part of CD4 on T-cells consist of 25 and 38 amino acids, respectively. Within the extracellular part of CD4, four regions D1-D4 have been characterized that represent immunoglobulin-like domains. Residues within the V2 region of CD4 (amino acids 40-55) are important for the bonding of gp120 to CD4 and this region overlaps the part of the CD4 where its natural ligands, HLA class II molecules, bind.

CD4, as a primary and necessary receptor for HIV-1, HIV-2 and SIV, was already characterized in 1984 (Dalgleish 1984, Klatzmann 1984). The identification of the gp120 binding site on the CD4 of CD4+ T-cells stimulated attempts to use soluble CD4 (sCD4) to neutralize the circulating virus in patients, the aim being the inhibition of viral spread (Schooley 1990). In the past couple of years, the idea of block-

ing CD4 as the primary cellular receptor of HIV has regained interest. PRO542 represents a genetically engineered tetravalent CD4-IgG2 fusion protein that not only inhibited viral replication in vitro, but also showed an impressive antiviral efficacy in patients with high viral load that were included in initial clinical trials (Olson 2004).

CD4 attaches to the T cell receptor complex (TCR) on CD4+ T-cells and binds to HLA class II molecules on antigen-presenting cells. The binding of gp120 to CD4 is not only a crucial step for viral entry, but also interferes with intracellular signal transduction pathways and promotes apoptosis in CD4+ T-cells (Banda 1992).

Interestingly, monoclonal antibodies against CD4 induced conformational (CD4i) epitopes to bind to the gp120 of CD4-independent viruses. This observation suggests that the gp120 of CD4-independent viruses already exposes the regions that are necessary for coreceptor recognition and binding and therefore binding to CD4 is not a prerequisite of entry for these viruses. CD4-independent viruses are easy to neutralize using the serum of HIV-infected patients, suggesting that the immune response selects against CD4-independent viruses (Edwards 2001).

Chemokine receptors as coreceptors for HIV entry

Experiments, using non-human cell lines transfected with human CD4, showed that expression of human CD4 on the cell surface of a non-human cell line was not sufficient to allow entry of HIV. Therefore the existence of additional human coreceptors necessary for viral entry was postulated. On the other hand, some laboratory HIV-1 isolates, as well as some HIV-2 and SIV isolates are able to infect human cells independently from CD4. A milestone for the characterization of the early events leading to HIV-1 entry was an observation by Cocchi and his co-workers in 1995. CD8 T cells from HIV-infected patients are able to suppress viral replication in co-cultures with HIV-infected autologous or allogenic CD4+ T-cells, and this is independent from their cytotoxic activity (Levy 1996). Cocchi identified the chemokines MIP-1α, MIP-1β and Rantes in supernatants from CD8+ T-cells derived from HIV-infected patients, and was able to show that these chemokines were able to suppress replication in a dose-dependent manner of some, but not all, viral isolates tested (Cocchi 1995). MIP-1α, MIP-1β and Rantes are ligands for the chemokine receptor CCR5, and a few months later several groups were able to show that CCR5 is a necessary coreceptor for monocytotropic (M-tropic) HIV-1 isolates (Deng 1996, Doranz 1996, Dragic 1998). A few weeks earlier, the chemokine receptor CXCR4 (fusin) was described as being the coreceptor used by T-cell-tropic (T-tropic) HIV isolates (Feng 1996). Monocytotropic (M-tropic) HIV-1 isolates are classically those viruses that are most easily propagated in macrophage cultures, are unable to infect T-cell lines (i.e., immortalized T-cells), but are able to easily infect primary T-cells from peripheral blood samples. Conversely, T-cell-tropic HIV-1 isolates have classically been identified as being those that are easily propagated in T-cell lines, and grow poorly in macrophages, but are also able to easily infect primary T-cells from peripheral blood samples. Thus, it should be noted that both M-tropic and T-tropic HIV-1 variants can easily infect primary human non-immortalized T-cells in vitro.

Chemokines ("**Chemo**tactic cyto**kines**") and their receptors have been previously characterized with regard to their role in promoting the migration ("chemotaxis") of

leukocytes and their pro-inflammatory activity. They are proteins of 68-120 amino acids which depend on the structure of their common cysteine motif, and which may be subdivided into C-X-C (α-chemokines), C-C (β-chemokines) and C-chemokines. Chemokines typically show a high degree of structural homology to each other and may share the receptors they bind to. Chemokine receptors belong to the group of receptors with seven transmembranic regions ("7-transmembrane receptors"), which are intracellularly linked to G-proteins.

SDF-1 ("stromal cell-derived factor 1") was identified as the natural ligand of CXCR4 and is able to inhibit the entry of T-tropic HIV-1 isolates into activated CD4+ T-cells. Rantes ("regulated upon activation T cell expressed and secreted"), MIP-1α ("macrophage inhibitory protein") and MIP-1β represent the natural ligands of CCR5 and are able to inhibit the entry of M-tropic HIV-1 isolates into T cells. A schematic model is depicted in Figure 4: T-tropic HIV-1 isolates mainly infect activated peripheral blood CD4+ T-cells and cell lines and use CXCR4 for entry into the CD4+ target cell. M-tropic isolates are able to infect CD4+ T-cells, monocytes and macrophages, and depend on the use of CCR5 and CD4 for viral entry.

The interaction of gp120 and the cellular receptors is now understood in more detail. Gp120 primarily binds to certain epitopes of CD4. Binding to CD4 induces conformational changes in gp120 that promote a more efficient interaction of the V3 loop of gp120 with its respective coreceptor. Membrane fusion is dependent on gp120 coreceptor binding. Gp41, as the transmembrane part of the envelope glycoprotein gp160, is crucial for the fusion of the viral and the host cell membrane. Similar to influenza hemagglutinin, it was postulated that consequent to the binding of gp120 to CD4, a conformational change is induced in gp41 that allows gp41 to insert its hydrophobic NH_2 terminal into the target cell membrane. Gp41 has been compared to a "mouse trap" and a crystallographic analysis of the ectodomanic structure of gp41 seems to confirm that hypothesis (Chan 1997). The identification of crucial amino acid sequences for this process was used to synthesize peptides that bind to gp41 within the domains, are critical for the induction of conformational changes, and that may inhibit membrane fusion.

T20 is the first of several peptides that bind to gp41 and has been tested in clinical trials for suppressing viral replication (see HAART chapter).

Using transfected cell lines, besides CCR5 and CXCR4, other chemokine receptors, such as CCR3, CCR2, CCR8, CCR9, STRL33 ("Bonzo"), Gpr 15 ("Bob"), Gpr 1, APJ and ChemR23, were identified and shown to be used for entry by certain HIV isolates (Deng 1997, Liao 1997). APJ may represent a relevant coreceptor within the central nervous system. Despite this broad spectrum of potentially available coreceptors, CCR5 and CXCR4 seem to represent the most relevant coreceptors for HIV-1 in vivo.

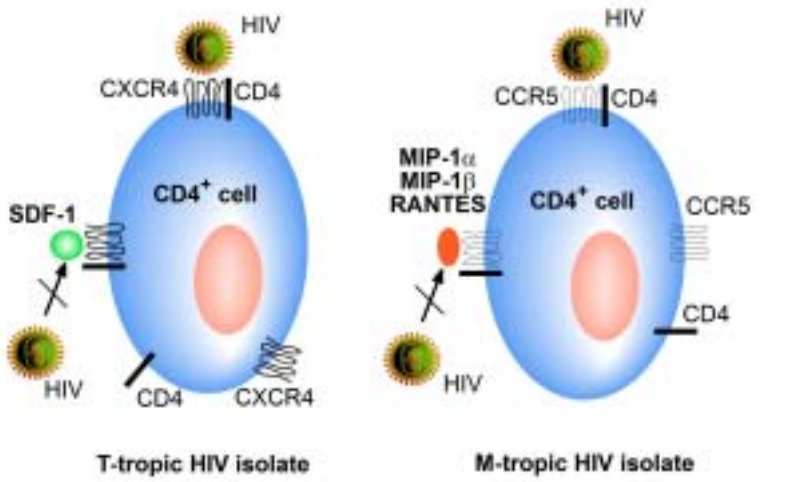


Figure 4: Inhibition of virus entry of CCR5-utilizing (monocytotropic) and CXCR4-utilizing (T-cell tropic) HIV isolates by the natural ligands of the chemokine coreceptors CCR5 and CXCR4.

The importance of CCR5 as the predominant coreceptor for M-tropic HIV isolates is underscored by another observation. The majority of individuals with a genetic defect of CCR5 are resistant to infection with HIV-1 (Liu 1996). In vitro experiments show that lymphocytes derived from these individuals are resistant to HIV-1 infection using M-tropic isolates but not to infection with T-tropic isolates. Lymphocytes from these individuals do not express CCR5 on their cell surface and genetically have a 32 base pair deletion of the CCR5 gene. Worldwide, a few patients have been identified that have acquired HIV-1 infection despite a homozygous deletion of the CCR5. As expected, all of them were infected with CXCR4-using HIV-1 isolates. In epidemiological studies, the allelic frequency of the CCR5 gene deletion is 10-20 % among Caucasians, particularly amongst those of Northern European descent. The frequency of a homozygous individual is about 1% in Caucasians (Dean 1996). Studies conducted on African or Asian populations, however, do not find this 32 base pair deletion of the CCR5, suggesting that this mutation arose after the separation of these populations in evolutionary history.

Individuals that are heterozygous for the 32 bp deletion of the CCR5 show a decreased expression of CCR5 on the cell surface and are more frequently encountered within cohorts of long-term non-progressors compared to patients who have a rapid progression of disease (Dean 1996). In addition, HIV-infected individuals who are heterozygous for the 32 bp deletion of the CCR5, have a slower progression to AIDS, a better treatment response to HAART and lymphoma incidence is decreased.

In addition to the 32bp deletion of the CCR5, other genetic polymorphisms, with regard to the chemokine receptors (CCR2) or their promoters (CCR5), have been described. Based on the occurrence of these polymorphisms within defined patient

cohorts, they were associated with a more rapid or a more favorable course of disease, depending on the particular polymorphism (Anzala 1998, Winkler 1998).

In patients who have a rapid progression of disease (rapid drop in CD4+ T-cell count), virus isolates that use CXCR4 as a predominant coreceptor tend to be frequently isolated from their cells, in comparison to patients with a stable CD4+ T-cell count.

The expression of coreceptors on CD4+ T-lymphocytes depends on their activation level. CXCR4 is mainly expressed on naive T-cells, whereas CCR5 is present on activated and effector/memory T-cells. During the early course of HIV-1 infection, predominantly M-tropic HIV-1 isolates are detected. Interestingly, M-tropic HIV-1 isolates are preferentially transmitted regardless of whether or not the "donor" predominantly harbors T-tropic isolates. At present, it remains unclear whether this "in vivo" preference of M-tropic HIV-1 isolates is determined by selected transportation of M-tropic isolates by sub-mucosally located dendritic cells or whether the local cytokine/chemokine milieu favors the replication of M-tropic viruses. Recent intriguing studies by Cheng Meyer et al. suggest that M-tropic HIV-1 viruses are able to 'hide' more easily from the immune system by replicating in macrophages, in comparison to T-tropic viruses, thus giving them a survival advantage in the infected individual.

The blockade of CCR5, therefore, seems to represent a promising target for therapeutic intervention (Figure 5). In vitro, monoclonal antibodies to CCR5 (2D7 and others) are able to block the entry of CCR5-using HIV isolates into CD4+ T cells and macrophages. Synthetic inhibitors of CCR5 have been designed and demonstrated a significant reduction of plasma viremia in HIV-infected patients in clinical trials. In vitro studies, as well as experiments using SCID mice, however, suggest that blockade of CCR5-using isolates may alter their tropism towards increased usage of CXCR4.

Small molecule inhibitors such as T22, ALX40-4C or AMD3100 are able to inhibit CXCR4 and are also subject to preclinical and clinical trials (see HAART chapter). Other CCR5 inhibitors have been used as mucosal microbicides in monkey models and could therefore represent a potential future preventive approach (Veazey 2005).

Strategies are currently being developed to modulate expression of chemokine receptors. Intrakines are chemokines that stay within the cytoplasm and are able to capture and bind to their corresponding receptor on its way to the cell surface (Chen 1997). "Short interfering RNA" (siRNA) represents a new molecular tool that is able to selectively inactivate target genes. Double-stranded RNA is split by the enzyme dicer-1 into short pieces ("21-23mers"). These oligomers may complementary bind to longer RNA sequences that are subsequently degraded. This strategy is currently employed in plants and used for its antiviral activity. The use of siRNA against CCR5 can prevent the expression of CCR5 in vitro.

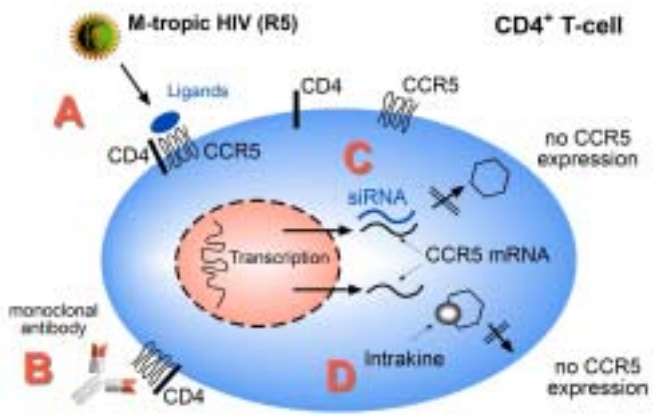


Figure 5: Strategies to block infection by CCR5-tropic HIV. Blochage of CCR5 on the cell surface by non-agonistic ligands (A) or monoclonal antibodies (B). Alternatively, CCR5 cell surface expression can be reduced by siRNA or intrakine. For further details see text.

Although the therapeutic use of chemokine receptor blockers seems promising, a lot of questions still remain unanswered. Using knockout mice it was demonstrated that the absence of CXCR4 or SDF-1 is associated with severe defects in hematopoiesis and in cerebellar development (Zou 1997). Currently, it remains unclear whether the blockade of CXCR4 in postnatal or adult individuals may also affect other organ systems.

2.2. Postfusion events

Following membrane fusion the virus core "uncoats" into the cytoplasm of the target cell. These "early events" have recently been studied in more detail. HIV can enter into rhesus lymphocytes but replication is stopped before or during early reverse transcription. This intracellular blockade is mediated by a cellular factor, TRIM5α, which is a component of cytoplasmic bodies and whose primary function is yet known. TRIM5α from various species exhibits differential inhibition on various retroviruses. For example, TRIM5α from rhesus macaques ($TRIM5\alpha_{rh}$) more profoundly inhibits HIV replication than human TRIM5α, whereas SIV (simian immunodeficiency virus) which naturally infects Old World monkeys, is less susceptible to either form of TRIM5α ,thus explaining in part the species specificity of HIV for human cells (Stremlau 2004). TRIM5α from human cells or non-human primates is able to inhibit replication of other lentiviruses and represents a novel cellular resistance factor whose definitive biological significance has yet to be fully characterized. It is unclear how exactly TRIM5α blocks reverse transcription and it has been hypothesized that TRIM5α interferes with the incoming virus capsid protein targeting it for ubiquitination and proteolytic degradation.

HIV-1 entry into quiescent T cells is comparable to HIV-1 entry into activated T cells, but synthesis of HIV-1 DNA remains incomplete in quiescent cells (Zack 1990). The conversion of viral RNA into proviral DNA, mediated by the viral enzyme reverse transcriptase (RT), occurs in the cytoplasm of the target cell and is a crucial step within the viral replication cycle (Figure 6). Blockade of the RT by the

nucleoside inhibitor zidovudine was the first attempt to inhibit viral replication in HIV-1 infected patients.

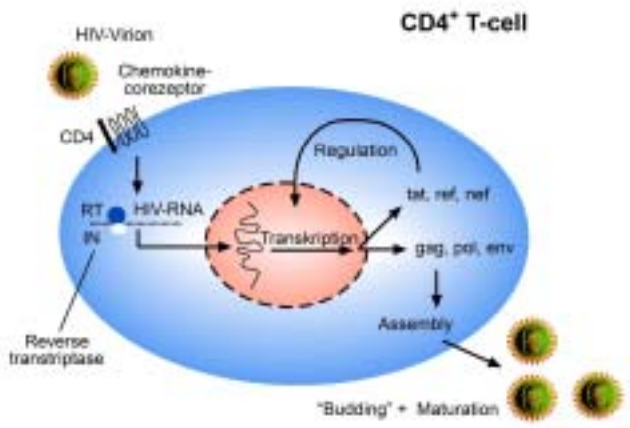


Figure 6: Life cycle of HIV.

Reverse transcription occurs in multiple steps. After binding of the tRNA primers, synthesis of proviral DNA occurs as a minus-strand polymerization starting at the PBS ("primer binding site") and extending up to the 5' repeat region as a short R/U5 DNA. The next step includes degradation of RNA above the PBS by the viral enzyme RNAase H and a "template switch" of the R/U5 DNA with hybridization of the R sequence at the 3' RNA end. Now the full length polymerization of proviral DNA with degradation of the tRNA is completed. Reverse transcription results in double-stranded HIV DNA with LTR regions ("long terminal repeats") at each end.

HIV-1 enters into quiescent T cells and reverse transcription may result in the accumulation of proviral, non-integrating HIV-DNA. However, cellular activation is necessary for integration of the proviral HIV DNA into the host cell genome after transportation of the pre-integration complex into the nucleus. Cellular activation may occur in vitro after stimulation with antigens or mitogens, in vivo activation of the immune system is observed after antigen contact or vaccination or during an opportunistic infection. In addition, evidence is emerging that HIV-1 gp120 itself may activate the infecting cell to enhance integration. Besides monocytes, macrophages and microglial cells, latently infected quiescent CD4+ T-cells that contain non-integrated proviral HIV DNA represent important long-living cellular reservoirs of HIV (Chun 1997). For integration of proviral DNA the viral enzyme integrase is essential. The integrase is highly conserved among different clinical HIV-1 isolates, and integrase inhibition has now been successfully explored in clinical trials (MK-0518, GS-9137) and approved for HIV-therapy (Lataillade 2006).

Since natural HIV-1 infection is characterized by continuing cycles of viral replication in activated CD4+ T-cells, viral latency in these resting CD4+ T-cells likely represents an accidental phenomenon and is not likely to be important in the pathogenesis of this disease. This small reservoir of latent provirus in quiescent CD4+ T-

cells gains importance, however, in individuals who are treated with HAART, since the antivirals are unable to affect non-replicating proviruses and thus the virus will persist in those cells and be replication competent to supply new rounds of infection, if the drugs are stopped. Thus, the existence of this latent reservoir has prevented HAART from entirely eradicating the virus from infected individuals.

Until recently it was not clear, why HIV replicates poorly in quiescent CD4+ T-cells. The cellular protein Murr1 that plays a role in copper metabolism is able to inhibit HIV replication in unstimulated CD4+ T-cells. Murr1 was detected in primary resting CD4+ T-cells and interferes with activation of the transcription factor NFκB by inhibiting the degradation of IκBα. IκBα prevents NFκB from migrating to the nucleus, especially after cytokine stimulation (e.g., TNFα). Because the HIV LTR region has multiple sites for NFκB, preventing NFκB migration to the nucleus should inhibit HIV replication. Inhibition of murr-1 by siRNA is associated with HIV replication in quiescent CD4+ T-cells (Ganesh 2003). Persistence of HIV in quiescent CD4+ T-cells and other cellular reservoirs seems one of the main reasons why eradication of HIV is not feasible. If it is ever possible to achieve, a more detailed knowledge of how and when cellular reservoirs of HIV are established and how they may be targeted is of crucial importance for the development of strategies aiming at HIV eradication.

Cellular transcription factors such as NFκB may also bind to the LTR regions. After stimulation with mitogens or cytokines, NFκB is translocated into the nucleus where it binds to the HIV-LTR region, thereby initiating transcription of HIV genes. Transcription initially results in the early synthesis of regulatory HIV-1 proteins such as *tat* or *rev*. *Tat* binds to the TAR site ("transactivation response element") at the beginning of the HIV-1 RNA in the nucleus and stimulates transcription and the formation of longer RNA transcripts. *Rev* activates the expression of structural and enzymatic genes and inhibits the production of regulatory proteins, therefore promoting the formation of mature viral particles. The proteins coded for by *pol* and *gag* form the nucleus of the maturing HIV particle; the gene products coded for by *env* form the gp120 "spikes" of the viral envelope. The gp120 spikes of the envelope are synthesized as large gp160 precursor molecules and are cleaved by the HIV-1 protease into gp120 and gp41. The *gag* proteins are also derived from a large 53 kD precursor molecule, from which the HIV protease cleaves the p24, p17, p9 and p7 *gag* proteins. Cleavage of the precursor molecules by the HIV-1 protease is necessary for the generation of infectious viral particles, and therefore the viral protease represents another interesting target for therapeutic blockade. The formation of new viral particles is a stepwise process: a new virus core is formed by HIV-1 RNA, *gag* proteins and various *pol* enzymes and moves towards the cell surface. The large precursor molecules are cleaved by the HIV-1 protease, which results in the infectious viral particles budding through the host cell membrane. During the budding process, the virus lipid membranes may incorporate various host cell proteins and become enriched with certain phospholipids and cholesterol. In contrast to T cells, where budding occurs at the cell surface and virions are released into the extracellular space, the budding process in monocytes and macrophages results in the accumulation of virions within cellular vacuoles.

The replication of retroviruses is prone to error and is characterized by a high spontaneous mutation rate. On average, reverse transcription results in 1-10 errors

per genome and per round of replication. Mutations can lead to the formation of replication-incompetent viral species. But, mutations causing drug resistance may also accumulate, which, provided that there is selection pressure under certain antiretroviral drugs and incomplete suppression of viral replication, may become dominant.

In addition, viral replication is dynamic and turns over quickly in infected individuals at an average rate of 10^9 new virus particles being produced and subsequently cleared per day. Thus, within any individual, because of the extensive virus replication and mutation rates, there exists an accumulation of many closely related virus variants within the 'population' of viruses, referred to as a viral "quasispecies". The selection pressure on mostly the pre-existing mutations may not only be exerted by certain drugs, but also by components of the immune system, such as neutralizing antibodies or cytotoxic T cells (CTL).

3. HIV and the immune system

3.1. The role of antigen-presenting cells

Dendritic cells as prototypes of antigen-presenting cells

Dendritic cells, macrophages and B cells represent the main antigen-presenting cells of the immune system. Dendritic cells (DC) are the most potent inducers of specific immune responses and are considered essential for the initiation of primary antigen-specific immune reactions. DC precursors migrate from the bone marrow towards the primary lymphatic organs and into the submucosal tissue of the gut, the genitourinary system and the respiratory tracts. They are able to pick up and process soluble antigens and migrate to the secondary lymphatic organs, where they activate antigen-specific T cells. Because DC have a crucial role in adaptive immunity, there is an increasing interest in using dendritic cell to induce or expand HIV-specific T-cells. DC from HIV-infected patients have been purified, incubated with inactivated, non-infectious HIV particles and subsequently used for vaccination (Lu 2004).

DC represent a heterogeneous family of cells with different functional capacities and expression of phenotypic markers, depending on the local microenvironment and the stage of maturation. Immature DC have the capacity to pick up and process foreign antigens, but do not have great T cell stimulatory capacities. However, mature DC show a predominant immunostimulatory ability. DC in tissues and Langerhans' cells, which are specialized DC in the skin and mucosal areas, represent a more immature phenotype and may take up antigen. Once these DC have taken up the antigen, they migrate to the lymphoid tissues where they develop a mature phenotype. Viruses may induce plasmacytoid DC to produce substantial amounts of IFN alpha with antiviral activity by stimulating Toll-like receptors (TLR) (Beignon 2005) therefore linking the innate to the adaptive immune system.

The stimulation of CD8 T-lymphocytes and the formation of antigen-specific cytotoxic T cells (CTL) depend on the presentation of a peptide together with MHC class I antigens. DC may become infected with viruses, for instance influenza. Viral

proteins are then produced within the cytoplasm of the cell, similar to cellular proteins, then degraded to viral peptides and translocated from the cytosol into the endoplasmic reticulum, where they are bound to MHC class I antigens. These peptide-MHC class I complexes migrate to the DC surface. Interestingly, efficacy of presentation of viral antigens is comparable regardless whether DC themselves or productively infected or not. An alternative way, where DC acquire exogenous antigens for MHC class I presentation from e.g. infected cells is termed cross-presentation and may be relevant for both classical and plamacytoid DC in HIV immunity (Rawson 2007, Hoeffel 2007).

The number of specific antigen-MHC class I complexes is usually limited and must eventually be recognized by rare T-cell clones, up to a ratio of 1:100.000 or less. The T-cell receptor (TCR) may display only a low binding affinity (1mM or less). The high density of co-stimulatory molecules on the DC surface, however, enhances the TCR-MHC: peptide interaction allowing efficient signaling to occur through the T-cell and resulting in proliferation (clonal expansion) of the T-cell. Virus-infected cells or tumor cells often do not express co-stimulatory molecules, and thus may not be able to induce a clonal expansion of effector cells. This underscores the importance of having a highly specialized system of antigen-presenting cells, i.e., DC, in operation to prime T-cells to expand and proliferate initially.

The interaction of dendritic cells and B/T-cells

B and T-lymphocytes may be regarded as the principle effector cells of antigen-specific immune responses. However, their function is under the control of dendritic cells. DC are able to pick up antigens in the periphery. These antigens are processed and expressed on the cell surface, together with co-stimulatory molecules that initiate T-cell activation. B-cells may recognize antigen after binding to the B-cell receptor. Recognition of antigen by T-cells requires previous processing and presentation of antigenic peptides by DC. T-cells express different T-cell receptors (TCR) that may bind to the peptide: MHC class I on the surface of dendritic cells to allow activation of CD8 T-cells, or to the peptide: MHC class II molecules, to activate CD4+ T-cells. The ability of DC to activate T-cells also depends on the secretion of stimulatory cytokines such as IL-12, which is a key cytokine for the generation and activation of T_H1 and natural killer (NK) cells.

Only a few DC and small amounts of antigen are sufficient to induce a potent antigen-specific T-cell response, thus demonstrating the immunostimulatory potency of DC. The expression of adhesion molecules and lectins, such as DC-SIGN, support the aggregation of DC and T-cells and promote the engagement of the T-cell receptor (TCR). DC-SIGN is a type C lectin that has also been shown to bind to lentiviruses, such as SIV and HIV-1 and -2 by interaction of gp120 with carbohydrates (Geijtenbeek 2000). Mycobacteria and Dengue virus may also bind to DC-SIGN. In vivo, immunohistochemical studies show expression of DC-SIGN on submucosal and intradermal DC, suggesting an implication of DC-SIGN in vertical and mucosal transmission of HIV. The expression of DC-SIGN was shown to enhance the transmission of HIV to T cells and allows utilization of coreceptors if their expression is limited. Thus DC-SIGN may be a mechanism whereby HIV-1 is taken up by DC in the mucosal tissues. It is then transported by the DC to the lymphoid tissues where HIV-1 can then infect all the residing CD4+ T-cells.

3.2. Lymphatic tissue as the site of viral replication

Viral replication within the lymphatic tissue is already extensive in the early stages of the disease (Embretson 2003, Pantaleo 1993). During the initial phase of HIV-1 infection, there is a burst of virus into the plasma, followed by a relative decline in viremia. During this time, a strong HIV-1 specific cytotoxic T-cell response is generated, which coincides with the early suppression of plasma viremia in most patients. Virions are trapped by the follicular dendritic cell (FDC) network within the lymphoid tissue. Macrophages, and activated and quiescent CD4+ T-cells are the main targets of infection. Permanent viral reservoirs, mainly in macrophages and latently infected CD4+ T-cells, are established in the early phase of infection and probably represent the major obstacle so far to successful eradication of HIV. During the whole course of infection with HIV-1, the lymphoid tissue represents the principle site of HIV-1 replication. The frequency of cells containing proviral DNA is 5-10x higher in lymphoid tissue than in circulating peripheral mononuclear cells in the blood, and the difference in viral replication in lymphoid tissue exceeds that in the peripheral blood by about 10-100x.

After entry of HIV-1 into a quiescent CD4+ T-cell and after completion of reverse transcription, the viral genome is represented by proviral unintegrated HIV DNA. In vitro experiments have shown that HIV-1 preferentially integrates into active genes ("hot spots") (Schroder 2002). The activation of CD4+ T-cells is necessary for the integration of the HIV DNA into the host cell genome and is therefore a prerequisite for the synthesis of new virions. In this regard, the micromilieu of the lymphoid tissue represents the optimal environment for viral replication. The close cell-cell contact between CD4+ T-cells and antigen-presenting cells, the presence of infectious virions on the surface of the FDC, and an abundant production of pro-inflammatory cytokines such as IL-1, IL-6 or TNFα promotes the induction of viral replication in infected cells and augments viral replication in cells already producing the virus. It should be noted that both IL-1 and TNFα induce NFκB, which binds to the HIV-1 LTR to promote proviral transcription. The importance of an antigen-induced activation of CD4+ T-cells is underlined by several in vivo and in vitro studies that demonstrate an increase in HIV-1 replication in association with a tetanus or influenza vaccination or an infection with Mycobacterium tuberculosis (O'Brian 1995). Even though the clinical benefit of vaccination against common pathogens (e.g. influenza and tetanus) in HIV-1-infected patients outweighs the potential risk of a temporary increase in viral load, these studies indicate that in every situation where the immune system is activated, enhanced viral replication can also occur.

Patients undergoing HAART demonstrate a dramatic decrease in the number of productively infected CD4+ T cells within the lymphoid tissue (Tenner-Racz 1998). However, in all patients examined so far, there persists a pool of latently infected quiescent T cells despite successful suppression of plasma viremia. It is these latently infected cells that may give rise to further rounds of viral replication, if the antiviral drugs are stopped. In addition, the long-term persistence of HIV-1 structural proteins and glycoproteins in germinal centers of lymph nodes in the absence of detectable virus replication in patients under HAART has been reported (Popovic 2005)

During the natural course of HIV-1 disease, the number of CD4+ T-cells slowly decreases while plasma viremia rises in most patients. If sequential analysis of the lymphoid tissue is performed, progression of the disease is reflected by destruction of the lymphoid tissue architecture and a decreased viral trapping. Various immunohistological studies indicate that the paracortex of the lymph nodes represents the primary site where HIV replication is initiated (Embretson 1993, Pantaleo 1993). Infection of the surrounding CD4+ T-cells, as well as the initiation of T-cell activation by DC, contributes to the spreading of HIV-1 within the lymphoid environment. Similar to SIV infection in rhesus macaques, HIV infection, at all stages of disease, is associated with preferential replication and CD4+ T-cell destruction in the gut lamina propria and submucosa than in lymph nodes (Brenchley 2004, Mehandru 2004). This is likely because the gut is predominantly populated by CCR5-expressing effector memory CD4+ T-cells, which are ideal targets for HIV replication compared to the mixed populations of CD4+ T-cells found within the lymph nodes. Several studies have demonstrated that, during acute infection, depletion of CD4+CCR5+ memory cells within the mucosa-associated lymphatic tissue is a hallmark of both HIV and SIV infection. In the early phase of SIV infection, up to 60 % of all CD4+ T-cells within the intestinal lamina propria were shown to express viral RNA. Most of these cells are destroyed by direct and indirect mechanisms within a few days. Further disease progression seems to depend largely on the capacity of the host to reconstitute the pool of memory cells within the mucosa-associated lymphoid tissue. In view of this data, some researchers argue that initiation of HAART during acute HIV infection is crucial in order to limit long-term damage to the immune system.

Chronic activation of the immune system is a hallmark of progressive HIV infection and predicts disease outcome. High-level immune activation and T cell apoptosis is absent from nonpathogenic SIV infections in natural primate hosts. Recently, it was reported that nef alleles from the great majority of primate lentiviruses, including HIV-2, downmodulate TCR-CD3 from infected T cells, thereby blocking their responsiveness to activation (Schindler 2006). In contrast, nef alleles from HIV-1 and a subset of closely related SIVs fail to downregulate TCR-CD3 and to inhibit cell death. Thus, Nef-mediated suppression of T cell activation is a fundamental property of primate lentiviruses that likely evolved to maintain viral persistence in the context of an intact host immune system. In addition, reaserch has shown that circulating microbial products, probably derived from the gastrointestinal tract, are a cause of HIV-related systemic immune activation (Brenchley 2006). The authors show that increased lipopolysaccharide is bioactive in vivo and correlates with measures of innate and adaptive immune activation. Effective antiretroviral therapy seemed to reduce microbial translocation partially. Furthermore, in nonpathogenic SIV infection of sooty mangabeys, microbial translocation did not seem to occur. These data establish a mechanism for chronic immune activation in the context of a compromised gastrointestinal mucosal surface and provide new directions for therapeutic interventions that modify the consequences of acute HIV infection.

Recent studies have also examined the effect of HIV infection on the thymus gland and its role in CD4+ T-cell depletion and homeostasis. Recent work has suggested that thymic output of CD4+ T-cells is decreased during HIV infection, particularly with older age, and that this defect is due to abnormalities of intra-thymic prolifera-

tion of T-cells, whose mechanism is still undefined, as thymocytes do not express CCR5 and should not necessarily be targets of HIV (Mehandru 2004, Douek 2001).

3.3. The HLA system and the immune response to HIV

CD8 T-cells recognize "their" antigen (peptide) in context with HLA class I molecules on antigen-presenting cells, whereas CD4+ T-cells require the presentation of antigenic peptides in context with HLA class II molecules. The generation of an HIV-specific immune response is therefore dependent on the individual HLA pattern.

Antigen-presenting cells may bind HIV peptides in different ways within "grooves" on the HLA class I molecules. Therefore, CD8 T-cells can be activated in an optimal or suboptimal way or may not be activated at all. Using large cohorts of HIV-1 infected patients, in whom the natural course of disease (fast versus slow progression) is known, HLA patterns were identified that were associated with a slow versus fast disease progression. These studies suggest that the HLA type could be responsible for the benign course of disease in about 40 % of patients with a long-term non-progressive course of disease. Homozygosity for HLA Bw4 is regarded as being protective. Patients who display heterozygosity at the HLA class I loci characteristically show a slower progression of immunodeficiency than patients with homozygosity at these loci (Carrington 1999). An initial study demonstrated that HLA B14, B27, B51, B57 and C8 are associated with a slow disease progression, however, the presence of HLA A23, B37 and B49 were associated with the rapid development of immunodeficiency (Kaslow 1996). All patients with HLA B35 had developed symptoms of AIDS after eight years of infection. More recent studies suggest that discordant couples with a "mismatch" at the HLA class I have a protective effect towards heterosexual transmission (Lockett 2001).

In vitro studies in HLA B57-positive patients demonstrate that these patients display HLA B57-restricted CTL directed against HIV-1 peptides. However, it is possible that the identification of protective HLA alleles or HLA-restricted peptides in HIV-1-infected patients with a benign course of disease does not necessarily indicate that the same alleles or peptides are crucial for the design of a protective vaccine. Kaul and co-workers were able to show that CD8+ T-cells from HIV-1-exposed but uninfected African women recognize different epitopes than CD8+ T-cells from HIV-1-infected African women (Kaul 2001). This suggests that the epitopes, that the immune system is directed against during a natural infection, might be different from those that are protective against infection. In addition, the individual HLA pattern may affect the adaptive immune response and the evolution of viral escape mutations (Friedrich 2004, Leslie 2004). CTL from patients with HLA B57 and B58 may "force" the virus to develop certain mutations in gag that enable the virus to escape the CTL response. However, these mutations result in a reduced replicative competence. If such a virus is transmitted to another individual with a different HLA background, the virus may "back" mutate to the original genotype and regain its full replicative competence. Similar MHC alleles as in monocygotic twins leat, at least during the early phase of the infection, to similar HIV-specific CTL-specificities (Draenert 2006).

HLA class II antigens are crucial for the development of an HIV-1-specific CD4+ T-cell response. Rosenberg (1997) was the first to show that HIV-1-infected pa-

tients with a long-term non-progressive course of disease had HIV-1-specific CD4+ T-cells that could proliferate against HIV-1 antigens. The identification of protective or unfavorable HLA class II alleles is less well elaborated than the knowledge about protective HLA class I alleles. Cohorts of vertically infected children and HIV-infected adults demonstrate a protective effect of HLA DR13 (Keet 1999).

KIR receptors ("Killer cell immunoglobulin like receptors") represent ligands that bind to HLA class I antigens and by functioning as either activating or inhibiting receptors they regulate the activation status of NK cells. Polymorphisms of KIR genes were shown to correlate with slow or rapid progression of HIV disease, especially when the analysis includes known HLA class I polymorphisms (Fauci 2005, Martin 2007) thereby indicating a relevant function of N cells in HIV immunity. During HIV infection, NK cells may not only be decreased, but may also show a diminished cytolytic activity. Preliminary results suggest that low numbers of NK cells are associated with a more rapid progression of disease.

In summary, various genetic polymorphisms have been identified that have an impact on the course of HIV disease. However, there is currently no rationale to recommend routine testing of individual patients or to base therapeutic decisions on genetic testing.

3.4. The HIV-specific cellular immune response

Cytotoxic T-cells (CTL) are able to recognize and eliminate virus-infected cells. A number of studies clearly demonstrate that CTL are crucial for the control of HIV replication and have a substantial impact on disease progression once infection is established. However, there is little evidence to assume that CTL play a major role in primary protection.

In comparison to HIV-1-infected patients with a rapid decline in CD4+ T-cell numbers, patients with a long-term non-progressive course of disease ("LTNP" = long-term non-progressors) have high quantities of HIV-1-specific CTL precursors with a broad specificity towards various HIV-1 proteins. The different capacities of certain HLA alleles to present viral particles more or less efficiently and to induce a generally potent immune response may explain why certain HLA alleles are associated with a more rapid or a slowly progressive course of disease (see above).

Individuals have been described, who developed CTL "escape" mutants after years of stable disease and the presence of a strong CTL response. The evolution of CTL escape mutants was associated with a rapid decline in CD4+ T-cells in these patients, indicating the protective role of CTL (Goulder 1997).

HIV-specific CTL responses have been detected in individuals exposed to, but not infected by HIV-1. Nef-specific CTL have been identified in HIV-1-negative heterosexual partners of HIV-infected patients and env-specific CTL have been found in seronegative healthcare workers after exposure to HIV-1-containing material by needle stick injuries (Pinto 1995). Unfortunately patients with a broad and strong CTL response do not seem to be protected from superinfection by a different, but closely related HIV isolate (Altfeld 2002).

The presence of a CTL response is not correlated just with the suppression of plasma viremia during the initial phase of HIV infection. Patients who underwent structured therapy interruptions, especially when HAART was initiated early fol-

lowing infection, demonstrated the appearance of HIV-specific CTL during the pauses.

However, it is still unclear in most patients who exhibit a potent temporary CTL response, why this CTL response diminishes later on. The appearance of viral "escape" mutants might explain why previously recognized epitopes are no longer immunodominant.

The *nef* protein may downregulate HLA class I antigens and therefore counteract the recognition of infected cells by CTL. In addition, the majority of infected individuals show detectable CTL responses. It is unclear why they are unable to control the virus. Interestingly, CTL from HIV-infected patients shows a lack of perforin and an immature phenotype in comparison to anti-CMV-directed effector cells (Harari 2002), even though the ability to secrete chemokines and cytokines is not impaired. Another recent study provided evidence that the killing capacity of HIV-specific CTL was associated with the ability to simultaneously produce interferon-γ and TNFα (Lichtenfeld 2004). Finally, it has been shown that HIV-infection is associated with upregulated or maintained high expression of PD-1 on CD4 and CD8 T cells and CTLA-4 on CD4 T cells specific for HIV. Both receptors lead to reversible T cell dysfunction with reduced proliferative capacity and cytokine production (Kaufmann 2007, Trautmann 2006).

CD8+ T-cells may also become infected with HIV (Saha 2001), although this was not demonstrated for HIV-specific CD8 T-cells. It is unclear, whether CD8 T-cells temporarily express CD4 and which chemokine coreceptors mediate infection of these CD8+ T-cells.

Proliferation and activation of CTL is dependent on antigen-specific T cell help. Rosenberg and his group were able to demonstrate that initiation of HAART during primary HIV infection was associated with persistence of an HIV-specific CD4+ T-cell response that was not detected in patients analyzed during the chronic stage of disease (Rosenberg 1997). HIV preferentially infects pre-activated CD4+ T-cells and as HIV-specific CD4+ T-cells are among the first cells to be activated during HIV infection, their preferential infection was demonstrated by Douek and his group (Douek 2002). Therefore, it is currently unclear whether the loss of HIV-specific CTL activity during the course of disease reflects an instrinsic defect of CTL or develops secondary to a loss of specific CD4+ T-cell help.

Various therapeutic vaccine strategies have been developed during the last few years and mostly tested in SIV-infected rhesus macaques aiming at inducing an SIV-specific CTL response that may alter the natural course of disease. Recently, a promising vaccine approach was reported using autologous dendritic cells in SIV-infected rhesus macaques that were pulsed with inactivated SIV (Lu 2003). In contrast to the unvaccinated control group, monkeys that were vaccinated showed a dramatic decrease in the viral load, and the development of anti-SIV-directed humoral and cellular immune responses. Similar strategies in HIV-infected individuals lead to significant reduction of viral load paralleled by detection of gag-specific CD8+ T-cells and HIV-specific CD4+ T-cells producing IFNγ and/or interleukin-2 (Lu 2004).

In addition to the cytotoxic activities directed against HIV-infected cells, CD8+ T-cells from HIV-1 infected patients exhibit a remarkable, soluble HIV-1 inhibitory activity that inhibits HIV-1 replication in autologous and allogeneic cell cultures

(Walker 1996). Despite multiple efforts, the identity of this inhibitory activity ("CAF") has not been clarified, although chemokines, such as MIP-1α, MIP-1ß or RANTES (Cocchi 1995), IL-16 (Baier 1995), the chemokine MDC (Pal 1997), and defensins (Zhang 2002), may account for at least some of the inhibition.

3.5. The T_H1/T_H2 immune response

Depending on the secretion pattern of cytokines, CD4+ T-cells may be differentiated into T_H1 and T_H2 cells. T_H1 CD4+ T-cells primarily produce interleukin-2 (IL-2) and IFNγ, which represent the cytokines that support the effector functions of the immune system (CTL, NK-cells, macrophages). T_H2 cells predominantly produce IL-4, IL-10, IL-5 and IL-6, which represent the cytokines that favor the development of a humoral immune response. Since T_H1 cytokines are critical for the generation of CTLs, an HIV-1-specific T_H1 response is regarded as being a protective immune response. Studies on HIV-exposed but non-infected individuals have shown, that following in vitro stimulation with HIV-1 env antigens (gp120/gp160) and peptides, T-cells from these individuals secrete IL-2 in contrast to non-exposed control persons (Clerici 1991). Similar studies were undertaken in healthcare workers after needle-stick injuries and in newborns from HIV-infected mothers. Although these observations may indicate that a T_H1-type immune response is potentially protective, it should be considered, that similar immune responses might also have been generated after contact with non-infectious viral particles and therefore do not necessarily imply a means of protection against a replication-competent virus.

3.6. HIV-1 specific humoral immune responses

The association between an HIV-1-specific humoral immune response and the course of disease is less well characterized.

In a SIV model, injection of an antibody cocktail consisting of various neutralizing antibodies is able to prevent SIV infection after a mucosal virus challenge (Ferrantelli 2004), indicating that primary protection is mainly dependent on a broad humoral immune response. This data suggests that HIV-specific antibodies are necessary for a preventive vaccine strategy. In contrast, B-cell depletion by a monoclonal antibody directed against B-cells in monkeys with already established SIV infection, does not affect the course of plasma viremia (Schmitz 2003).

A slow progression of immunodeficiency was observed in patients with high titers of anti-p24 antibodies (Hogervorst 1995), persistence of neutralizing antibodies against primary and autologous viruses (Montefiori 1996), and lack of antibodies against certain gp120 epitopes (Wong 1993).

Long-term non-progressors with HIV tend to have a broad neutralizing activity towards a range of primary isolates and show persistence of neutralizing antibodies against autologous virus. At present, it is unclear whether the presence of neutralizing antibodies in LTNP represents part of the protection or whether it merely reflects the integrity of a relatively intact immune system. Individuals that have a substantial risk for HIV-1 infection, but are considered "exposed, non-infected", by definition represent individuals with a lack of a detectable antibody response to HIV-1. This definition implies that a systemic humoral immune response may not

represent a crucial protective mechanism. It has been shown that these individuals may demonstrate a local (mucosal) IgA response against HIV-1 proteins that are not detected by the usual antibody testing methods (Saha 2001). Thus, local IgA, rather than systemic IgG, may be associated with protection against HIV-1 infection. There is also some evidence that some anti-HIV-1 antibodies can enhance the infection of CD4+ T-cells.

A number of old and recent studies have shown that neutralizing antibodies do exist in HIV-1-infected individuals, however, there is a time lag in their appearance. That is, individuals will develop neutralizing antibodies to their own viruses with time, however, by the time these antibodies develop, the new viruses circulating in the individual's plasma will become resistant to neutralization, even though the older ones are now sensitive to the current antibodies in the patient's serum. Thus, the antibody response appears to be hitting a 'moving' target, allowing viruses to escape continuously. Further knowledge gained on understanding the mechanisms of humoral escape will likely lead to potential new therapies.

A few years ago, selected patients with advanced HIV infection were treated with plasma from HIV-infected patients at an earlier stage of the disease. No significant effect on the course of disease was notable (Jacobson 1998). The therapeutic application of neutralizing antibodies with defined specificity looked more promising, since a few acute and chronically infected patients were able to control their viral load at least temporarily after stopping antiretroviral therapy (Trkola 2005).

3.7. A vaccine against HIV ?

Improved knowledge and understanding of the pathophysiological mechanisms during the course of HIV-1 infection have not only contributed to the development of antiretroviral treatment strategies, but have given rise to new therapeutic approaches, such as cytokine therapies, e.g., IL-2 and therapeutic vaccination. However, the most important challenge and thus, the demand for a better understanding of the immunopathogenesis of HIV-1 infection, remains the development of a protective vaccine, which is urgently needed to interrupt the epidemic especially in countries of the Sub-Sahara and Southeast Asia.

The documentation of exposed but uninfected individuals and findings in LTNP suggests that, besides a genetic predisposition, HIV-specific protective immune mechanisms could potentially confer protective and possibly even preventive immunity. Results from animal studies suggest that immune protection might be generated when the immune system is stimulated in the appropriate way. The induction of an HIV-specific CD8 response in non-human primates is able to ameliorate the course of disease. On the other hand, in vivo depletion of CD8+ T-cells in non-human primates by monoclonal antibodies will lead to an increase in viral load. Immunogens that induce neutralizing antibodies in non-human primates will prevent infection with the homologous viral strain. Transfer of neutralizing antibodies to uninfected primates or human SCID mice is able to prevent infection with the homologous HIV strain.

The spectrum of vaccine strategies against HIV includes HIV-derived peptides or proteins, the use of viral or bacterial vectors, naked DNA, pseudovirions or the use of live attenuated HIV strains. The discussion about whether a vaccine should primarily aim at inducing a humoral or a cellular based protective immune response

has now resulted in the belief that both humoral and cellular mechanisms contribute to protection.

Many neutralizing antibodies either do not or only poorly show inhibition of primary viral isolates. A major problem lies in the high variability of the gp120 glycoprotein itself. Furthermore, gp120 epitopes may be highly glycosylated and certain structural domains are hidden, at least temporarily, so that immunodominant epitopes may not be recognized (Chen 2005, Derdeyn 2005). In addition, there is no evidence that a cytotoxic T-cell response can prevent an uninfected individual from exogenous HIV infection. A report from Altfeld (2002) is interesting in this regard. It concerns an HIV-infected patient who was started on HAART during primary infection. The patient developed a robust anti-HIV CD8+ T-cell response that was closely monitored and documented by in vitro experiments. In spite of the strong CTL response, superinfection with a second HIV strain occurred, despite cross-reactive CTL epitopes.

The discussion about how to best monitor the induction of protective immune responses remains controversial. Does a CTL response as measured by its cytolytic activity or by cytokine production the in vitro correlate of protection? How are *in vitro* tests linked to *in vivo* protection? Despite all efforts undertaken so far, the way to an effective and universally applicable preventive vaccine still seems to be a long one.

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Part 2

HAART

5. ART 2007

1. History

Christian Hoffmann and Fiona Mulcahy

There isn't any field of medicine that has been through such dramatic developments as that of antiretroviral therapy. Few other areas have been subject to such fast- and short-lived trends. Those who have experienced the rapid developments of the last few years have been through many ups and downs.

Following the hope of the early years, from 1987-1990, and the modest successes with monotherapy (Volberding 1990, Fischl 1990), the results of the Concorde Study (Concorde 1994) plunged both patients and clinicians into a depression that was to last for several years. AZT, introduced in March 1987 with great expectations, did not seem to provide durable efficacy – at least as a monotherapy and on early application. The same was true for the nucleoside analogs ddC, ddI, and d4T, introduced between 1991 and 1994. The lack of treatment options led to a debate that lasted for several years about which nucleoside analogs should be used, when, and at what dose. One such question was: "Should the alarm clock be set to go off during the night for the fifth dose of AZT?"

Many patients, who were infected up until the mid-80s, began to die. Hospices were established, as well as more and more support groups and ambulatory nursing services. One became accustomed to AIDS and its resulting death toll. There was, however, definite progress in the field of opportunistic infections – cotrimoxazole, pentamidine, gancyclovir, foscarnet, and fluconazole saved many patients' lives, at least in the short-term. Some clinicians dreamed of a kind of "mega-prophylaxis", but the picture was still tainted by an overall lack of hope. Many remember the somber, almost depressed mood of the IXth World AIDS Conference in Berlin, in June 1993. Between 1989 and 1994, the mortality rates hardly changed.

Then, in September 1995, the results of the European-Australian DELTA Study (Delta 1996) and the American ACTG 175 Study (Hammer 1996) attracted attention. It became apparent that two nucleoside analogs were more effective than monotherapy. Indeed, the differences made on the clinical endpoints - AIDS and death - were highly significant. Both studies demonstrated that it was potentially of great importance of starting treatment immediately with two nucleoside analogs, as opposed to using the drugs successively.

This was by no means the final breakthrough, but by this time, the first studies with protease inhibitors (PIs), a completely new drug class, had been running for months. PIs had been designed using the knowledge of the molecular structure of HIV and protease – their clinical value was uncertain. Preliminary data, combined with rumours, were already circulating. Patients and clinicians were waiting impatiently. In the fall of 1995, a fierce competition started up between Abbott, Roche and MSD. The licensing studies for the PIs, ritonavir, saquinavir and indinavir, were pursued with a great vigour. The monitors of these studies in the different companies "lived" for weeks in the clinical centers. Deep into the night, case report files had to be perfected and thousands of queries answered. All these efforts led to

a fast track approval, between December 1995 and March 1996, for all three PIs – first saquinavir, followed by ritonavir and indinavir – for the treatment of HIV.

Many clinicians (including the author) were not really aware of what was happening during these months. AIDS remained ever present. Patients were still dying, as only a relatively small number were participating in the PI trials – and few were adequately treated according to current standards. Doubts remained. Hopes had been raised too many times before by alleged miracle cures. In January 1996, at the 5th Munich AIDS Conference, other topics were more important: palliative medicine, treatment of CMV, wasting, and pain management; euthanasia was even a theme. The few contributions here and there on "new beginnings" produced no more than restrained optimism.

In February 1996, during the 3rd Conference on Retroviruses and Opportunistic Infections (CROI) in Washington, many caught their breath as Bill Cameron reported the first data from the ABT-247 Study during the late breaker session. The auditorium was absolutely silent. Electrified, listeners learned that the mere addition of ritonavir oral solution decreases the frequency of death and AIDS from 38 % to 22 % (Cameron 1998). These were sensational results in comparison to everything else that had been previously published!

Although some severely ill patients with AIDS managed to recover during these months, for many the combinations that were now – at the beginning of 1996 - widely used, came too late. Then in June 1996, the World AIDS Conference in Vancouver reported on the new "AIDS cocktails" and the strangely unscientific (and rather ridiculous) expression "highly active antiretroviral therapy" (HAART) began to spread irreversibly. Clinicians were only too happy to become infected by this enthusiasm.

Meanwhile, David Ho, Time magazine's "Man of the Year" in 1996, had clarified the hitherto completely misunderstood kinetics of HIV with his breakthrough trials (Ho 1995, Perelson 1996). A year earlier, Ho had already initiated the slogan "hit hard and early", and almost everyone was now taking him by his word. With the knowledge of the high turnover of the virus and the relentless daily destruction of CD4 cells, there was no consideration of a "latent phase" – and no life without antiretroviral therapy. In many centers, almost every patient was treated. Within three years, from 1994-1997, the proportion of untreated patients in Europe decreased from 37 % to 9 %, whilst the proportion of HAART patients rose from 2 % to 64 % (Kirk 1998).

A third drug class was introduced in June 1996, with the licensing of the first non-nucleoside reverse transcriptase inhibitor (NNRTI), nevirapine. Nelfinavir, a new PI, also arrived. Most patients seemed to tolerate the pills well. 30 pills a day? No problem, if it helps. And how it helped! The number of AIDS cases diminished. Within four years, between 1994 and 1998, the incidence of AIDS in Europe sank from 30.7 to 2.5/100 patient years – i.e. to less than a tenth. Opportunistic infections (OI) such as CMV and MAC became almost rare (Mocroft 2000). HIV ophthalmologists had to look for new areas of work. The OI trials, planned only a few months before, faltered due to a lack of patients. Hospices, which had been receiving substantial donations, had to shut down or reorientate themselves. Patients left hospices, nursing services shut down; and AIDS wards became occupied by other patients.

In 1997, some patients began to complain of a fat stomach, but was this not a good sign after the years of wasting and supplementary nutrition? Not only did the PIs contain lactose and gelatin, but also the lower viremia was thought to use up far less energy. It was assumed that, because patients were less depressed they would eat more. At most, it was slightly disturbing that the patients retained thin faces. However, more and more patients began to complain about the high pill burden.

In June 1997, the FDA published a warning about the development of diabetes mellitus associated with the use of PIs. At the CROI in February 1998, a number of posters showed pictures of buffalo humps, thin legs faces. A new term was introduced, which would influence antiretroviral therapy: lipodystrophy. The old medical wisdom was also shown to hold true for HAART: all effective drugs have side effects. The actual cause remained unclear. Then, in early 1999, a new hypothesis emerged from the Netherlands: "mitochondrial toxicity" (Brinkman 1999). It has become a ubiquitous term in HIV medicine today, occupying a whole chapter of this book. A chapter on lipodystrophy is long overdue.

The dream of eradication (and a cure), still widely hoped for in the beginning, eventually had to be abandoned In 1997, mathematical models were still based on viral suppression of approximately three years. After this period, it was predicted that all infected cells would presumably have died. Eradication was a magic word. At every conference since then, the period of three years has been adjusted upwards. Nature is not so easy to predict, and more recent studies have come to the sobering conclusion that HIV remains detectable in latent infected cells, even after long-term suppression. Nobody knows how long these latent infected cells survive, and whether even a small number of them would be sufficient for the infection to flare up again as soon as treatment is interrupted. Finally, during the Barcelona World AIDS Conference, experts in the field admitted to bleak prospects for eradication. The most recent estimate for eradication of these cells stands at 73.3 years (Siciliano 2003). Such number games say one thing: HIV will not be curable in the short term. The latent reservoirs will not simply let themselves be wiped out. On the other hand, if the subject of cure is not spoken about, it will never be reached.

Although it still seemed utopian ten years ago, it is now realistic to expect to control HIV for the longer term. This results in huge challenges for patients and clinicians. The industry needs to develop improved pill combinations.Fortunately, once-daily regimens are already available, and a complete HAART regimen in a single pill is imminent. CCR5 antagonists and integrase inhibitors are being developed. They may even partially replace the current antiretroviral therapy. In June 2006, HIVID™ was withdrawn from the market – a novelty for HIV medicine. Other long-serving substances will follow. In ten years time, antiretroviral treatment will be completely different.

With increasing knowledge of the risks of antiretroviral therapy many treatment recommendations are revised. Instead of "hit hard and early", today we hear "hit HIV hard, but only when necessary" (Harrington 2000). The question of "when to start?" is still the subject of major debate.

HIV clinicians are well advised to keep an open mind for new approaches. Those, who do not make a constant effort to broaden their knowledge, will be treating their patients inadequately within a short period of time. Those who adhere strictly to evidence-based HIV medicine, quickly become outdated. HIV medicine is ever

changing. Treatment guidelines remain just guidelines. They are often out of date by the time of publication. There are no laws set in stone.

HIV remains a dangerous and cunning opponent. Patients and clinicians must tackle it together. The following describes how this can be done.

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2. Overview of antiretroviral agents

Christian Hoffmann and Fiona Mulcahy

Table 2.1: Antiretroviral agents

Trade name	Abbrev.	Drug	Manufacturer
Nucleoside and Nucleotide Reverse Transcriptase Inhibitors (NRTIs)			
Combivir™	CBV	AZT+3TC	GSK
Emtriva™	FTC	Emtricitabine	Gilead
Epivir™	3TC	Lamivudine	GSK
HIVID™*	ddC	Zalcitabine	Roche
Kivexa/Epzicom™	KVX	3TC+ABC	GSK
Retrovir™	AZT	Zidovudine	GSK
Trizivir™	TZV	AZT+3TC+ABC	GSK
Truvada™	TVD	FTC+TDF	Gilead
Videx™	ddI	Didanosine	BMS
Viread™	TDF	Tenofovir	Gilead
Zerit™	d4T	Stavudine	BMS
Ziagen™	ABC	Abacavir	GSK
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)			
Rescriptor™	DLV	Delavirdine	Pfizer
Sustiva/Stocrin™	EFV	Efavirenz	BMS/MSD
Viramune™	NVP	Nevirapine	Boehringer Ingelheim
Protease Inhibitors (PIs)			
Aptivus™	TPV	Tipranavir	Boehringer-Ingelheim
Agenerase™	APV	Amprenavir	GSK
Crixivan™	IDV	Indinavir	MSD
Invirase 500™	SQV	Saquinavir	Roche
Kaletra™	LPV	Lopinavir/ritonavir	Abbott
Norvir™	RTV	Ritonavir	Abbott
Reyataz™	ATV	Atazanavir	BMS
Telzir/Lexiva™	FPV	Fosamprenavir	GSK
Viracept™	NFV	Nelfinavir	Roche/Pfizer
Fusion inhibitors			
Fuzeon	T-20	Enfuvirtide	Roche
Entry inhibitors			
Celsentri/Selzentry™	MVC	Maraviroc	Pfizer

*Distribution ceased

Currently, 25 single or combination preparations from four classes of drugs are licensed: nucleoside and nucleotide analogs (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs) and fusion inhibitors. Further drugs and new classes of drugs can be expected in the next few years.

The following chapter provides an overview of the individual agents and their specific features and problems. Common combinations are described in the chapter on "Which HAART to Start With".

Nucleoside analogs (NRTIs)

Mechanism of action

Nucleoside analogs ("nukes") are also referred to as nucleoside reverse transcriptase inhibitors. Their target is the HIV enzyme reverse transcriptase. Acting as alternative substrates or "false building bricks", they compete with physiological nucleosides, differing from them only by a minor modification in the ribose molecule. The incorporation of nucleoside analogs induces the abortion of DNA synthesis, as phosphodiester bridges can no longer be built to stabilize the double strand.

Nucleoside analogs are "prodrugs", which means that they are absorbed unchanged and only activated when three phosphates are attached by intracellular phosphorylation in a stepwise process. It is the triphosphate derivative that is efficacious. AZT and d4T are thymidine analogs, while FTC and 3TC are cytidine analogs. Combinations containing AZT + d4T or FTC + 3TC are therefore pointless, since both drugs compete for the same bases (Havlir 2002). ddI is an inosine analog, which is converted to dideoxyadenosine; abacavir is a guanosine analog. There is a high degree of cross-resistance between nucleoside analogs (see also "Resistance").

Nucleoside analogs were the first drugs to be used in HIV treatment, and therefore, most of the experience is based on them. They are easy to take, and once-daily dosing is sufficient for most. Overall initial tolerability is fairly good. However, frequent complaints during the first weeks are fatigue, headache and gastrointestinal problems, which range from mild abdominal discomfort to nausea, vomiting and diarrhea. The gastrointestinal complaints are easily treated symptomatically (see "Side Effects").

However, nucleoside analogs can cause a wide variety of long-term side effects, including myelotoxicity, lactate acidosis, polyneuropathy and pancreatitis. Although lipodystrophy was initially linked exclusively to treatment with PIs, many metabolic disorders, and especially lipoatrophy, are now also attributed to nucleoside analogs (Galli 2002). They are probably related to mitochondrial toxicity, which was first described in 1999 (Brinkmann 1999). Mitochondrial function requires nucleosides. The metabolism of these important organelles is disrupted by the incorporation of false nucleosides, leading to mitochondrial degeneration. There are probably considerable differences between the individual drugs with regard to mitochondrial toxicity (for further details see "Mitochondrial toxicity").

Nucleoside analogs are eliminated mainly by renal excretion and do not interact with drugs that are metabolized by hepatic enzymes. There is therefore little potential for interaction. However, ribavirin, for example, can also reduce intracellular phosphorylation of AZT or d4T (Piscitelli 2001). In contrast to the PIs and NNRTIs, the doses have to be adjusted for patients with renal insufficiency.

Individual agents

Abacavir (Ziagen™) is a guanosine analog, which can lower viral load by approximately 1.4 logs within 4 weeks (Harrigan 2000). Abacavir is phosphorylated intracellularly to carbovir triphosphate, which has a long half-life (Harris 2002). In

October 2004, following larger studies, abacavir was licensed for once-daily therapy (Moyle 2005, Sosa 2005). It is also a component of Trizivir™ and Kivexa™.

In combination with AZT+3TC (Trizivir™, see also Triple Nuke), abacavir was less effective than efavirenz (Gulick 2004). The randomized, double blind CNA3005 Study also showed lower efficacy in comparison to indinavir, particularly with higher viral load (Staszewski 2001). In contrast, efficacy was comparable to that of nelfinavir (Matheron 2003). When combined with 3TC, the efficacy is similar to that of 3TC plus either AZT (DeJesus 2004) or d4T (Podzamczer 2006).

A regimen that is failing virologically can be successfully intensified with abacavir if it is added early enough, and if the viral load is not too high (Katlama 2000, Rozenbaum 2001). Abacavir is also used to simplify HAART. Numerous randomized studies have demonstrated that patients on a successful PI- or NNRTI-regimen can switch relatively safely to abacavir plus two NRTIs (Clumeck 2001, Katlama 2003, Martinez 2003, Bonjoch 2005). However, there is a certain degree of risk associated with this, and particularly in extensively pretreated patients, virological failure is possible (Opravil 2002, Martinez 2003). Caution therefore must be taken when combining tenofovir with 3TC as resistance mutations can rapidly develop (see section on "Triple Nuke").

With respect to mitochondrial toxicity, abacavir is more favorable than several other substances. In comparison to d4T, the lipoatrophy risk is low (Podczamcer 2006). Lipoatrophy improves on changing from d4T to abacavir (Carr 2002, John 2003, Moyle 2003, McComsey 2004). This also applies to an increase in mitochondrial DNA (Hoy 2004, Martin 2004, McComsey 2005).

One drawback to the use of abacavir is the risk of a hypersensitivity reaction (HSR), an allergic reaction that is associated with fever and lethargy (see chapter on Side Effects). This occurs in 4-6 % of patients, almost always within the first six weeks of treatment. In acutely infected patients, the risk seems to be higher (up to 18 %), and abacavir should be avoided (Stekler 2006). On re-exposure, HSR can even be fatal. Severe HSR can occur after only a single abacavir tablet (De la Rosa 2004) or even after treatment interruption despite prior tolerability (El-Sahly 2004). The combination of strongly worded warnings contained in the package insert and the unspecific symptoms of HSR poses a constant challenge to the physician. A genetic predisposition exists, so that patients with HLA type B5701 are at a higher risk than others - with HSR occurring in up to 80 % of them (Mallal 2002, Hetherington 2002). However, HSR is also possible in the absence of this HLA type. Data from the PREDICT study, in which the predictive value of the HLA type was prospectively investigated in approximately 2,000 patients, is being eagerly awaited. In the future, it may be possible to assess HLA type before administration of abacavir, a strategy already practiced in some countries.

AZT (Zidovudine, Retrovir™) was the first antiretroviral agent to be put on the market, in 1987. An initial study on AZT monotherapy showed a survival benefit – at least in significantly immunocompromised patients (Fischl 1987). In contrast, two other early, very large studies, ACTG 016 and 019, demonstrated no significant survival benefit in asymptomatic patients, although the risk for progression was significantly reduced in both (Fischl 1990, Volberding 1990). Even at that time, it started to become apparent that the success of AZT monotherapy was likely to be limited. The Concorde Study has even brought AZT from time to time into disre-

pute: it showed that there was no long-term benefit of AZT treatment. In addition, the higher doses that were given in these first few years led to considerable myelotoxicity (Fischl 1990a), something which should also not be underestimated for the standard current doses – check the blood count! Long-term treatment almost always increases MCV (mean corpuscular volume of erythrocytes), which is useful as a means of assessing adherence. Gastrointestinal complaints, especially initially, may present a further problem. In contrast, AZT-related myopathy or even cardiomyopathy is quite rare. A "logical" disadvantage of AZT is that it has to be taken twice daily, disqualifying it as a substance for once-daily combinations. Furthermore, AZT finally came under pressure when, in the 934 study, it scored significantly worse than tenofovir, mainly due to poorer tolerability. Severe anemia was significantly increased in the AZT-arm in comparison to tenofovir, causing 5.5 % of cases to drop out (Gallant 2006).

Lack of neurotoxicity and good CNS penetration are some of the advantages of this drug. Therefore, AZT still remains a component of many regimens and transmission prophylaxes. AZT is also a component of both Combivir™ and Trizivir™, at a slightly higher dose (300 instead of 250 mg), which may occasionally lead to higher myelotoxicity. It is noteworthy that the US-patent protection of AZT expired in 2005, so that AZT could soon become much cheaper.

ddC - Zalcitabine (HIVID™) was, in 1992, the third NRTI to reach the market. The weak efficacy as well as problems with the pharmacokinetics and side effects resulted in ddC being taken from the market in 2006 - a first for HIV medicine.

ddI – (Didanosine, Videx™) in 1991, was the second nucleoside analog to be licensed. The introduction of acid-resistant tablets, which, in 2000, replaced the chewable tablets, improved tolerability and patient acceptance significantly. Early studies showed a survival advantage for treatment-naïve patients with AZT+ddI compared to AZT monotherapy. This effect of ddI was less marked in AZT-pretreated patients. Therefore, the addition of ddI in the Delta 2 study led to significant survival benefit, although this was not the case in CPCRA007 (Saravolatz 1996). In ACTG 175, monotherapy with ddI was more potent than AZT, even with regard to disease progression (Hammer 1996). However, this predominance was not confirmed in other studies (Dolin 1995, Floridia 1997). Following failure of AZT, ddI is much more effective than d4T (Havlir 2000).

In more recent studies, ddI is only used seldomly. Gastrointestinal complaints and polyneuropathy are the main side effects. Pancreatitis is more specific, occurring in up to 10 %, and can be fatal in individual cases. This toxicity is probably dose-dependent (Jablonowski 1995). This is possibly related to disorders of purine metabolism (Moyle 2004). Special caution should be given to combinations with ribavirin, hydroxyurea or tenofovir (Havlir 2001, Martinez 2004). Concomitant administration of these drugs should be avoided. Even the combination with d4T, is no longer recommended, especially in primary therapy (see especially the chapter on "Problematic primary therapy"). Patients with a history of pancreatitis should not be treated with ddI. If the body weight is less than 60 kg, the dose should be reduced from 400 mg to 250 mg. ddI has to be administered on an empty stomach. In view of its toxicity ddI has become less popular but is useful in certain resistance situations (Molina 2005).

d4T (Stavudine, Zerit™) was the second thymidine analog to be introduced after AZT. Subjectively, d4T is often initially tolerated better than AZT (less gastrointestinal side effects and limited myelotoxicity), is certainly just as effective (Spruance 1997, Squires 2000), and used to be one of the most frequently prescribed HIV drugs. However, several studies have since placed it under a lot of pressure. In the Gilead 903 Study, d4T was tested in a double blind design against tenofovir in treatment-naïve patients. Both drugs showed comparable efficacy, but d4T had considerable mitochondrial toxicity (Gallant 2004). In fact, the FTC-301 Study, in which d4T was tested in a double blind design against FTC had to be prematurely terminated, because d4T was not only more toxic, but also weaker (Saag 2004).

It is now beyond doubt that long-term toxicity occurs more frequently with d4T than with other NRTIs. The data is depressing: not only from the laboratory (Martin 2004, McComsey 2005), but also from clinical observations. d4T is a risk factor for lactic acidosis, hyperlactacidemia and Guillain-Barré-like syndromes (Mokrzycki 2000, John 2001, Shah 2003). In cohort studies, the risk of lipoatrophy on d4T doubled in one year (Mauss 2002); it tripled in two years (Bernasconi 2002). Other studies point in the same direction (Mallal 2000, Chene 2002, Mallon 2003, Podcamzer 2006). Furthermore, numerous studies have now been published in which substitution of d4T with other NRTIs, particularly abacavir or tenofovir, had positive effects on lipoatrophy and other metabolic disorders (Carr 2002, John 2003, Moyle 2003, Martin 2004, McComsey 2004, Libre 2006).

Based on current data, d4T should be avoided wherever possible and replaced, ideally with abacavir or tenofovir if the resistance profile permits (Moyle 2006).

In the so-called developing countries, the situation is different, and it remains an important combination partner, particularly due to the lack of myelotoxicity.

3TC (Lamivudine, Epivir™) was, in August 1996, the fifth NRTI to be licensed in Europe. It is a well-tolerated cytidine analog, whose substantial disadvantage is rapid development of resistance. A single point mutation (M184V) is sufficient to cause loss of efficacy. On monotherapy, this mutation is likely to lead to resistance after only a few weeks (Eron 1995). The full effect of 3TC only emerges in combination with other NRTIs. As a component of Combivir™, Kivexa™ and Trizivir™, 3TC is actually one of the most frequently used antiretroviral agents of all. In studies such as NUCB 3002 or CAESAR, 3TC significantly improved disease progression and survival when added to NRTI therapy (Staszewski 1997). However, the M184V point mutation can increase susceptibility of certain AZT-resistant viruses and also impair viral fitness (Miller 2002). The continuation of 3TC-monotherapy in treatment-experienced patients with the M184V mutation was associated with a smaller increase in the viral load and drop in CD4 cell count than the complete interruption of HAART (see also “Salvage Therapy”). Keeping 3TC as part of the therapy despite proven resistance is therefore sensible to conserve the M184V mutation and thus reduce the replicative capacity of HIV.

In the Atlantic Study, 3TC in combination with d4T+ddI proved weaker virologically than indinavir or nevirapine (Van Leeuwen 2003). Combination with abacavir and tenofovir is now not recommended as a triple nucleoside regimen (see the section “Triple Nuke”). The antiviral potency is approximately comparable to that of the “main competitor” FTC (Rousseau 2003, Benson 2004).

Although the half-life is not as long as for FTC, 3TC is also licensed for once-daily dosing (DeJesus 2004). An important effect of 3TC is also its relatively good efficacy against hepatitis B viruses, although this is again limited by the relatively rapid development of resistance.

FTC (Emtricitabine, Emtriva™) is a cytidine analog, which is biochemically very similar to 3TC, but has a longer half-life. Once-daily dosing is possible. Like 3TC, it has HBV efficacy, tolerability is good, and it has a narrow interaction potential (Framptom 2005). FTC seems to have a low affinity for the mitochondrial polymerase, so the risk of mitochondrial toxicity is likely to be relatively low. In monotherapy studies as well as in combination with AZT, FTC was at least as effective as 3TC (Rousseau 2003, Benson 2004). However, as with 3TC, efficacy is limited by the M184V point mutation.

Subsequent to data from the FTC-301 Study (Saag 2004), the drug was licensed in 2003. This randomized, double blind trial showed that FTC was clearly more effective and tolerable than d4T (Gallant 2006), although this was probably not due to differences between FTC and 3TC. The ALIZE study demonstrated the good long-term tolerability and efficacy of a once-daily combination of FTC+ddI+efavirenz (Molina 2005).

Today, FTC is an important combination partner in HAART, particularly in the fixed-dose combination with tenofovir (Truvada™). In contrast, FTC alone only has a minor role to play.

TDF (Tenofovir, Viread™) acts as a false building block similar to nucleoside analogs, targeting the enzyme reverse transcriptase. However, in addition to the pentose and nucleic base, it is monophosphorylated and therefore referred to as a nucleo**t**ide analog. The accurate description of the substance is tenofovir DF (tenofovir disoproxil fumarate = TDF), referring to the phosphonate form from which the phosphonate component is only removed by a serum esterase, and which is activated intracellularly in two phosphorylation steps (Robbins 1998).

In the 902 and 907 studies, in which tenofovir was added to existing HAART, the viral load fell by approximately 0.6 logs after 48 weeks (Schooley 2002, Squires 2003). Tenofovir is tolerated very well: side effects were as low as in the placebo arm. In the 903 Study, in which tenofovir was tested against d4T in treatment-naïve patients, results showed at least equivalent potency (Gallant 2004). However, the incidences of polyneuropathy and dyslipidemias were significantly reduced. Analogous to this are the in vitro data, which show that phosphorylated tenofovir only has a low affinity for mitochondrial polymerases (Suo 1998). As a result of this convincing clinical data and its licensing in 2001, the drug is now very widely used. Furthermore, in the 934 study, TDF+FTC was significantly better than AZT+3TC (Gallant 2006), particularly due to the improved tolerability. Tenofovir can also help to improve d4T-induced lipoatrophy and dyslipidemias (Moyle 2006, Llibre 2006).

However, the extensive use has revealed a few problems. In particular, the combination of ddI should be avoided for diverse reasons (see “Problematic Primary Therapy”). An unfavorable interaction occurs with atazanavir, which means atazanavir has to be boosted (Taburet 2004). Reduced efficacy occur with particular triple nuke combinations(see corresponding section). In the case of virological

treatment failure on tenofovir, the K65R mutation, a problematic nucleoside analog resistance, is frequently found.

However, the potential risk of nephrotoxicity is a serious problem for tenofovir (see the chapter "HHIV and Kidneys"), which is associated with a mild to moderate disturbance of renal function (Gallant 2005, Mauss 2005, Thompson 2006, Heffelfinger 2006). Severe disturbances are rare. In the Swiss cohort, 46 out of 2,592 patients (1.6 %) had to stop tenofovir because of renal toxicity, after on average 442 days (Fux 2007).

Renal failure on tenofovir can also be observed in the context of a Fanconi syndrome, a defect of proximal tubular transport (Karras 2003, Schaaf 2003, Peyriere 2004). Patients with renal disease should either not be treated with tenofovir, or at least receive a lower dose (see "Drugs"). Elderly and lighter patients are particularly at risk (Crane 2006), although it is not possible to predict patients at risk. According to the current data, it is important to remain alert and to regularly check renal function on therapy.

The choice of NRTI backbones

Until now, all classical HAART regimens have always contained two nucleoside analogs or nucleotide analogs as the "backbone" ("nuke backbone"). As knowledge has grown about the mitochondrial toxicity of some nucleoside analogs, this concept is now being questioned by an increasing number of experts. However, data on combinations that are completely without NRTIs (see "Nuke Sparing") are still relatively sparse, so that there are currently no recommendations for such strategies.

Earlier NRTI backbones usually contained a thymidine analog (TA), in the form of AZT or d4T. However, because of the toxicity problems of both substances, as well as the problematic resistances associated with failure of therapy (see "Resistance"), it is usually changed to a TA-free backbone. The most important are TDF+3TC, TDF+FTC and ABC+3TC. These combinations have the advantage that they can be administered once daily: TDF+FTC and ABC+3TC can even be taken in a single tablet. Therefore, they have replaced the long-standing backbone of AZT+3TC.

TDF+3TC/FTC

Good data is available for tenofovir-based therapy (Molina 2004), especially in combination with efavirenz. In the Gilead 903 Study, the combination of TDF+3TC was not only as virologically effective as d4T+3TC, but was also tolerated much better (Gallant 2004).

Since the introduction of FTC and the combined tablet Truvada™ in August 2004, tenofovir has been administered more frequently together with FTC than with 3TC. TDF+FTC is currently the most commonly used backbone in Phase III/IV studies. In the Gilead 934 Study (Gallant 2006), using 509 treatment-naïve patients, TDF+FTC was compared to AZT+3TC (both with efavirenz). At 48 weeks, more patients on TDF+FTC reached a viral load of less than 50 copies/ml (80 versus 70 %). The significant differences were primarily related to the poorer tolerability of AZT+3TC, which often resulted in the discontinuation of therapy (9 versus 4 %). Virological failure and resistance mutations were approximately equal in both arms and were infrequent. At 96 weeks, no further significant differences were observed, although lipoatrophy side effects were rarer with TDF+FTC than with AZT+3TC

(Pozniak 2006). In the future, tenofovir therapy will play an important role - providing no undesirable surprises arise with regard to nephrotoxicity.

ABC+3TC

A real alternative to AZT+3TC is ABC+3TC, which is available in a fixed combination as Kivexa™ or Epzicom™. The double blind randomized CNA30024 Study showed the non-inferiority of ABC+3TC in comparison to Combivir™ (DeJesus 2004). It even led to a significantly higher rise in CD4 cells, although there was a higher rate of allergies at 9 versus 3 % (DeJesus 2004). The ZODIAC study also demonstrated good potency for ABC+3TC and efavirenz (Moyle 2004). In the ABCDE study, ABC+3TC had the same efficacy as d4T+3TC, but was also less toxic (Podzamczer 2006).

So far, there are no comparable studies on TDF+FTC. It is important to note that ABC+3TC has a significantly shorter half-life. Whether this could result in less "forgiveness" for irregular dosing and the development of resistances, is still not clear.

In comparison to TDF+FTC there could be an advantage in that L74V, usually occurring alongside the M184V mutation, is associated with less cross-resistance than the tenofovir-associated K65R mutation. However, a significant disadvantage of the combination with NNRTIs is the higher risk of occurrence of allergies under both abacavir and NNRTIs, making it difficult to distinguish between a NNRTI rash and the abacavir HSR. We therefore do not recommend using these at the same time, as treatment options may be unnecessarily eliminated.

It should be noted that most of the studies cited here were investigating first-line therapy. In treatment-experienced patients, numerous other individually tailored backbones may become necessary as a result of resistance and intolerability. However, the combinations discussed below should be avoided if possible.

AZT+3TC

In many guidelines, AZT+3TC is still regarded as the standard backbone for first-line therapy. There is more experience with this combination than with any other. The resistance profile is favorable: the M184V mutation that frequently develops during 3TC treatment probably increases sensitivity to AZT. AZT+3TC is usually given as Combivir™. Although the licensing study for Combivir™ showed no differences in toxicity (Eron 2000), in our experience the 300 mg AZT dose in Combivir™ is too high for some patients (e.g. pregnant women) and can lead to anemia. In such cases, it is worth trying AZT+3TC as individual formulations, so that the dose of AZT can be reduced to 250 mg.

AZT+3TC has comparable efficacy to d4T+3TC (Foudraine 1998, Eron 2000, Squires 2000), or AZT+FTC, which were frequently used earlier (Benson 2004). The ACTG 384 study showed superiority of AZT+3TC over d4T+ddI (Robbins 2003, Shafer 2003), which underpinned its status as a standard therapy. In the last few years, this has started to crumble: the initially lower rate of lipoatrophy (Molina 1999) actually just occurs later than with d4T+ddI. Furthermore, AZT+3TC were shown by the Gilead 934 Study to be less effective (tolerated less) than TDF+FTC (Gallant 2006, Pozniak 2006). In contrast to ABC+3TC, immune reconstitution appears to be worse (DeJesus 2004).

Poor and non-recommended backbones

Almost all guidelines now explicitly recommend avoiding the previously popular d4T+ddI combination. Mitochondrial toxicity is too high, and it is inferior to AZT+3TC (Robbins 2003). In cases of treatment failure, thymidine analog mutations (TAMs) are usually present, which can limit future options. In view of the wide selection of NRTIs available today, ddI+d4T is no longer justified at least for first-line therapy.

d4T+3TC is another combination recommended only in certain situations for first-line therapy. Although it is subjectively very well tolerated initially, d4T leads to problems with long-term toxicity. Studies such as ABCDE or 903 have shown that d4T+3TC cause more lipoatrophy than ABC+3TC or TDF+3TC (Gallant 2004, Podzamczer 2006). We would only use d4T+3TC today when neither AZT nor TDF could be used due to co-morbidity, for example in renal disease, anemic patients, in whom a HRS is difficult to manage (accompanying infections, poor compliance). If therapy with d4T+3TC has been started, it should be rapidly replaced.

Because ddI has to be taken on an empty stomach (whilst AZT is tolerated better when taken with a meal), and in particular due to the greater risk of gastrointestinal side effects, AZT+ddI is contraindicated. TDF+ddI are relatively toxic and, recently, many studies have shown lower efficacy (see also "Problems with Initial Therapies"). TDF+ABC is likely to be problematic due to rapid development of resistance. AZT+d4T and FTC+3TC are antagonistic.

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Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

Mechanism of action and efficacy

NNRTIs were first described in 1990. As with the nucleoside analogs, the target enzyme is reverse transcriptase. However, NNRTIs bind directly and non-competitively to the enzyme at a position in close proximity to the substrate binding site for nucleosides. The resulting complex blocks the catalyst activated binding site of the reverse transcriptase. This, in turn, can bind fewer nucleosides, slowing polymerization down significantly.

In contrast to NRTIs, NNRTIs do not require activation within the cell. The three available NNRTIs – nevirapine, delavirdine and efavirenz – were introduced between 1996 and 1998. Although studies such as the ACTG 241 or INCAS had already clearly demonstrated the superiority of triple therapy compared to double nuke therapy (D'Aquila 1996, Raboud 1999, Conway 2000), the "rise" of the NNRTIs was rather hesitant, and did not receive the media attention given to the PIs. This was due to the early observation that functional monotherapy with NNRTIs, i.e. the mere addition of a NNRTI to a failing regimen, showed practically no effect. There were also initial difficulties in dealing with the development of problematic resistance: the risk of resistance is not only very high, but it can also develop very rapidly. Once it occurs, it almost always indicates resistance to the entire class. Waiting too long, when there is insufficient suppression of viral load, is almost certain to lead to complete resistance to this class of drugs. One point mutation at position 103 (K103N) of the hydrophobic binding site is enough to eliminate the entire drug class! Resistance has now even been described in women who have taken a single dose of nevirapine as mother-to-child transmission prophylaxis. In large studies, the frequency of NNRTI mutations following, in some cases, a single perinatal nevirapine mono-prophylaxis was between 14 and worryingly 65 % (Cunningham 2002, Jourdain 2004, Johnson 2005). This is possibly promoted by the long half-life of NNRTIs (Muro 2005). Thus, it is recommended to stop NNRTIs a few days prior to the other drugs if treatment interruption is necessary (see chapter on Treatment Interruption). The rapid development of resistance is also reflected in the increasing number of primary transmitted resistances: in 2001/2002 almost 10 % of all acute infections in Europe had a NNRTI resistance (Wensing 2005). If a resistance is present, there is no need to start or continue treatment with a NNRTI – it will not change the immunological or virological status (Picketty 2004), because the ability of HIV to replicate is not reduced as much by NNRTI mutations as by some PI or NRTI mutations.

Despite the problems with resistance, numerous studies have demonstrated that NNRTIs are extremely effective when combined with nucleoside analogs. The immunological and virological potency of NNRTIs in treatment-naïve patients is at least equivalent, if not superior, to that of PIs (Staszewski 1999, Torre 2001, Podzamczer 2002, Robbins 2003). Newer studies such as ACTG 5192 or FIRST appear to support the predominance (MacArthur 2006, Riddler 2006). In contrast to PIs, however, the clinical benefit has not yet been proven as the studies that led to the licensing of NNRTIs all used surrogate markers. The efficacy of NNRTIs in

treatment-experienced patients is probably weaker in comparison to PIs (Yazdanpanah 2004).

The simple dosing and the overall good tolerability have enabled nevirapine and efavirenz to become important components of HAART regimens, which are often even ranked above those containing PIs. Over the last few years, many randomized studies have demonstrated that it is possible to switch from a PI to a NNRTI if good virological suppression has already been achieved. The efficacy was sometimes even better on NNRTIs than on the continued PI regimen (see also "When to change HAART").

Like efavirenz, nevirapine is metabolized by the cytochrome p450 system. Nevirapine is an inducer, whereas efavirenz is an inducer and an inhibitor of p450. In the combination of efavirenz with saquinavir or lopinavir the effects are so strong that dosage adjustment is necessary.

So far, no study has provided definitive evidence that one NNRTI is more potent than another. Although delavirdine no longer has any role, due to diverse reasons (see below), nevirapine and efavirenz have an equal standing. Cohort studies from the last few years suggest a slight superiority of efavirenz (Phillips 2001, Cozzi-Lepri 2002). However, these studies have only limited value as they included very heterogeneous patient groups. In treatment-naïve patients, the difference is small (Nunez 2002). In the 2NN Study ("The Double Non-Nucleoside Study"), nevirapine and efavirenz were compared for the first time in a large-scale randomized study (Van Leth 2004). In total, 1,216 patients received d4T+3TC with either nevirapine 1 x 400 mg, nevirapine 2 x 200 mg, efavirenz 1 x 600 mg or efavirenz 1 x 800 mg plus nevirapine 1 x 400 mg. The only significant virological difference was an advantage of the efavirenz arm over the double NNRTI arm, mainly due to higher toxicity in the latter. In the nevirapine arm with 1 x 400 mg, severe hepatic side effects occurred more frequently than in the efavirenz arm; on the other hand, lipids were more favorably influenced in the nevirapine groups. The hepatic toxicity associated with once-daily doses of nevirapine was almost exclusively observed in a single center in Thailand (Storfer 2005). 2NN as well as switch studies, such as NEFA (Martinez 2003), demonstrate that the choice of NNRTI should be based mainly on the different side effect profiles (see below), and patient-specific factors should also be taken into account (Recent review: Sheran 2005). A second generation NNRTI, etravirine, which is also effective against NNRTI-resistances, will be available for the first time in EAP programs in 2007.

Individual agents

Nevirapine (Viramune™) was the first licensed NNRTI. The combination with AZT+ddI is probably the oldest HAART combination of all. It was investigated in 1993, in the ACTG 193A Study, where it proved to be superior to monotherapy and dual therapy in severely immunocompromised patients. However, this was only true for progression and not for survival (Henry 1998). In addition, the AZT+ddI+nevirapine combination was well investigated in the INCAS and ACTG 241 Studies (Raboud 1999, D'Aquila 1996). Nevirapine has also been tested against PIs in randomized studies. In the Atlantic Study, combination with d4T+ddI was approximately as effective as indinavir (van Leeuwen 2003); given with AZT+3TC in the Combine Study, the trend was somewhat better than nelfinavir (Podzamczer

2002). The pharmacokinetics of nevirapine appear to allow once-daily dosing (Van Heeswijk 2000). Various studies such as 2NN or Atlantic have already successfully used 400 mg once daily (van Leeuwen 2003, Van Leth 2004), although this dosage has not yet been approved in all countries. A new extended-release formulation is currently being developed.

Nevirapine causes elevation of liver enzymes in up to 20 %, which may occasionally be severe. Lead-in dosing is always required. One study which reported that lead-in dosing is not required if efavirenz was previously administered (Winston 2004) still requires confirmation. During the first eight weeks on nevirapine, biweekly monitoring of transaminases is recommended. A rash develops in 15-20 % of cases and leads to discontinuation in up to 7 % (Miller 1997). Prophylactic administration of antihistamines or steroids does not prevent the rash (GESIDA 2004, Launay 2004). In the case of an isolated rash or isolated elevation of transaminases (up to five times the upper limit of normal), treatment can usually be continued. But, caution when both occur simultaneously! It is recommended to stop treatment if a rash occurs together with even a slight elevation of transaminases (> 2-fold of norm). It is important to note that hepatotoxicity can still appear several months later (Sulkowski 2002). Patients with chronic hepatitis are at risk, as are women with a low body weight (Sulkowski 2000, Sanne 2005, Kappelhoff 2005). An increased risk has also been reported for patients with a preserved immune status. Women with CD4 cell counts above 250/µl have a 12-fold elevated risk (11 versus 0.9 %), and the FDA even issued a warning relating to this in 2004. In treatment-naïve patients, the cut-off for women is 250, for men 400 CD4 cells – nevirapine should not be introduced above these values. However, in recent months a few studies have not been able to reproduce the association with the immune status (Wolf 2006). In particular, the risk does not seem to be increased in treatment-experienced patients, who change to nevirapine, even when CD4 cell levels are good (De Lazzari 2006, Mocroft 2006).

There does not appear to be any correlation between side effects and drug plasma levels (Kappelhoff 2005). There is probably a genetic disposition for reactions to nevirapine – associated with HLA type - (Martin 2005), and drug-transporter gene variants have been described (Haas 2006, Ritchie 2006). Permanent and significant γGT elevations are very common, which may subject patients to false suspicions of excess alcohol consumption.

Nevirapine has a good lipid profile. Studies such as Atlantic or 2NN, discovered comparably favorable lipid changes for cholesterol and triglycerides (Van der Valk 2001, Van Leth 2004), as well as with efavirenz albeit to a lesser extent (Fisac 2005). It is not clear whether these positive effects will have clinical relevance over time and actually help to prevent cardiovascular events.

Efavirenz (Sustiva™ or **Stocrin™)** was the third NNRTI to be approved, and the first for which it could be shown that NNRTIs were at least as effective and probably even better than PIs in untreated or only short term treatment-experienced patients. The 006 Study showed a superiority of efavirenz over indinavir (Staszewski 1999). Since then, efavirenz has been compared to other drugs in many studies. Efavirenz almost always did well. In ACTG 5095, efavirenz in combination with AZT+3TC was better than abacavir (Gulick 2004); in ACTG 384 it was better than nelfinavir (Robbins 2003, Shafter 2003); and in AI424-034 it was at least as effec-

tive as atazanavir (Squires 2004). ACTG 5192 demonstrated superiority over lopinavir/r (Riddler 2006).

Moderate CNS side effects are often typical for efavirenz, which should therefore be taken in the evening before sleeping. Patients should be warned about these side effects, which usually include dizziness and numbness, but may also manifest as vivid dreams or even nightmares. In addition, patients should be warned about potentially hazardous tasks such as driving or operating machinery. The side effects probably correlate with high plasma levels (Marzolini 2001), and black African patients in particular seem to have a genetic predisposition (Haas 2004). Studies show that efavirenz disrupts the sleep architecture (Gallego 2004). In one study, after four weeks of treatment with efavirenz, 66 % of patients complained of dizziness, 48 % of abnormal dreams, 37 % of somnolence and 35 % of insomnia (Fumaz 2002). Although these symptoms seem to resolve during the course of treatment, they may persist in about one fifth of patients (Lochet 2003). Efavirenz should then be replaced.

Liver problems occur less frequently than with nevirapine, and lead-in dosing is not necessary. Once-daily dosing is safe due to the long half-life, and, in contrast to nevirapine, is also licensed. However, lipids are not as favorably affected as with nevirapine. Gynecomastia is also typical for efavirenz, which is not only a psychological burden, but can also be painful (Rahim 2004). In such cases, efavirenz should be replaced with nevirapine if possible.

Efavirenz is contraindicated in pregnancy. In women of childbearing age, its use must be considered carefully and if pregnancy is a possibility, nevirapine is preferable.

Table 2.2. Frequency of the most important side effects of nevirapine and efavirenz (The numbers are based on various studies referenced in this chapter)

	Nevirapine	Efavirenz
CNS side effects	Rare	58-66 %
Severe CNS side effects	Very rare	5-7 %
Hepatotoxicity	17 %	8 %
Dyslipidemia	No	Frequent
Gynecomastia	No	Occasional
Rash	15 %	5 %

Delavirdine (Rescriptor™) was, in April 1997, the second NNRTI to be licensed by the FDA. Due to the pill burden and the required three times daily dosing, delavirdine is currently rarely prescribed. Delavirdine is not licensed in Europe where, in 1999, an application for licensure was rejected due to insufficient efficacy data. Nevertheless, delavirdine is likely to be as effective as the other NNRTIs (Conway 2000). In DLV 21, AZT+3TC+delavirdine was tested against AZT+3TC and AZT+delavirdine on 369 mostly treatment-naïve patients. After one year, 68 % had a viral load below 50 copies/ml in the triple combination arm compared to less than 10 % in the other two arms (Conway 2000). Rash (30 %) probably occurs more frequently than with other NNRTIs. Delavirdine increases plasma levels of various PIs (Harris 2002). However, use of this as a strategy for boosting, has not been widely accepted.

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Protease inhibitors (PIs)

Mechanism of action and efficacy

The HIV protease cuts the viral gag-pol polyprotein into its functional subunits. If the protease is inhibited and proteolytic splicing prevented, non-infectious virus particles will result. With the knowledge of the molecular structure of the viral protease, the first protease inhibitors (PIs) were designed in the early nineties; these substances were modified in such a way that they fit exactly into the active enzyme site of the HIV protease (review: Eron 2001).

Since 1995, protease inhibitors have revolutionized the treatment of HIV infection. At least three large studies with clinical endpoints have demonstrated the efficacy of indinavir, ritonavir and saquinavir (Hammer 1997, Cameron 1998, Stellbrink 2000). Although PIs have been criticized at times due to their frequently high pill burden and side effects (see below), they remain an essential component of HAART. With growing knowledge of the mitochondrial toxicity of nucleoside analogs and through the introduction of easy-to-take PIs, this class of drugs is currently experiencing a renaissance –even PI-only regimens are now being investigated.

As with the NNRTIs, initially, there was competition among pharmaceutical companies to establish which PI had superior efficacy. Only a few comparative randomized studies have been performed. But even in the case of PIs, the differences observed so far are not so significant as to compromise individual members of this class. Two exceptions that have since been taken off the market are: the hard gel capsule saquinavir and ritonavir on its own. Boosted PI combinations are more effective than unboosted regimens (see below).

Apart from gastrointestinal side effects and high pill burden, all PIs used in long-term therapy encounter problems – to a greater or lesser extent, all are associated with lipodystrophy and dyslipidemia (review: Nolan 2003). Cardiac arrhythmias (Anson 2005) and sexual dysfunction have also been attributed to PIs (Schrooten 2001), although the data does not remain unchallenged (Lallemand 2002).

There is a high degree of cross-resistance between protease inhibitors, which was described before PIs were put on the market (Condra 1995). All PIs are inhibitors of the CYP3A4 system and interact with many other drugs (see "Drug Interactions"). Ritonavir is the strongest inhibitor, saquinavir probably the weakest.

"Boosting" protease inhibitors – why and how?

Ritonavir is a very potent inhibitor of the isoenzyme 3A4, a subunit of the cytochrome P450 hepatic enzyme system. Inhibition of these gastrointestinal and hepatic enzymes allows the most important pharmacokinetic parameters of almost all PIs to be significantly increased, or "boosted" (Kempf 1997): maximum concentration, trough levels and half-life. The interaction between ritonavir and the other PIs allows a reduction in the frequency and number of pills simplifying daily dosing and makes the resorption partially independent of food intake.

Some PIs can now be used in twice-daily regimens and current trials are investigating the possibility of once daily dosing of many PIs.

Boosting with ritonavir is usually indicated by the addition of an "/r" after the drug name. Boosting can be effective against resistant viral strains as a result of the elevated plasma drug levels (Condra 2000). Resistance is less commonly observed on boosted PIs, at least in patients naïve to antiretroviral therapy, as the genetic barrier is very high. Although most of the data available relates to lopinavir/r, this also applies to fosamprenavir/r (Eron 2006), atazanavir/r (Malan 2006) and saquinavir/r (Ananworanich 2006). Boosting nelfinavir with ritonavir is not useful as plasma levels do not rise significantly (Kurowski 2002).

Ritonavir boosting is also associated with risks as there is a very high degree of inter patient variability in plasma drug levels. Higher peak levels may lead to more side effects. If in doubt (reduced efficacy, side effects), plasma drug levels should be measured in all cases of boosting, especially in patients with severe hepatic diseases. Furthermore, apart from boosted atazanavir, all other boosted combinations appear to increase lipid levels (Van der Valk 2003).

Table 2.3: Current doses of protease inhibitors with ritonavir boosting.

	Dose (mg)	Pills*/day	Comment
Atazanavir/r	1 x 300/100	1 x 3	Only approved for treatment-experienced patients
Darunavir/r	2 x 600/100	2 x 3	Only available in EAP**
Fosamprenavir/r	2 x 700/100	2 x 2	Should be used instead of amprenavir
Fosamprenavir/r	1 x 1400/200	1 x 4	Only approved for PI-naïve patients
Indinavir/r	2 x 800/100	2 x 3	High rate of nephrolithiasis (?)
Lopinavir/r	2 x 400/100	2 x 3	Only fixed booster combination
Lopinavir/r	1 x 800/200	1 x 6	Currently only licensed in the USA
Saquinavir/r	2 x 1000/100	2 x 3	Officially licensed for boosting
Tipranavir/r	2 x 500/200	2 x 4	Only approved for treatment-experienced patients

* Number of pills including the ritonavir dose. **EAP = expanded access program

Individual agents

Amprenavir (Agenerase™) was the fifth PI to enter the European market, in June 2000. Due to the further development of fosamprenavir (Telzir™, see below), it was replaced in 2004 (Rodriguez 2004). Only the suspension and the 50 mg tablet are available for children.

Atazanavir (Reyataz™) was the first once-daily PI to be licensed in 2004. It is currently only licensed for treatment-experienced patients. In order to expand the license, atazanavir is being tested in therapy-naïve patients against lopinavir. In Phase II studies, atazanavir was better tolerated than nelfinavir, although the antiretroviral potency was comparable (Murphy 2003, Sanne 2003). In a Phase III study, atazanavir had a virological efficacy equivalent to efavirenz (Squires 2004). Unboosted atazanavir is slightly less effective than lopinavir in treatment-experienced patients (Cohen 2005). This does not seem to be the case if boosted, at least when PI resistance is limited (Johnson 2006). The primary resistance mutation for this drug is I50L, which does not impair sensitivity to other PIs, and possibly even increases it (Colonno 2003). On the other hand, there are a number of cross-resistance mutations, and susceptibility to many virus isolates with moderate PI resistance is reduced (Schnell 2003).

In contrast to other PIs, atazanavir does not have a negative influence on lipid profiles (Sanne 2003, Squires 2004, Johnson 2006), which is its main advantage besides the once-daily dosing. It has been shown that lipids improve when other PIs are replaced by atazanavir (Wood 2004, Gatell 2006). It also does not induce insulin resistance (Noor 2004). In our experience, it is still questionable whether this will be reflected clinically with less lipodystrophy, as suggested in some studies (Haerter 2004, Jemsek 2006). In contrast to earlier reports, boosting of atazanavir with ritonavir does have negative effects on lipid levels (Malan 2006). Atazanavir should always be boosted with ritonavir in combinations with NNRTIs or tenofovir, which significantly lower atazanavir levels (Le Tiec 2005). Furthermore, unfavorable interactions occur particularly in combination with proton pump inhibitors (see "Drug Interactions").

One problem with atazanavir is that more than half the patients experience elevated bilirubin levels, which can reach grade 3-4 in approximately one third of all cases, and which occur more frequently with boosting (Squires 2004, Malan 2006). Some patients develop clinical jaundice. The mechanism for this resembles that of Gilbert's syndrome (and the increased levels with indinavir); there is reduced conjugation in the liver. Recently, a genetic predisposition has been identified (Rotger 2005). Although the hyperbilirubinemia is supposed to be harmless and only a few cases of serious hepatic disorders have been described to date (Eholie 2004), liver function should be monitored when on atazanavir, and treatment discontinued in cases of jaundice or significantly elevated bilirubin (> 5-6 times the upper limit of normal). Despite this, atazanavir is a PI, which in industrialized countries competes with lopinavir for the place of the most prescribed PI.

Darunavir (Prezista, earlier TMC-114) is a PI, which was developed by the Belgian company Virco/Tibotec (since bought by Johnson & Johnson). In view of its significant efficacy against PI-resistant viruses (Koh 2003, King 2004), darunavir is currently one of the most interesting agents in HIV treatment. Two large Phase IIb studies, POWER 1 (USA) and 2 (Europe), led to the accelerated licensing of darunavir in June 2006 in the USA in treatment-experienced patients. The approval in Europe is expected in early 2007, and an expanded access program is already running.

The POWER study included almost 600 patients. Pre-treatment was intensive, with three classes (median 11 drugs), and multiple resistance mutations at baseline. Several ritonavir-boosted doses of darunavir were tested against a boosted comparison PI. In the 600 mg group (600/100 bid), the viral load remained under 50 copies/ml in 46 % of patients, even after 48 weeks (Lazzarin 2006) - a significantly better result than with the control PI (10 %), and in a patient group that until now had extremely limited treatment options and no observable success. The results from POWER 3, a further, non-randomized study on long-term tolerability in 458 treatment-experienced patients, confirmed this response (Saag 2006).

Of course the effectiveness of darunavir is not limitless. A total of 11 resistance mutations were identified in the POWER studies. Mainly found on codons 32, 47, 50 and 87 (DeMeyer 2006), three or more mutations significantly reduce the efficacy of darunavir.

Darunavir is very usually well tolerated and the diarrhea may be milder than with other PIs (Lazzarin 2006). Dyslipidemias and elevation of liver enzymes, which occur with the main competitor PI tipranavir, appear to be less frequent. Relevant interactions exist with lopinavir, which decrease the plasma level of darunavir, and therefore the combination should be avoided. This also applies to combinations with sildenafil and some estrogen preparations.

At present, numerous studies with darunavir are underway. It will be interesting to see the comparison studies between lopinavir on therapy-naïve (C211, ARTEMIS) and treatment-experienced (C214) patients, the results of which are not yet available. Darunavir is currently also being investigated in combination with etravirine (DUET study), and as a monotherapy. The full potential of this substance will only be revealed in the next two to three years.

Fosamprenavir (Telzir™ or Lexiva™), as a calcium phosphate ester, has better solubility and absorption than amprenavir, reducing the number of pills to be taken.

Fosamprenavir was licensed for treatment-naïve and –experienced patients in 2004. The possible doses are either a) 1400 mg bid (2 pills bid), b) 700 mg bid plus 100 mg ritonavir bid (2 pills bid) or c) 1400 mg plus 200 mg ritonavir once daily (4 pills qd). Once-daily dosing is not recommended for treatment-experienced patients, and, like the unboosted dose, is not licensed in Europe. One advantage of the drug is that there are no restrictions with respect to food intake, and it can be taken on an empty stomach or with a meal.

Several studies have compared fosamprenavir to other PIs. In treatment-naïve patients in the NEAT Study, unboosted fosamprenavir was slightly more effective and had better tolerability than nelfinavir (Rodriguez-French 2004). However, high dropout rates limited this study. In the SOLO study, boosted once-daily fosamprenavir was about as effective as nelfinavir (Gathe 2004); this was also the case in comparison to atazanavir/r in the relatively small ALERT study (Smith 2006). No resistance mutations were found on fosamprenavir/r at 48 weeks (MacManus 2004). In the KLEAN study, in comparison to lopinavir there were no differences: severe diarrhea (13 versus 11 %) or increases in the cholesterol levels (11 versus 9 %) were no less rare on fosamprenavir (Eron 2006). In treatment-experienced patients in the CONTEXT Study, a somewhat (non-significant) reduced effect was seen with fosamprenavir/r in contrast to lopinavir/r (Elston 2004). Efavirenz and nevirapine as potent inducers of amprenavir metabolism, can significantly (probably with clinical relevance) lower plasma levels. This does not occur when fosamprenavir is boosted with ritonavir. Beware of the combination with lopinavir as plasma levels (AUC, Cmin) of both drugs are lowered! This unfortunately seems to eliminate what would otherwise have been an interesting salvage option (see “ Interactions”).

Indinavir (Crixivan™) is one of the oldest PIs, which was initially very successful in large studies (Gulick 1997, Hammer 1997). Later, indinavir had mixed success, at least when unboosted: in the Atlantic Study, it was about as effective as nevirapine (Van Leeuwen 2003), but in the 006 Study it was clearly weaker than efavirenz (Staszewski 1999). In the double blind, randomized CNAAB3005 Study, indinavir was more effective than abacavir, particularly in patients with high viral load at baseline (Staszewski 2001). In the CHEESE Study and MaxCmin1 studies, the efficacy was comparable to saquinavir-SGC (Cohen-Stuart 1999, Dragstedt 2003). Low protein binding (60 %) seems to allow better CNS penetration than with other PIs (Martin 1999).

There are, however, a number of problems associated with indinavir. Firstly, it causes nephrolithiasis in approximately 5-25 % of patients (Meraviglia 2002), and thus requires good hydration (at least 1.5 liters daily). Unboosted indinavir must be taken three times daily on an empty stomach (Haas 2000), and for this reason, boosting with ritonavir is recommended – good pharmacokinetic data is available for 2 x 800/100 mg daily (Van Heeswijk 1999), although more side effects occur (Arnaiz 2004). In MaxCmin1, the dropout rate on indinavir/r versus saquinavir/r was notably higher (Dragstedt 2003). Specific side effects associated with indinavir include mucocutaneous side effects reminiscent of retinoid therapy: alopecia, dry skin and lips, and ingrown nails. Many patients may also develop asymptomatic hyperbilirubinemia. Although it seems that the dose and thus toxicity can be reduced in most patients by boosting and monitoring plasma levels, indinavir now has only a minor role in current antiretroviral regimens.

Lopinavir/r (Kaletra™) is, since its licensing in April 2001, the first (and so far the only) PI with a fixed booster dose of ritonavir, which increases concentrations of lopinavir by more than 100 fold (Sham 1998). In the middle of 2006, the soft capsules, which had been used up until that time were replaced by tablets manufactured using melt extrusion technology("Meltrex"). This allowed a reduction to 2 x 2 tablets, and refrigeration of the tablets was not necessary. Since May 2005, in the USA, lopinavir/r has also been licensed for once daily administration, which is possibly equivalent in previously untreated patients (Johnson 2006). Large randomized studies are currently underway to compare the soft capsules with the tablets. It is still unclear whether the results of the earlier studies with the capsules can be equally applied to the tablets. They should nevertheless be briefly outlined.

In *treatment-naïve* patients in a randomized double-blind study, lopinavir/r was significantly superior to unboosted nelfinavir (Walmsley 2002). This does not seem to be the case for other PIs, such as fosamprenavir (Eron 2006) and possibly saquinavir (Slim 2006). In ACTG 5142, lopinavir/r was even inferior to efavirenz (Riddler 2006), possibly because of the worse tolerability. In *treatment-experienced* patients in an open-label randomized (MaxCmin2) trial on a heterogeneous population lopinavir/r showed better results than boosted saquinavir (in the old Fortovase™ formulation). This was particularly true for tolerability and efficacy (Dragstedt 2005). In contrast, in two randomized studies, it was virologically no better than atazanavir (Johnson 2006) or fosamprenavir (Elston 2004) – although the patient numbers in these studies were relatively small.

Development of resistance on lopinavir/r first-line therapy is rare, but is theoretically possible (Kagan 2003, Conradie 2004, Friend 2004). Lopinavir/r has a high genetic barrier to resistance, and it is likely that at least 6-8 cumulative PI resistance mutations are necessary for treatment failure (Kempf 2002). Lopinavir/r monotherapy, is therefore currently being intensively investigated (see Chapter 6).

Gastrointestinal side effects (diarrhea, nausea), are commonly described but are significantly less on the new formulation. Lipodystrophy and dyslipidemia, occurs more frequently than with nelfinavir (Walmsley 2002), but no more than with fosamprenavir.

A number of interactions should also be considered (see "Interactions"). The dose must be increased in combination with efavirenz and nevirapine.

Nelfinavir (Viracept™) was, in 1998, the fourth PI on the market and was for a long time one of the most frequently used PIs. The dose of five capsules twice daily is as effective as three capsules three times daily. Boosting with ritonavir does not improve the plasma levels (Kurowski 2002). The most important side effect of nelfinavir is diarrhea, which may be considerable. The drug is otherwise very well tolerated. In the pivotal 511 Study, 61 % of patients on nelfinavir (with AZT+3TC) had a viral load below 50 copies/ml at 48 weeks (Saag 2001). In the open-label, randomized CNAF3007 Study, the decrease in viral load was comparable to abacavir (Matheron 2003).

In comparison to NNRTIs or other PIs, nelfinavir is probably slightly less potent. In the Combine Study, nelfinavir was weaker (not significantly) than nevirapine (Podzamczer 2002). In ACTG 384 and 364, nelfinavir was inferior to efavirenz in both treatment-naïve and treatment-experienced patients (Albrecht 2001, Robbins

2003). This was also the case in comparison to lopinavir/r in the double blind, randomized M98-863 Study (Walmsley 2002).

Nelfinavir is only rarely effective if a PI-containing therapy has failed (Lawrence 1999, Hammer 2002). In a few studies, nelfinavir was combined with saquinavir, which then significantly elevated plasma levels and thereby partially increased the efficacy (Moyle 2000, Chavanet 2001). However, such a combination is no longer acceptable due to the high pill burden and high incidence of diarrhea.

Ritonavir (Norvir™) was the first PI for which efficacy was proven on the basis of clinical endpoints (Cameron 1998). However, ritonavir is now obsolete as a single PI, since tolerability is too poor. As gastrointestinal complaints and perioral paresthesias can be very disturbing, ritonavir is now only given to boost other PIs. The "baby dose" used for this purpose (100 mg bid) is tolerated better.

Ritonavir inhibits its own metabolism via the cytochrome P450 pathway. The potent enzyme induction results in a high potential for interactions; thus, many drugs are contraindicated for concomitant administration with ritonavir. Metabolic disorders occur more frequently than with other PIs. Caution should be exercised in the presence of impaired liver function. It is important to inform patients that ritonavir capsules must be stored at cool temperatures, which can often be a problem when traveling.

Saquinavir (**Invirase 500™,** previously **Invirase™, Fortovase™**) was, in December 1995, the first PI to be licensed for HIV therapy and is still today one of the few substances whose efficacy has been proven based on clinical end points (Stellbrink 2000). Boosting with ritonavir raises the plasma level considerably (review: Plosker 2003). The same applies to a simultaneous food intake. Saquinavir is well tolerated – there are hardly any serious side effects. With no serious short-term problems, Saquinavir is an attractive PI for patients who need a boosted PI-regimen. The earlier hard gel (Invirase™) and soft gel (Fortovase™) capsules were replaced in 2005 by Invirase 500™ tablets, which through the same pharmacokinetics (Bittner 2005), significantly reduced the number of pills to six a day (2 x 2 à 500 mg plus 2 x 100 mg ritonavir).

It is possible that a lot of data from the time of Fortovase™ are probably not easily transferable to the Invirase 500™, but should be briefly mentioned. In the CHEESE Study, there was no difference between saquinavir soft gel and indinavir (Cohen-Stuart 1999). In MaxCmin1, in which saquinavir as well as indinavir were boosted with ritonavir, both demonstrated similar efficacy, although saquinavir was tolerated better (Dragstedt 2003). In MaxCmin2, boosted saquinavir-SGC compared slightly less favorably to lopinavir/r (Dragstedt 2005). In Staccato, a trial from Thailand, 89 % of all patients achieved a viral load below 50 copies/ml after 24 weeks (Ananworanich 2005) on a once-daily regimen (1,600 saquinavir/100 mg ritonavir). With the Invirase 500™ tablet, saquinavir has once again become an interesting option, due to its good tolerability. The preliminary data from the GEMINI study at least seem to indicate the absence of any serious inferiority to lopinavir/r (Slim 2006).

Tipranavir (Aptivus®) – the first non-peptidic PI – was licensed in July 2005 for pre-treated patients. In order to improve the oral bioavailability, tipranavir should be boosted with 2 x 200 mg (2 x 2) ritonavir (McCallister 2004). It is recommended that it be taken with food. A high-fat meal raises the plasma levels.

Tipranavir has good efficacy against PI-resistent viruses (Larder 2000). For the licensing, two randomised Phase III studies were performed (RESIST-1 in the US and -2 in Europe) on 1,483 intensively pretreated patients. All patients received either tipranavir or a comparison PI, each combined with optimized background therapy (OBT). After 48 and 96 hours, tipranavir was immunologically and virologically superior to the comparison arm (Hicks 2006, Gazzard 2006). Good efficacy is maintained with up to 8 mutations in the RT gene as well as when less than 3 key PI mutations (L33I/V/F, V82A/F/L/T, I84V, and L90M) are present (Hall 2003, Baxter 2006). Tipranavir has therefore become an important option in salvage therapy. There is currently no license for use in therapy-naïve patients.

The increases in triglycerides were more marked in the tipranavir group of the RESIST studies than in the comparison PIs (grade 3-4 increases/100 treatment years; 31% versus 23%), and transaminases were also significantly raised in some cases (GPT grade 3-4: 10% versus 3%). However, the incidence of unwanted side effects leading to discontinuation was comparable in both groups (Hicks 2006). Consequently, lipids and transaminases should be carefully monitored under tipranavir.

Tipranavir has a relevant interaction potential. Combination with etravin is not possible (Schöller 2006). The levels of lopinavir, saquinavir, atazanavir, and amprenavir fall significantly (Curry 2004), so that double PI therapy with tipranavir is out of the question. In contrast, combination with substances such as maraviroc or raltegravir is possible (Abel 2005, Wennig 2006).

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Entry inhibitors

There are three crucial steps for entry of HIV into the CD4 cell:

1. Binding of HIV to the CD4 receptor,
2. Binding to co-receptors, and finally
3. Fusion of virus and cell.

Every step of HIV entry can theoretically be inhibited. All three drug classes, namely attachment inhibitors, co-receptor antagonists and fusion inhibitors (FIs) are currently summarized as entry inhibitors (see the following chapter). In 2003, Fuzeon™ – the first and so far only drug of this class – was licensed.

T-20 (Enfurvitide, Fuzeon™) is the prototype of the FIs. Since May 2003, it has been licensed in Europe and the US for the treatment of HIV-1 infection in treatment-experienced adults and children over 6 years of age. It is preferable to treat patients within clinical studies, so that clinical experience with this new drug can be collected. As a relatively large peptide (36 amino acids) it has to be administered by subcutaneous injection (Review: Oldfield 2005). T-20 binds to an intermediate structure of the HIV gp41-protein, which appears during fusion of HIV with the target cell.

In early studies on intravenous monotherapy, the fall in viral load was, dose dependent, between 1.6 and 2 logs (Kilby 1998 + 2002). The first studies on subcutaneous administration showed an effect at up to 48 weeks: however, it became obvious that those patients, who received additional new antiretroviral drugs to which they were susceptible did better (Lalezari 2000 + 2002).

Two Phase III studies led to the licensing of T-20. TORO 1 ("T-20 versus Optimized Regimen Only") enrolled 491 extensively pretreated patients in North and South America, most with multiresistant viruses; in TORO 2, 504 patients in Europe and Australia were enrolled. Patients, on an optimized HAART regimen, either received 90 mg T-20 bid subcutaneously or none at all (Lalezari 2003, Lazzarin 2003). In TORO-1, the viral load fell on T-20 at 48 weeks by a median of 0.94 logs; in TORO-2 it was 0.78 logs (Nelson 2005). A clear benefit was seen with T-20 in combination with the new PIs such as tipranavir and darunavir. In the RESIST and POWER studies, the response rates of these agents were considerably improved with T-20 (Youle 2006). In the MOTIVATE studies with the CCR5 antagonist maraviroc, this was not the case (Nelson 2007, Lalezari 2007).

The success of T-20 therapy should be monitored early on. Patients without a decrease in viral load of at least one log after 8-12 weeks will not benefit from T-20 (Raffi 2006), and can be spared the required two injections per day. It is also not recommended to inject double the dose just once a day: although 1 x 180 mg has the same bioequivalence (as measured by AUC) as the standard 2 x 90 mg dose, a recent study showed a trend towards a lesser decrease in viral load with the 180 mg dose that was clearly associated with lower trough levels (Thompson 2006).

Unexpectedly, a new occurrence under T-20 in the TORO studies was the increased frequency of lymphadenopathy and bacterial pneumonia (6.7 versus 0.6/100 patient years) (Trottier 2005). Septicemia also occurred more often, but the difference was again not significant. The reason for the increased rate of infections has so far remained unclear, but binding of T-20 to granulocytes has been suspected. Substantial side effects remain almost obligatory (98 % in TORO 1/2), and severe local skin reactions can sometimes occur at the injection site. They can be particularly painful, and result every so often in interruption of therapy: 4.4 % of cases in the TORO studies. In our experience of everyday clinical treatment, therapy is interrupted much more frequently due to the skin problems over a short or long time. After a certain amount of time, many patients refuse to continue with T-20 or to restart an interrupted therapy. Local reactions (see "Side Effects") can be reduced by using a bioinjection system, in which T-20 is pressed into the skin (Harris 2006).

Resistance mutations develop relatively rapidly on T-20, but seem to reduce viral fitness (Lu 2002, Menzo 2004). Receptor tropism of the virus seems to be less significant than initially thought. Many more seem to have changes to a short sequence on the gp41 gene, causing reduced susceptibility; this requires only simple point mutations (Mink 2005, Melby 2006). However, viruses resistant to conventional HAART (NRTIs, NNRTIs, PIs) are susceptible (Greenberg 2003). As T-20 is a relatively large peptide, it induces antibody production. However, this does not impair the efficacy (Walmsley 2003). More disturbing, is the fact that, in a large TDM study, there were big differences between individuals, and extremely low plasma levels were usually measured (Stocker 2006).

In summary: patients with a well-controlled viral load or who still have options with "classical" HAART do not require T-20. For salvage therapy, however, it remains a viable option. It is academically interesting to consider its potential in increasing HAART to empty latent reservoirs (Lehrmann 2005, Molby 2006). The price remains an important aspect of T-20. The company claims that it is one of the most complicated drugs it has ever manufactured, thus doubling the cost of HAART. This is unlikely to change even if an improved agent becomes available – the company is currently working on an improved formulation (but not pegylation) of T-20, which would allow weekly dosing.

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3. ART 2007/2008: The horizon and beyond

Christian Hoffmann and Fiona Mulcahy

Despite all the advances, the need for new drugs is growing. This is not just true for patients with multiresistant viruses awaiting new treatment options, but for all patients with HIV. Because eradication is currently not possible, significant problems related to compliance and long-term toxicity can be anticipated with decade-long therapies. As a result, there is a need for new drugs that are less toxic and easier to take. To eventually reach the goal of eradication, new drugs need to be more potent if possible than those available today. The following overview of the substances today (beginning of 2007) that promise the most, does not claim to be complete.

Refurbished old drugs

Several currently available drugs are under further development, the most important goals being the reduction of pill burden, and easier dosing. Three such preparations to have recently entered the market are Invirase 500™, Truvada™ and Kivexa™; Atripla™ will arrive soon. New improvements are being developed.

Atripla™ is the combination of tenofovir+FTC (Truvada™) and efavirenz (Sustiva™). This preparation is unique in that it is the first in the history of HIV medicine in which companies have come together to produce a combination tablet: TDF+FTC come from Gilead; efavirenz comes from BMS. Atripla™ is regarded (together, Truvada™ and Sustiva™ are just two tablets, anyway) as psychologically important for patients and clinicians. One tablet a day is a complete and effective therapy! Some experts, who remember the early HAART regimens with six tablets three times a day, will be very pleased. The production of the combination was not easy, and a two-layer film-coated tablet was decided upon, in which both preparations - Truvada™ and Sustiva™ - are simply pressed together. Bioequivalence to the individual agents has been shown (Mathias 2006). Atripla™ was licensed by the FDA in July 2006. and is expected in Europe at the end of 2007.

Nelfinavir 625 mg – this new formulation was approved in the US in April 2003. It reduces the nelfinavir dose to 2 tablets bid. One study has shown that this formulation is better tolerated, particularly with respect to gastrointestinal side effects – despite the fact that plasma levels are around 30 % higher than with the previous nelfinavir formulation (Johnson 2003, Kaeser 2003). In Europe, where nelfinavir is produced and sold by Roche instead of Pfizer, the 625 mg tablet is not available.

Zerit PRC™ (PRC = "prolonged release capsule", or XR = "extended release") is a capsulated formulation of d4T (Baril 2002), which was approved in Europe in October 2002, but which never reached or will reach the market. D4T is definitely "out". Instead, other attempts are currently underway to improve d4T through modifications to its molecular structure (Haraguchi 2003, Dutschman 2004).

Viramune™ Extended-Release is an improved formulation of conventional nevirapine. It should allow once daily dosing of nevirapine in one tablet. Boehringer is currently conducting extensive studies on this formulation.

Norvir™ tablets are actually the bioequivalent to the capsules used until now, as shown in an initial study on a healthy proband (Cai 2007). When this has been confirmed on larger patient numbers the bothersome refrigeration of ritonavir could finally become superfluous.

Generic combinations are not so difficult to produce, as experience in Africa, India or Thailand has shown. Bioequivalence can also usually be demonstrated (Laurent 2004). Fixed combinations such as Triomune from Cipla (d4T+3TC+nevirapine), GPO (d4T+3TC+nevirapine) or Zidovex-LN from Imunus (AZT+3TC+nevirapine) are just a few examples. These preparations are not currently as important in industrialized countries,but this may change in the future as patents for several agents run out.

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New nucleoside analogs

Since the development of DAPD and dexelvucitabine (reverset) came to a halt, hopes are now limited that there will be new nucleoside analogs on the market in the near future. At the moment, nothing has past Phase II studies in the development – it seems to be difficult to find new NRTIs, which have a reduced mitochondrial toxicity and efficacy against resistant viruses.

Apricitabine (AVX-754, earlier SPD-754) is a heterocyclic cytidine analog that was sold by Shire Biochem to Avexa at the beginning of 2005. In vitro, Apricitabine, which is chemically similar to 3TC, is active against a broad spectrum of TAMs, and up to 5 NRTI mutations do not significantly impair its activity (Bethell 2005, Gu 2006). In a placebo-controlled study, the viral load decreased on a 10-day monotherapy by 1.2 to 1.4 logs – good potency for a NRTI (Cahn 2006). Apricitabine has been well tolerated and has good oral bioavailability (Francis 2003). What about long-term toxicity? In monkeys, there were minor skin problems, usually hyperpigmentation, after 52 weeks of exposure. Apricitabine was thus signifi-

cantly less toxic than its racemate BCH-10652, which caused severe degenerative dermatopathy in the monkeys (Locas 2004). 3TC and FTC lower intracellular levels of apricitabine, and the combination with other cytidine analogs is therefore problematic. Avexa is currently planning Phase IIb studies, and Apricitabine is expected to come onto the market in 2009.

Dioxolanthymidine (DOT) is a new thymidine analog – one of the few new substances in this sub-group. Dioxolanthymidine appears relatively good in preclinical trials (Chung 2005, Liang 2006) – now clinical studies have to show what is possible with DOT. Phase I studies are underway.

Elvucitabine (or **ACH-126,443)** is a nucleoside analog developed by Achillion Pharmaceuticals. It is an enantiomer of dexelvucitabine, with the chemical name beta-L-D4FC, and is also effective against HIV and HBV. In vitro studies show potency even in the presence of numerous NRTI mutations, and viruses with completely unique resistances, such as M184I or the so far unknown mutant D237E, are selected for (Fabrycki 2003). It is also of interest because it seems to have low mitochondrial toxicity, as well as an extremely long half-life of 150 hours (Dunkle 2001, Colucci 2005). Phase II studies are underway on HIV and HBV. A small, double blind study showed a reduction in viral load of between 0.7 - 0.8 logs after 28 days in HIV patients with the M184V mutation. However, this study had to be terminated, as 6/56 patients developed leukopenia on a dose of 100 mg elvucitabine (Dunkle 2003). Several patients also developed rashes. In vitro, mitochondrial toxicity is less than with dexelvucitabine, and the binding affinity to reverse transcriptase resistant viruses may also be less (Murakami 2004). Does the improved tolerability compromise the efficacy? At the moment, studies are being conducted with a low dose (10 mg) on patients with the M184V mutation.

Fosalvudine, produced by Heidelberg Pharma, is a NRTI, which consists of a carrier molecule coupled to an intermediate stage (= "enhanced pro-drug principle") of fluorothymidine alovudine. The active portion is only released after enzymatic cleavage in the tissue. The idea is that the usual toxicities are thus reduced. Fosalvudine is currently in Phase I/II trials.

Fozivudine has also been developed from AZT on the "enhanced pro-drug principle" by Heidelberg Pharma. In Phase I/II studies (Bogner 1997, Girard 2000), fozivudine was well tolerated, but only moderately virologically effective – after 4 weeks on the highest dose, the viral load fell by just 0.7 logs (Girard 2000). According to the company, they are currently looking for a partner to enter into Phase IIb/III studies.

KP-1461 from Koronis is an oral pro-drug from KP-1212, an NRTI that remains clearly effective in the presence of numerous NRTI resistances. The method of action (selective viral mutagenesis) distinguishes it from classical NRTIs, which induce interruption of the chain (Harris 2005). There are no cross-resistances to other NRTIs and also no mitochondrial toxicity. In Phase Ia studies, this exciting agent was well tolerated by a healthy proband. At the end of 2006, the first Phase Ib study on HIV-infected patients was completed.

MIV-210 is a precursor of the guanosine analog FLG from Medivir, which also has HBV efficacy and maintains its efficacy in vitro against diverse NRTI resistances (multiple TAMs, as well as T69-insertions) (Zhang 2002). In 2003, a collaboration between Medivir and GSK was agreed upon, although GSK have since withdrawn

again – the development of MIV-210 should go ahead nevertheless. In September 2005, a Phase IIa study was started on HIV-infected patients. Because similar (fluoridated) agents, such as lodenosine were above all hepatotoxic, one of the main foci is on tolerability.

Phosphazide (Nicavir), which is very similar to AZT, is a nucleoside analog that was developed (and is already marketed) in Russia. After 12 weeks of phosphazide monotherapy (400 mg), viral load dropped by median 0.7 logs. Since phosphazide is a prodrug of AZT, it requires an additional activation step. The D67N mutation seems to reduce efficacy (Machado 1999). further studies have shown potency in combination with ddI and nevirapine (Kravtchenko 2000), or saquinavir (Sitdykova 2003). It is hard to see the advantage over AZT – although better tolerability had been presumed, this has not been proven.

Racivir is a cytidine analog produced by Pharmasset. It is a mixture of FTC and its enantiomer. Possibly, both enantiomers have different resistance profiles so that, theoretically, the development of resistance is impeded (Hurwitz 2005). It has shown good antiviral activity in combination with d4T and efavirenz after two weeks (Herzmann 2005). A double blind, randomized study on 42 patients with the M184V mutation still showed an effect of 0.4 logs at 28 days (Cahn 2007).

Stampidine is a nucleoside analog developed by the American Parker Hughes Institute. It resembles d4T and is apparently 100 times more potent than AZT in vitro (Uckun 2002). It also has activity against HIV mutants with up to 5 TAMs (Uckun 2006). It could potentially also be used as a microbicide (D'Cruz 2004). Studies on HIV patients were announced some time ago, but data are not yet available.

Out of sight, out of mind: the following NRTIs are not being pursued:

- Adefovir dipivoxil from Gilead, hardly any activity against HIV, nephrotoxicity
- FddA (Lodenosine™) from Bioscience, 1999, severe liver/kidney damage
- dOTC from Biochem Pharma, toxicity in monkeys
- Lobucavir from BMS, carcinogenicity
- GS 7340 from Gilead, stopped at the beginning of 2004 due to changes in the eye lenses. Development may possibly be resumed ?
- DAPD (Amdoxovir) from Gilead, beginning of 2004, changes to the lenses in the eyes, possibly being developed further (?)
- SPD-756 (BCH-13520) and SPD-761
- MIV-310 (Alovudin, FLT) from Boehringer, March 2005, disappointing Phase II study.
- Dexelvucitabine (Reverset) from Incyte, 2006, pancreatitis

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New NNRTIs

As with any other drug class, me-too-drugs are not needed here. Many have already been abandoned; the road to approval is especially hard for NNRTIs. Since efavirenz in 1998, no NNRTI has made it onto the market. In view of increasing resistance there is an urgent need for new NNRTIs - not only for treatment-experienced patients but also for newly infected patients - almost 10 % of patients in Europe with an acute HIV infection have viruses with at least one NNRTI resistance mutation (Wensing 2005). The most significant problem in development is the proof of action in Phase II/III studies. The hurdle is the correct design: because the single substitution of a NNRTI into a failing regimen is not ethically permissible, the remaining ART always has to be optimized - with options that are often so effective that the effect of the new NNRTI cannot be determined. The latest example of this dilemma was capravirine, which was curtailed in 2005, following a disastrous Phase II study (Pesano 2005).

Etravirine (TMC 125), from Tibotec, is the furthest developed. As a diarylpyrimidine (DAPY) analog and a second-generation NNRTI, it works well against the wild-types, the resistant mutants, and, in particular, against the classical NNRTI mutations such as K103N. The resistance barrier is higher than that of other NNRTIs. By changing its confirmation, etravirine can bind flexibly to the reverse transcriptase (Vingerhoets 2005). Mutations of the enzyme binding site therefore have less effect on the binding and consequently on the potency (Das 2004).

In Phase I/II studies, etravirine lowered viral load by a considerable 2.0 logs in treatment-naïve patients after one week (Gruzdev 2003), and still by 0.9 logs in the presence of NNRTI mutations (Gazzard 2003, Sankatsing 2003). In C233, a Phase II trial on 199 patients with NNRTI- and PI-mutations, who have previously been treated, the viral load was significantly less than with placebo after 48 weeks (Cohen 2006). However, the overall effect decreased with increasing NNRTI resistances: with one resistance, it was 1.38; with more than two, it was 0.54 logs. In vitro, Y181C together with mutations on the codons 101, 179, 190, and 230, increase the resistance to etravirine (Vingerhoets 2006).

A further Phase II study produced the first setback: in this trial on 116 patients with NNRTI failure, etravirine was compared to a PI chosen by the investigator. The

study was stopped prematurely because etravirine was significantly inferior (Woodfall 2006). Tibotec argued that the baseline resistances in this study, conducted in Thailand and South Africa, were more prolific than expected. Etravirine, at a dose of 800 mg (2 x 200 mg tablets bid), is currently being investigated together with the PI darunavir in Phase III studies (DUET). This study will show the true value of the drug.

Etravirine has so far been well tolerated, although the typical problems of efavirenz and NNRTIs (dizziness, rash) are to be expected. In the C233 trial, 20 % of patients developed a skin rash and some had to stop etravirine. However, the rash is mild in most cases. There do not seem to be any relevant interactions, with one exception: the level of etravirine sinks significantly when combined with tipranavir (Kakuda 2006). An Expanded Access Program is being launched in February 2007.

Rilpivirine (TMC 278) first appeared in February 2005. Like etravirine, the substance is also a DAPY-NNRTI (Janssen 2005). Rilpivirine is effective against most NNRTI-resistant viruses. In three placebo-controlled dose-finding studies (up to 150 mg over 14 days) the substance was well tolerated (de Bethune 2005). A Phase IIa study on therapy-naïve patients receiving monotherapy for 7 days produced an average decrease in the viral load of 1.2 logs. In addition, there was no dose-dependent effect between 25 and 150 mg (Goebel 2005). A considerable advantage of rilpivirine is its very long half-life of 40 hours. In combination with lopinavir, the level is significantly increased, necessitating dose adjustment (Hoetelmans 2005).

In a randomized Phase IIb study, 368 therapy-naïve patients received 2 NRTIs at different doses (25, 75, 150 mg) or efavirenz (Pozniak 2007). Only the rilpirvirine doses were blinded, and not whether rilpivirine or efavirenz were given: in addition, the NRTIs were chosen by the investigator. After 48 weeks, the effect with efavirenz was comparable, but with significantly less CNS side effects and increases in lipids. Despite the rather unusual design of the trial, rilpivirine could be serious competition for efavirenz (and etravirine) in the future. Phase III studies will continue with the 75 mg dose.

GW5634 is a benzophenone NNRTI, resulting from its predecessors GW8248 and GW8635, both of which had poor oral bioavailability. GW5634 is the prodrug of GW8248, which has good efficacy in vitro against NNRTI resistant viruses (Freeman 2003, Romines 2003, Hazen 2003). However, individual resistance mutations have been detected (V106I, P236L, E138KL), indicating that GW5634 is not invincible. In 2005, the first in vivo data was published (Becker 2005). In 46 HIV patients with NNRTI mutations the viral load sank by 1.2–1.6 logs after 7 days, a respectable result for a NNRTI.

BIRL 355 BS is a second generation NNRTI from Boehringer. It also seems to have a wide efficacy against resistant viruses (Coulombe 2005). However, in the presence of the mutations Y188L and Y181C/G190A the effect is limited (Wardrop 2005). Pharmacokinetic data show that boosting with ritonavir is not necessary (Huang 2006). In Germany, a Phase IIa study is planned for 2007.

Calanolide A has been in development since 1997 by Sarawak MediChem Pharmaceuticals. This NNRTI with its natural origin – it was extracted from plants that grow in the Malayan rainforest - seems to be effective against the Y181C and K103N mutations (Quan 1999). Tolerability is good (Creagh 2001), and in HIV-infected patients, the virus load was reduced by 0.8 logs after 14 days (Shereer

2000). According to the firm, Phase II/III studies were planned for 2005 - but since then, nothing has been heard. There is doubt that it will go any further.

The following NNRTIs are no longer being developed:

- Atevirdine from Upjohn, the company prioritized development of delavirdine (the right decision?)
- DPC 083 (BMS-561390) – May 2003 - poor PK/safety data
- DPC 961 – suicide thoughts in healthy volunteers; DPC 963
- Emivirine (MKC-442, Coactinone) – quite far developed by Triangle, but too weak
- GW420867X - GSK, classical me-too drug
- GW8248 - GSK, poor bioavailability
- HBY-097 - Hoechst-Bayer, unfavorable side effects
- Loviride - Janssen Pharmaceuticals, too weak in (at that time, relatively advanced) clinical trials (CAESAR Study)
- MIV-150 - Medivir/Chiron, poor bioavailability, being developed further as a microbicide
- PNU142721 - Pharmacia & Upjohn, too similar to efavirenz (me-too)
- TMC120 (dapivirine) - Tibotec, poor oral bioavailability
- Capravirine (AG1549), probably too weak, Pfizer returned the rights to Shionogi in July 2005. The future is uncertain.

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New protease inhibitors (PIs)

In view of the increasingly large competition within this group, the demands on new PIs have become immense. Companies are losing interest in further research within this field and development in many new PIs has been terminated.

PL-100 is a PI from the Canadian firm Ambrilla Biopharma, which now cooperates with Merck. The substance is given as the pro-drug PPL-100 and is then metabolized to the active substance, which, with a high genetic barrier, is supposedly active against PI-multiresistant viruses (Dandache 2006). The PK data from healthy probands look good so far, and the long half-life of 30-37 hours makes this an interesting agent. PL-100 may even be suitable for boosting other PIs (Wu 2006).

AG-001859 is an allophenylnorstatin-containing PI from Pfizer, being investigated in Phase I studies. In vitro data shows that this substance has antiviral activity even in the presence of multiple primary and secondary PI mutations (Hammond 2004).

SM-309515 is a new PI from Sumitomo Pharmaceuticals, which should be in Phase I studies. Earlier versions failed due to the short half-life (Mimoto 2003). PK data in dogs seemed to be comparable to atazanavir. The drug remained effective against mutations such as S37N, I47V, R57K, and I84V. Conversely, sensitivity to all other PIs remained despite resistance against SM-309515. Ritonavir boosting is now being tested in humans.

SPI-256 is a PI from Sequioa Pharmaceuticals. In vitro, the efficacy against PI-resistant viral isolates is impressive (Gulnik 2006); in vivo data is not yet freely available. Studies should, however have been started in 2006.

Out of sight, out of mind – development of the following PIs has been stopped:

- DPC 684 – cardiotoxic, apparently with a narrow therapeutic range
- DPC 681 – bought by BMS, which is not interested in further development
- GS 9005 (previously GS 4338) – from Gilead
- JE-2147 (AG1776, KNI-764) – from Pfizer, (nothing new since 1999)
- KNI-272 (Kynostatin), poor PK data
- Mozenavir (DMP-450) – development stopped by Gilead in 2002 as there were no advantages to other PIs
- RO033-4649 – from Roche, probably too similar to saquinavir
- SC-52151 and SC-55389A – poor bioavailability
- TMC 126 – Tibotec is concentrating on TMC 114 – darunavir
- Brecanavir – from GSK – stopped end of 2006 due to poor PK data

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Entry inhibitors

There are three crucial steps for entry of HIV into the CD4 cell:

1. binding of HIV via the gp120 envelope protein to the CD4 receptor ("attachment" – target of attachment inhibitors),
2. binding to co receptors (target of co-receptor antagonists) via conformational changes, and finally
3. fusion of virus and cell (target of fusion inhibitors).

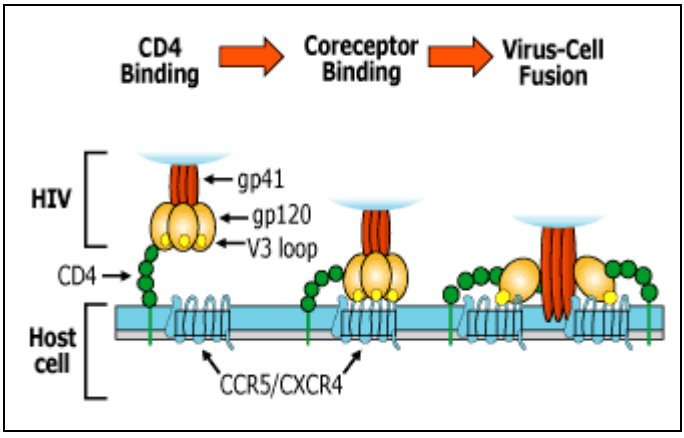

Figure 1: The three main steps of HIV entry into the cell (from: Moore JP, Doms RW. The entry of entry inhibitors: a fusion of science and medicine. PNAS 2003, 100:10598-602, adapted with permission).

Although very heterogeneous, attachment inhibitors, co-receptor antagonists and fusion inhibitors are at present grouped together as entry inhibitors. It already seems clear that fascinating new possibilities will open up with these drugs. On the other hand, a lot of the data does not go beyond basic science at this stage, and many of the drugs discussed below may eventually disappear; some have already done so.

Attachment inhibitors

The docking of the HIV glycoprotein gp120 on the CD4 receptor is the first step towards entry of HIV into the cell. Theoretically, the docking (attachment) or interaction between gp120 and CD4 can be inhibited through different mechanisms – so that the CD4 receptor as well as the binding site for gp120 can be blocked. Both are currently being investigated. The attachment inhibitors are very heterogeneous, so it is not possible to speak of a single drug class.

Since the beginning of the nineties, there have been a number of investigations into soluble CD4 molecules that prevent the attachment of HIV to the CD4 cell (Daar 1990, Schooley 1990). But, the effect seen in vitro was not observed in vivo, probably due to the very short half-life of the soluble CD4 (a few minutes). With the growing knowledge of the mechanism of HIV entry into the cell, as well as following the success of T-20 as the first entry inhibitor, the development of attachment inhibitors has been reinvigorated. However, most drugs are not far advanced in their development yet, often have problematic PK data and are therefore still in the proof-of-concept stage.

TNX-355 (previously "Hu5A8") is a monoclonal antibody that binds directly to the CD4 receptor and thereby prevents the entry of HIV. However, the mechanism of action has still not been completely explained. In contrast to other attachment inhibitors, TNX-355 does not seem to prevent binding of gp120 to CD4, but rather the conformational changes and thereby the binding of gp120 to CCR5 and CXCR4. It is currently being developed by Tanox Biosystem (Houston, Texas). It can only be administered intravenously. Following the initial early studies (Jacobsen 2004, Kuritzke 2004), 48-week data from a placebo-controlled Phase II trial are now available (Norris 2006). In this study, extensively pretreated patients received TNX-355 as an infusion every two weeks for a year in two different doses (10 or 15 mg/kg) or placebo in addition to an optimized ART regime. After 48 weeks, there was a long-lasting decrease in the viral load of approximately one log in both verum arms of the study.

With respect to these data, TNX-355 is one of the most exciting new substances in HIV medicine. There seems to be an inverse correlation between the sensitivity to TNX-355 and soluble CD4; possibly TNX-355 resistant viruses are over sensitive for soluble CD4, which does not work alone (see above) (Duensing 2006). It is still questionable whether the function of the CD4 cell is affected. So far, no negative effects on the CD4 cells have been determined, and the TNX-355 binding site on CD4 is allegedly located differently to the binding site on the natural CD4 ligand on the HLA class II molecule. The CD4 cells should be able to perform their normal functions, even when TNX-355 is occupying the HIV binding site. At least we hope this is the case.

BMS-488,043 is an early attachment inhibitor from BMS, which binds specifically and reversibly to HIV gp120 and thereby prevents attachment to the CD4 cell. Unlike TNX-355, BMS-488043 does not bind to the CD4 receptor. In early 2004, the first results in HIV-infected patients were published (Hanna 2004). On 800 mg and 1,800 mg, both twice daily, the viral load dropped after 7 days of monotherapy by a median of 0.72 or 0.96 logs, respectively. In 15/24 patients, viral load was reduced by more than one log. The substance was well tolerated in this study. However, pill burden is still high, and the formulation requires further improvement. In addition, resistances may arise rapidly as the gp120-binding site is one of the most variable positions of all. This type of attachment inhibitor may be useful in the development of microbicides (Kadow 2006).

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Co-receptor antagonists

In addition to CD4 receptors, HIV also requires so-called co-receptors to enter the target cell. The two most important ones, CXCR4 and CCR5, were discovered in the middle of the 1990s. These receptors, of which there are probably more than 200, are named after the natural chemokines that usually bind to them. Their nomenclature is derived from the amino acid sequence. For CCR5 receptors these are the "CC-chemokine" MIP and RANTES, for CXCR4-receptors it is the "CXC-chemokine" SDF-1.

HIV-variants use either the CCR5- or the CXCR4-receptors for entry into the target cell. According to their receptor tropism, HIV variants are termed R5 if they use CCR5 as a co-receptor, whereas viruses with a preference for CXCR4 are termed X4-viruses. R5 viruses are viruses that predominantly infect macrophages (previously: "M-trope" viruses); X4 viruses mainly infect T cells (previously: "T-trope" viruses). "Dual-trope" viruses can use both receptors, and in addition, there are still mixed populations of R5- and X4 viruses. In most patients, R5 viruses are found in the early stages of infection; the more virulent X4 viruses, which are probably able to infect a wider spectrum of cell types, first occur in the later stages. The change in the tropism is frequently a consequence of illness progression (Connor 1997, Scarkatti 1997). It is still not clear why this happens after several years of infection, although the tropism shift only needs a few small mutations. It is possible that R5 viruses are less flexible overall with regard to the cell type, but are therefore not recognized so well by the immune system. X4 viruses are more flexible because of their low glycosylation, but are also more immunogenic. They are neutralized better by the immune system and it is likely that they only become apparent when there is a significant immune deficiency.

In large cohorts, approximately 80 % of all viruses showed CCR5 tropism, i.e., were R5 viruses. The receptor tropism correlated with the stage of the infection. The higher the CD4 cell count and the lower the viral load, the more R5 viruses tended to be present (Moyle 2005, Brumme 2005). In contrast, X4 viruses are almost exclusively found in advanced stages of the disease. When the CD4 count is above 500 CD4 cells/µl, they are only found in 6 %; and in more than 50 % of patients at less than 25 CD4 cells/µl (Brumme 2005). They also seem to be more frequent in treatment-experienced patients (Demarest 2004). In addition, X4 viruses almost always occur in X4/R5-mixed populations; pure X4 virus populations are very rare.

CCR5- and CXCR4-antagonists can be distinguished according to their specificity. They block the respective co-receptor in a similar way to the natural chemokine, which they partially resemble chemically. The development of CCR5 antagonists (some of which have "-viroc" at the end of their names) is more advanced than for CXCR4 antagonists. This is mainly because the blockade of CCR5, at least theoretically, has less clinical consequences. Individuals with a congenital CCR5 receptor defect are healthy. With CXCR4, it is not so certain. A congenital, harmless defect in humans is not known, and in trials on animals, CXCR4 blockade had far-reaching consequences.

In the development of CCR5 antagonists, a few setbacks have had to be overcome. As usual: the more one learns about a drug class, the more questions arise. The most important are:

Are CCR5 antagonists hepatotoxic? In October 2005, the development of the CCR5 antagonist aplaviroc was stopped after a few cases of severe hepatotoxicity were reported (Steel 2005). Since then, all CCR5 antagonists have been under close observation. So far, no negative data has been received on vicriviroc, but, at the end of 2005, Pfizer reported one case of hepatic failure with subsequent liver transplant in a patient on maraviroc. However, the patient, who was from Thailand, had also received hepatotoxic isoniazid. Interim result: there is currently no evidence to suggest that all CCR5 antagonists are hepatotoxic, but vigilance is required.

Which patients would CCR5 antagonists be suitable for? In the first instance, it is only for those with R5-tropic viruses, that is the viruses that use the CCR5 co-receptor. Although past studies demonstrated that the proportion of X4-tropic viruses is around 20 % overall (Brumme 2005, Moyle 2005), it seems that particularly patients with advanced HIV infection and extensive prior therapy would consequently hardly benefit. In ACTG 5211, a Phase IIb study on vicriviroc in 368 pretreated patients, only 48 % had R5-tropic viruses, 48 % had X4/R5 combinations, and 4 % pure X4-tropic viruses (Wilkin 2006). This means that CCR5 antagonists are not suitable as a salvage strategy in many patients.

Will the expected X4 shift cause any harm? It is known that X4 viruses are associated with rapid CD4 cell decline and disease progression (Connor 2997, Scarkatti 1997). On CCR5 antagonists, a shift to X4 viruses can be expected due to the selection pressure, and this has also been observed in a few patients in some studies. Although phylogenetic studies have demonstrated that X4-tropic viruses emerging under treatment with CCR5 antagonists are probably selected from pre-existing pools and do not develop as a result of a switch in receptor usage (Westby 2006), the consequences of the X4 selection for the patient remain uncertain. One impor-

tant study was recently published, in which patients with X4/R5 mixed populations received maraviroc. After 24 weeks, the CD4 cells were increased in contrast to placebo (Mayer 2006) – progression of HIV under CCR5 antagonists seems to be rather unlikely at the moment, at least in the mid-term.

What are the other consequences of CCR5 antagonists? Patients with congenital co-receptor defects are healthy. Nevertheless, it is feared that blockade of these receptors could have negative consequences. Moreover, the action of coupling to the receptor could possibly induce an autoimmune reaction. So far, neither problem has been observed in monkey models (Peters 2005). In an analysis of completed Phase I-II studies with maraviroc, no negative effects on the immune function were detected (Ayoub 2007). In contrast, the reports of tumors (especially malignant lymphoma) in one study with vicriviroc were somewhat unsettling (Gulick 2006). There is no explanation for this at the moment, given that HIV patients with a congenital defect in the CCR5 co-receptor rarely develop lymphoma (Rabkin 1999). So far, these results have not been seen in other studies.

Does the tropism have to be tested in each patient prior to therapy? An important problem is how to test for viral tropism. Although the administration of a CCR5 antagonist does not seem to have any negative effects even in mixed X4/R5 populations (see above), a test is necessary before treatment on the grounds of costs alone, in order to individually assess whether the use of a CCR5 antagonist is appropriatet. Only a few laboratories can perform the tropism test as it is very complicated and requires living cells. Therefore, an attempt is being made to determine HIV tropism genetically, and thereby develop simpler and faster test methods. Research so far has concentrated on the V3 loop of the envelope protein gp120, because HIV binds with this region on the co-receptor (Jensen 2003, Briz 2006). However, the tropism does not seem to be determined through the sequence of the V3 loop alone – viruses with identical V3 loops can be distinguished from each other by their tropism (Huang 2006). In other words: it will take some time before a simple tropism test is ready. It has also not been clarified who is supposed to pay for the tropism test before the start of therapy with CCR5 antagonists. Health insurances will not jump to reimburse the costs, and therefore it will probably be the responsibility of the manufacturers of the CCR5 antagonists to start with.

What is known about resistances? Because the co-receptor antagonists all bind similarly to the receptor, there is a theoretical risk of classical predominant cross resistance. There are no data available from in vivo studies,although this has been debated in several in vitro studies (Westby 2006, Mosley 2006). There is also a possible a synergy between individual agents, as indicated in one recent study (Murga 2006). A combination of CCR5 antagonists seems to be at least theoretically possible. The mechanisms of the development of resistances have not yet been completely explained, and resistance testing is still problematic (Pugach 2006). However, it seems that resistance does not necessarily imply a shift in tropism from R5 to X4. Viruses can be resistant to CCR5 antagonists, but still have R5 tropism.

Maraviroc (UK 427,857, Celsentri™, Selzentry™) from Pfizer is currently the most promising CCR5 antagonist. In a double blind randomized study, in which 63 patients with R5-trope viruses received different doses of maraviroc, the median drop in virus load was 1.6 logs after 10-15 days on maraviroc 2 x 100 mg/day (Fätkenheuer 2005).

Three large Phase II/III trials on R5 viruses are currently running on therapy-naïve patients (1,026 studies) as well as on pre-treated patients with class 3 resistance (MOTIVATE-1 and -2). In the Maraviroc arms of the MOTIVATE trials, the virus load was one log less than on placebo after 24 weeks (each with optimized concomitant antiretroviral therapy). In the Maraviroc arms with twice daily dosing, 45% of the patients achieved a viral load of less than 50 copies/ml versus 23% on placebo (Nelson 2007, Lalezari 2007). Of the patients who had no active substance in the background therapy (genotypical resistance testing), 41% reached a viral load of less than 400 copies/ml versus 6% on placebo (FDA Briefing Document Maraviroc).

What is the anti-viral effect on non-R5 viruses? In a double blind, randomized, Phase II pilot study on 113 pre-treated patients with X4-trope viruses, as expected, there was no visible significant difference in the reduction of viral load. Indeed, surprisingly, the CD4-cell count increased markedly (Mayer 2006).

In the 1026 studies, the 917 therapy-naïve patients who received treatment with AZT + 3TC, were also given efavirenz, Maraviroc 300 mg twice daily, or Maraviroc 300 mg once daily. However, at the beginning of 2006, the once-daily arm of Maraviroc was prematurely terminated – performance was worse in comparison to the control arm with efavirenz. The Maraviroc arm with twice daily dosing is still running unchanged, and the results of the trial are expected in the middle of 2007.

The first resistance data have also been made available recently: mutations on the codons A316T and I323V in the V3-loop of the envelope protein together cause resistance to Maraviroc (Mosley 2006).

Caution has to be taken with interactions when prescribing. Maraviroc itself does not seem to affect the level of other medications, but it is influenced as a CYP3A4 substrate by protease inhibitors (except tipranavir/r) and efavirenz. The dose of Maraviroc should be halved when given together with a protease inhibitor, tipranavir excluded, and doubled when given together with efavirenz if no additional PI is used concomitantly (Abel 2005, Abel 2006).

So far, the tolerability in the above studies has been outstanding: comparable to placebo. The only specific side effect is obviously an orthostatic hypotonia, which is however rare with the usual doses.

Maraviroc is therefore an interesting substance for patients with resistant R5-viruses, and it may also help to save HAART toxicity. The data on therapy-naïve patients are excitedly awaited. The Expanded-Access-Program for more than 30 countries started in May 2007 and the license is expected this year.

Vicriviroc (SCH-D, **or 417690)** is a CCR5 antagonist from Schering-Plough with oral bioavailability. Its binding affinity for the CCR5 co-receptor is greater than that of its predecessor SCH-C (Stritzki 2005). Vicriviroc is already in Phase II studies. In the Phase I studies, the highest dose of 50 mg daily induced an average drop in the viral load of 1.62 logs (Schürmann 2004). The substance has been well tolerated. Arrhythmias (QT elongation), such as those on SCH-C, were not observed (Sansone 2005).

Data from a Phase II study on therapy-naïve patients has shed doubt on the long-term effects of vicriviroc (Greaves 2006). Vicriviroc was compared in various doses to efavirenz (all 91 patients also received AZT and 3TC), but after an average ob-

servation period of 32 weeks, the trial was prematurely ended, because therapy failure occurred more frequently in vicriviroc patients (> 50 copies/ml in 57 % on 25 mg, 45 % on 50 mg, 22 % on 75 mg) than in efavirenz patients.

The observation that the rate of therapy failure at the higher doses was relatively low, provides hope that the problem with vicriviroc is dose dependent. The ACTG 5211 trial on treatment-experienced patients seems to support this hypothesis (Gulick 2006). After 24 weeks, on 5, 10 and 15 mg vicriviroc – boosted each time with 100 mg ritonavir – there was a significant drop in the viral load of at least one log in comparison to placebo. Of course, in the light of these data, it would appear that vicriviroc needs to be boosted with ritonavir. However, it was worrying that 4 out of 118 patients developed a malignant lymphoma – an unusual proportion, even in this advanced patient group. Since then, no new cases have arisen, so that vicriviroc development is progressing forward.

TAK-652 is a CCR5 antagonist from the Japanese company Takeda. It has good oral bioavailability (Baba 2005) and shows synergistic effects with T-20 in vitro (Tremblay 2005). Laboratory data also show that for complete resistance there have to be several mutations in the V3 region (and in the *env* gene) at the same time. The tropism does not appear to change with the mutations (Baba 2006).

INCB9471 is also an orally available CCR5 antagonist from Incyte. Phase I trials on healthy subjects were started in 2006. The data from these are not yet available, and the first studies on HIV patients were planned for the end of 2006.

Pro-140 is a CCR5 antagonist from Progenics, which acts as a monoclonal antibody (Trkola 2001). It is therefore not a chemokine derivative like maraviroc or vicriviroc, and appears to even have a synergistic reaction with these agents (Murga 2006). Pro-140 has to be infused. In animal studies (SCID mouse model), single doses of the drug achieved significant and dose-dependent reductions in viral load without evidence of rebound under treatment (Franti 2002). The normal function of CCR5 receptors is apparently not disturbed, at least not at the doses that are required for inhibition of HIV replication (Gardner 2003). In summer 2005, the first clinical data were published – 20 healthy volunteers tolerated the single intravenous dose well, and dose-dependent concentrations were measured (Olson 2005). The long-lasting effect of pro-140 was surprising. The CCR5 receptors were blocked for more than 60 days in some cases. Despite good tolerability, the firm decided to observe the probands for longer than was planned (Olson 2006). In December 2006, one study on 39 HIV patients with single intravenous doses of 0.5, 2.0 or 5.0 mg/kg was completed – the results are expected soon.

CCR5mAb004 from Human Genome Sciences is also a monoclonal antibody, which is currently in Phase I studies. The resistance barrier was very high in vitro, (Giguel 2006).

Aprepitant (Emend™) is a neurokine-1 receptor antagonist, which is licensed as an anti-emetic for highly emetic chemotherapy. The substance clearly has an effect on R5-trope viruses via the down-regulation of CCR5 receptors. The initial laboratory data have shown relatively impressive, dose-related effects on HIV replication (Wang 2006).

AMD 11070 is a CXCR4 receptor antagonist from AnorMED. In two pilot studies (Moyle 2007, Saag 2007), the efficacy in HIV-infected patients with dual trope vi-

ruses was proven. After 10 days of monotherapy, the viral load dropped by at least one log in 4/9 or 3/6 patients respectively. However, the latest reports are that development of AMD 11070 has been prematurely stopped due to hepatotoxicity. Binding to the X4 receptor is localized somewhat differently to the predecessor agent AMD 3100, which gives us a bit of hope that there is still some room in the development for newer, more potent and hopefully less toxic CXCR4 antagonists (Wong 2007) – with AMD 11070, the start has at least been made.

KRH-3955 and KRH-3140 are two new CXCR4 antagonists that have been shown to be effective at least in mice (Tanaka 2006).

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Fusion inhibitors

(For T-20, see above)

Although the fusion inhibitor (FI) T-20 was the first entry inhibitor, there has still been little development in this field. The usually necessary subcutaneous injections are unappealing for patients and clinicians – expectations in the HAART era are high. It still needs to be demonstrated whether "small molecule" FIs, a new group of fusion inhibitors with oral bioavailability, are effective (Jiang 2004 + 2005).

T-649 is a T-1249 analog that binds to the HR2-region of gp41, like T-20. However, the binding site overlaps only partially with that of T-20 (Derdeyn 2001). Mechanisms for T-649 resistance have also been discovered (Heil 2002), and since the end of T-1249, the future of T-649 is in doubt.

FP-21399 is being developed by Lexigen (previously Fuji ImmunoPharmaceutical). A single dose shows good tolerability, with the most frequent side effects being discoloration of the skin. The initial viral load data were not convincing – only 2 out of 13 HIV patients had a decrease in viral load of at least 1 log after 4 weeks (Dezube 2000). Since then, not much has been heard and further development is in doubt.

TRI-999 and **TRI-1144** are two new second generation FIs, that were developed by Trimers in cooperation with Roche (Delmedico 2006). According to studies on monkeys, the potency and pharmacokinetics of these peptides are much improved in comparison to T-20. Although administration is still by injection, it may be possible to limit this to once a week. The data from human investigations are not yet available, but TRI-1144 will probably continue.

Sifurvitide is a new FI, which is being developed in China. In monkeys it has demonstrated a long half-life in contrast to T-20, but oral administration is not possible (Dai 2005). Phase I trials are allegedly being carried out on humans.

Out of sight, out of mind: terminated entry inhibitors:

- AMD 3100 (CXCR4A), AnorMed, cardiotoxicity
- SCH-C/Ancriviroc (CCR5A), Schering-Plough, arrhythmias
- TAK-779, TAK-220 (CCR5A), Takeda, replaced with TAK-652
- Aplaviroc/GW873140/AK602 (CCR5A), GSK, hepatotoxicity
- BMS 806 (attachment inhibitor), poor pharmacokinetics
- Pro-542 (attachment inhibitor), Progenics, concentrated on Pro-140
- T-1249 (fusion inhibitor) Roche/Trimeris, little prospect of success

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Integrase inhibitors

General

The development of integrase inhibitors have been relatively slow. Suitable investigation methods to test the integrase inhibition effect were lacking, and some identified substrates were too toxic. The development first started to gather speed around 2000. At that time, the principle of strand transfer inhibition was discovered (Hazuda 2000). Since 2005, clinical studies have proceeded rapidly, and lately, following the first data from raltegravir (MK-0518, see below), integrase inhibitors became the promising new drug class in HIV medicine.

Integrase, along with reverse transcriptase and protease, is one of the three key enzymes in the HIV-1 replication cycle. This enzyme, which consists of 288 amino acids and is coded by the HIV *pol* gene, is involved in the integration of viral DNA into the host genome, and is essential for the proliferation of HIV (Nair 2002). This fact makes it an interesting starting point for antiviral drugs. A further, at least theoretical advantage: integrase is probably not present in human cells.

The integration of viral DNA takes place in at least four steps, all of which can be theoretically inhibited by different integrase inhibitors. Analogous to the entry inhibitors, one may be able to distinguish different active groups (Reviews: Pommier 2005, Lataillade 2006).

The steps are as follows:

1. Binding of the integrase inhibitor in the cytoplasm to the viral DNA: thus forming a relatively stable pre-integration complex → this step can be prevented by pyranodipyridimine as an integrase-DNA-binding inhibitor.
2. 3′-processing: in an initial catalytic step, the integrase excises a dinucleotide from either end of the viral DNA to produce 3′-hydroxyl ends within the pre-integration protein complex → this can be inhibited by processing inhibitors include styrylquinolone or di-ketoacids.

3. Strand transfer: after the changed pre-integration complex has been transferred into the nucleus of the cell through the nuclear pores, the integrase binds to the host DNA. In this way, it mediates the docking and the irreversible binding of the hydroxyl ends of viral DNA to the phosphodiesterases bridges of the host DNA → this step is inhibited by the two integrase inhibitors that are currently the furthest developed, raltegravir and elvitegravir, so-called strand transfer inhibitors (STIs).
4. Gap repair: the combination of viral DNA and host DNA is an intermediate product with gaps, which are repaired by host-cell repair enzymes. Integrase is probably not needed for this → but the repair can be inhibited by methylxanthine, for example.

As with all new classes of drugs, there are still a lot of unanswered questions about integrase inhibitors. For example, the tolerability over a few weeks is known to be good, but nothing is known about long-term toxicity. This also applies to the development of resistances: according to initial laboratory data, a cross-resistance that overlaps classes through single mutations seems to be possible. The following briefly describes some of the drugs in more detail.

Individual substances

Raltegravir (MK-0518, Isentress™) is an integrase inhibitor (or more exactly a strand-transfer inhibitor, STI) from MSD, and currently the most exciting new drug of all in the treatment of HIV. Raltegravir is a naphtyridinecarboxamide with a wide efficacy against R5- and X4 –tropic viruses. Even HIV-2 is suppressed. On monotherapy, the viral load dropped by 1.7-2.2 logs after 10 days (Markowitz 2006). The data from a Phase II study are still impressive (Grinzstein 2006): 116 patients with a long pre-treatment (median 10 years, in which approximately 30 % had no more active substances in resistance testing) received 200-600 mg raltegravir bid or placebo. After 8 weeks, 63-67 % of the patients had attained a viral load of less than 50 copies/ml, in contrast to 8 % in the placebo group - a truly exceptional result for such an intensively pre-treated patient group. This was confirmed by BNCHMRK-1 and -2, two large Phase III trials, in which 699 patients with three-class resistance received either 2 x 400 mg raltegravir daily or placebo in addition to an optimal therapy (Cooper 2007, Steigbigl 2007). After 16 weeks, 79 % (versus 43 %) reached a viral load below 400 copies/ml. Even in those patients in whom genotypic testing failed to identify a single active drug, the rate was an impressive 57 % (versus 10 %). Tolerability in these studies was excellent and comparable to the placebo arm. Similarly encouraging were the results of the double-blind, randomized Phase II study on 197 therapy-naïve patients. With a backbone of TDF+FTC, they received either efavirenz or different doses of raltegravir (Markowitz 2006). The proportion of patients under 50 copies/ml increased in the raltegravir arms more quickly than in the efavirenz arm, and was equally high in both arms after 24 weeks. The tolerability of raltegravir was very good here, too. CNS disturbances or dyslipidemia were seen less frequently than on efavirenz (Teppler 2006).

Data on the development of resistances is still limited, but there appears to be two genetic resistance strains, either through the mutation N155H or Q148K/R/H, which are located in the catalytic nucleus of the integrase (Cooper 2007). Plasma levels are significantly elevated by atazanavir (Mistry 2006), but reduced by tipranavir.

The expanded-access program was announced at the beginning of 2007.

Elvitegravir (GS 9137, earlier **JTK-303)** is an integrase inhibitor produced by Gilead, and is biochemically similar to the quinolone antibiotics (Sato 2006). Like raltegravir, elvitegravir also inhibits strand transfer. Single doses had oral bioavailability, were safe and well tolerated (Kawaguchi 2006), and in vitro, a synergy existed with other medicines (Matsuzaki 2006). In a study on 40 HIV-infected patients (therapy-naïve and pre-treated), the viral load sank by approximately 2 logs after 10 days of monotherapy (DeJesus 2006). Significant disadvantages seem to be that elvitegravir has to be boosted with 100 mg of ritonavir (Kearney 2006), but then single daily dosing is possible. The preliminary data from a Phase II study, in which 278 patients were either given three boosted doses (20, 50 and 125 mg) of elvitegravir or a new boosted PI, showed a good response (Zolopa 2007). Although the 20 mg arm had to be stopped early due to a high failure rate, more patients in the higher-dosed arms had a viral load under 50 copies/ml (approximately 40 versus 30 %) after 16 weeks. Before the data is rapidly compared with the raltegravir data, be warned that this study was constructed differently – the comparison was with an active PI and not with placebo. As with raltegravir, the tolerability was very good.

Even with elvitegravir, resistance mutations can be selected through in-vitro passages and there also seem to be two resistance pathways over T66I or E92Q (Jones 2007). Above all, E29Q seems to be responsible for higher resistance (36 times). The resistances of elvitegravir and raltegravir overlap partially, and cross-resistances that overlap classes might also be possible (Kodama 2006, Jones 2007). Hopefully clinical data will refute these suspicions.

GSK-364735 is an integrase inhibitor from GSK, which has been developed together with Shionogi. In a Phase I study, on 79 healthy probands, between 50 and 400 mg/day was well tolerated (Reddy 2007). Phase II studies are underway.

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Maturation inhibitors

Maturation inhibitors inhibit HIV replication in a late phase of the reproduction cycle, i.e., by the budding of new virions.

Bevirimat (PA-457) is a derivative of betulinic acid, which is isolated as triterpene carbonic acid from birch bark. Bevirimat (manufacturer: Panacos) inhibits replication in a very late phase of the reproduction cycle, i.e. the budding or maturation of new virions (Li 2003). Bevirimat inhibits the transition of the capsid precursor (p25) into the mature capsid protein (p24), to produce non-infectious viruses. Because of its novel method of action, bevirimat is also effective against resistant viruses. Following the publication of the first results of a small study on HIV patients at the start of 2005 (Martin 2005), the data of a Phase IIa placebo-controlled trial were published in autumn 2005, in which patients received an oral once-daily monotherapy of PA-457 for 10 days (Beatty 2005). In the highest dosage group (200 mg) a reduction in viral load of 1.03 logs was reached; in the 100 mg group it was just 0.48 logs. However, some patients had no significant reduction in the viral load. Fortunately, the drug has a long half-life, and a once daily dose will definitely

be possible (Smith 2006). Bevirimat has so far been well tolerated. Resistance has not yet been observed in humans, although in the laboratory, resistance mutations in the capsid and in the gag regions can be selected. Because these were point mutations, a low resistance barrier is suspected. Resistant mutants are therefore less capable of reproducing than the wild-type viruses (Adamson 2006). Bevirimat also works synergistically with other antiviral drugs (Kilgore 2006).

UK-201844 is a maturation inhibitor from Pfizer. It was discovered after the screening of more than one million drugs (Blair 2006). The method of action seems to lie in the interaction with gp160 processing, which leads to the production of non-infectious virus.

Maturation inhibitors are, without a doubt, an interesting class of new drugs. Whether a prototype, such as bevirimat, will make it as far as the clinic, is still unclear Phase IIb/Phase III studies are awaited.

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Immunotherapy

In addition to conventional ART, immunomodulatory treatment strategies have been investigated (Reviews: Mitsuyasu 2002, Sereti 2001). All of these therapies still lack proof of clinical benefit. Some approaches are nevertheless addressed briefly below.

Interleukin-2 (IL-2, Aldesleukin, Proleukin™) is a cytokine that is produced by activated T cells and which induces proliferation and cytokine production in T-, B- and NK cells (Review: Anaya 2005). It is licensed in Europe for the treatment of metastatic renal cell carcinoma. At the beginning of the 90s, IL-2 was already used intravenously in HIV-infected patients (Wood 1993), but it is now administered subcutaneously.

The most important effect is the increase in CD4 and CD8 cells (Kovacs 1996). Memory cells initially increase, followed by naïve T cells (Chun 1999, Carcelain 2003). The CD4 nadir is predictive for the CD4 cell increase (Markowitz 2003). The increasing CD4 cells under IL-2 probably have the same qualities as "normal" CD4 cells (Valdez 2003). The source of the CD4 cell increases is also a subject of some discussion. Some authors suspect that the increase is more due to peripheral expansion than to increased thymus output (Lu 2003), others have assigned greater importance to the thymus (Carcelain 2003). Newer studies suggest that the effect of IL-2 is above all based on a reduced T-cell turnover or cell death (Kovacz 2005, Sereti 2005, Vento 2006).

Table 3.1: Larger, randomized IL-2 studies on HIV-infected patients.

Study	n	Patients (CD4 median at baseline)	Doses of Interleukin-2 (MIU)	Main results (In each case with versus without IL-2)
ANRS 079 Levy 2001	118	PI-naïve (CD4 200-550)	2 x 5 for 5 days 10 cycles	Median CD4 increase (865 versus 240 after 74 weeks) No difference in VL
ACTG 328 Mitsuyasu 2001	174	HAART (CD4 264)	1 x 7.5 for 5 days every 8 weeks	Median CD4 increase (614 versus 396 after 84 weeks)
CPCRA 059 Abrams 2002	511	HAART (> 300 CD4)	2 x 1.5-7.5 for 5 days every 8 weeks	CD4 increase in the IL-2 arms higher by 251 at month 12, no difference in viral load
Lalezari 2002	115	HAART (< 300 CD4)	1 x 1.2 daily for 6 months	No difference in CD4, but in NK and naïve CD4
ANRS 082 Katlama 2002	72	HAART (< 200 CD4)	2 x 4.5 for 5 days every 6 weeks	Median CD4 increase (51 versus 11 after 24 weeks)
Davey 2000	82	HAART (CD4 2-500)	2 x 7.5 for 5 days every 6 weeks	Median CD4 increase (384 versus 64 after 52 weeks) VL –0.28 vs 0.09 log (p=0.03)
ACTG 248 Vogler 2004	115	ART (CD4 3-700)	1 x 1.0 daily	No significant difference

VL = viral load, MIU = Million International Units

The duration of treatment interruption cannot be lengthened if IL-2 is given beforehand (Henry 2006).

It is still not clear whether the increase in CD4 cells on IL-2 has a clinical benefit. In order to answer this question, two large randomized studies, funded for years, were designed, ESPRIT and SILCAAT. In view of the low number of clinical events neither of these studies will provide definitive answers.

ESPRIT (http://www.espritstudy.org) is a study in which around 4,000 patients with more than 300 CD4 cells/µl are being treated in addition to HAART with IL-2 or placebo (Emery 2002). After three cycles, 64 % of patients in the IL-2 arm had an increase in CD4 cells of at least 200/µl (Weiss 2003).

SILCAAT has a similar concept, but enrolled patients with 50-299 CD4 cells/µl. Patients receive a total of 6 cycles of IL-2 subcutaneously over 5 days every 8 weeks. After enrolment of 1,957 patients, the study was stopped in 2002, as it was simply too expensive for the manufacturer. However, SILCAAT is now continuing again. In the first analyses (Levy 2003), 449 patients, had a median CD4 cell increase of 123/µl after one year. This gain was greater with better CD4 cells at baseline. It seems to indicate that even IL-2 has limited effects for reconstituting the immune system once it has been destroyed.

Summary: despite SILCAAT and ESPRIT, IL-2 therapy must be viewed skeptically at the moment. In our view, there are only a few patients who should potentially be considered for therapy with IL-2. These are patients with no immunological response, whose CD4 cell counts remain low despite good viral suppression over longer periods of time (Crespo 2006). It is still not clear whether in these patients, who only rarely develop AIDS, it is simply a question of laboratory cosmetics.

Interleukin-12 stimulates T lymphocytes and NK cells to generate a Th1-type immune response. In a randomized Phase I study with 100 ng/kg 2 x/week, the drug was well tolerated but had no effect on lymphocyte subpopulations, antigen-specific immune response or viral load (Jacobson 2002). Further development is therefore uncertain. The same would appear to be true for **interleukin-10** (Angel 2000) or **interleukin-15** (Ahmad 2005). In the age of HAART, such experimental therapies have to meet ever-increasing standards.

Interleukin-7 seems to be more promising. This cytokine plays a fundamental role in T-cell homeostasis and influences amongst other things the formation and maturation of CD4 cells. In two pilot studies, 6 and 16 HIV patients received different doses injected subcutaneously (Levy 2007, Sereti 2007). In both trials, good CD4 increases were observed together with good tolerability. The IL-2-type side effects were not observed. If these results can be confirmed in large studies, interleukin-7 could become an option for those patients in whom immune reconstitution remains low despite good viral suppression

Other Immunotherapies than interleukins (listed alphabetically)

Other immunotherapies

The prototype of a therapeutic vaccination already suffered disaster years ago: Remune™, a vaccine developed by a team headed by the late Jonas Salk, is comprised of an envelope-depleted (gp120) virus which, although indeed immunogenic, does not seem to provide any clinical benefit. One trial was interrupted prematurely in May 1999. More than 2,500 patients had taken part for a mean of 89 weeks in this multinational study, which was designed to evaluate the addition of Remune™ to HAART. As well as the lack of clinical benefit advantages with respect to CD4 cell count or viral load were not shown (Kahn 2000).

Cyclosporin A (Sandimmune™) – Immune activation may lead to increased HIV replication, and an attractive treatment hypothesis has been to suppress the immune system in an attempt to slow down viral replication. Cyclosporin, which is normally used for prophylaxis of organ transplantation rejection, could be such an inactivator of the immune system (Rizzardi 2002). However, in clinical studies, cyclosporin A is disappointing: it has no effect on CD4/CD8 cells, nor on expression of activation

markers (Calabrese 2002, Lederman 2006). Cyclosporin A therefore has no future in the therapy of chronically infected HIV patients. Whether cyclosporin A might improve treatment of acute HIV infection needs to be clarified in further studies.

G-CSF and **GM-CSF** are used in HIV patients for a variety of reasons. The cytokine G-CSF (granulocyte colony stimulating factor) is available as filgastrim (Neupogen™), pegfilgastrim (Neulasta™) and lenogastrim (Granocyte™). GM-CSF (granolocyte macrophage stimulating factor) is available as sargramostim (Prokine™) or molgramostin (Leucomax™). G-CSF is licensed for treatment of prolonged neutropenia in patients with advanced HIV infection to reduce the risk of bacterial infections. Treatment with G-CSF can be particularly useful in patients on chemotherapy or myelosuppressive drugs such as gancyclovir or AZT. G-CSF significantly reduces bacterial infections in neutropenic HIV patients. In a randomized study on 258 neutropenic HIV patients with CD4 cell levels below 200/µl, the rate of severe neutropenia after 24 weeks was 2 versus 22 % in the control group (Kuritzkes 1998). The incidence of bacterial infections was reduced by 31 %, and the number of inpatient days was reduced by 45 %. There was no effect on viral load. In patients with CMV retinitis, G-CSF was also shown to have significant survival benefit (Davidson 2002).

GM-CSF achieved a slight decrease in viral load in three double-blind, randomized studies (Angel 2000, Skowron 1999, Brites 2000); however, in one study in patients with uncontrolled infection there was a slight increase (Jacobsen 2003). GM-CSF seems to prevent significant loss of CD4 cells during longer treatment interruptions (Fagard 2003). However, in view of the costs and side effects outside clinical studies such approaches cannot be recommended

Hydroxyurea (HU, Litalir™) is an old chemotherapeutic agent, which is still used today in chronic myeloproliferative illnesses. It inhibits DNA synthesis via ribonucleotide reductase and leads to an intracellular deficiency in deoxynucleoside triphosphate.

As early as 1994, the synergistic effects with ddI on HIV replication were shown (Lori 1994). In 1998, a placebo controlled Swiss study on 144 patients showed that after 12 weeks on HU, 54 % versus 28 % in the placebo arm reached a viral load below 200 copies/ml (Rutschmann 1998). HU really became fashionable with the case of the "Berlin patient" – the patient that took HU in addition to indinavir+ddI in the acute phase and later had no measurable viremia, even without HAART (Lisziewiez 1999). Was this due to hydroxyurea? Smaller studies seemed to confirm this (Hellinger 2000, Lori 1999, Rodriguez 2000), and many doctors started to prescribe HU, even to children. Some dreamed of a cheap alternative to ddI for Africa. But, the hopes rapidly disappeared. Above all, the combination with ddI+d4T proved to be problematic – the incidence of polyneuropathy increased to almost 30/100 patient years (Moore 2000). In ACTG 5025, in which HU was tested as a "stabilizer" of virologically sufficient therapy, three patients died of pancreatitis (Havlir 2001). The risk of pancreatitis seems to increase 4-fold on HU (Moore 2001). At least 3 controlled studies showed no positive effects, just toxicity (Blackenberg 2004, Stebbing 2004, Swindells 2005). It had no effect in randomized studies of primary infection – the Berlin patient could not be "reproduced" (Zala 2002).

Interferons have an antiretroviral effect (Mildvan 1996) of 0.5-1 logs on 3 mill IU daily (Haas 2000, Hatzakis 2001). Because interferons have to be injected subcuta-

neously and have side effects which are not insignificant, they are not being pursued further in HIV medicine. It is not clear whether the pegylation of interferons will change anything.

Corticosteroids have been and continue to be discussed. However, this treatment has so far not stood the test of controlled studies. In a placebo-controlled study with 0.5 mg prednisone/kg over 8 weeks, there were no effects on CD4 cells or viral load (McComsey 2001). In ACTG 349, 24 patients were treated with 40 mg prednisone daily or not in a double-blind randomized design (Wallis 2003). After 8 weeks, there was a trend towards higher levels of CD4 cells in the prednisone arm (> 40 %, p = 0.08), but there were no effects on activation markers or apoptosis. Two patients on prednisone developed necrosis of the femoral head. This study should advise caution before the use of steroids for "immunological" reasons is considered.

Murabutide is a synthetic muramyldipeptide with a variety of effects on the immune system. It can raise unspecific resistance to infection, induce anti-inflammatory cytokines and growth factors, and strengthen the anti-viral effects of cytokines such as IL-2 or interferon. In HIV patients in France, it is mainly used as an immune modulator, although with, at most, moderate effects (Bahr 2003).

Mycophenol (Cellcept™) - is an inhibitor of inosine monophosphate (IMP) dehydrogenase and is normally used for prophylaxis of acute transplant rejection as well as for some autoimmune diseases. Through the inhibition of lymphocyte proliferation and the subsequent reduction of target cells, the replication of HIV should be inhibited. Initial reports seem to demonstrate an effect on viral load at least in some patients (Margolis 2002, Press 2002). Whether this will be confirmed by randomized trials seems uncertain (Sankatsing 2004, Margolis 2006).

THC, Cannabinoids have no effect. A prospective randomized study, in which patients could either smoke marijuana or receive TCH tablets (dronabinol, Marinol™) or placebo in addition to HAART, showed no effects on lymphocyte subpopulations or lymphocyte function after three weeks (Bredt 2002). THC, which is metabolized via the cytochrome P450 system, however, had no detrimental effects on viral load or plasma levels of protease inhibitors (Abrams 2003).

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4. Therapeutic Goals

Christian Hoffmann and Fiona Mulcahy

In the daily chaos of CD4 cells, viral load, routine laboratory, genotypic and phenotypic resistance testing, tropism and HLA typing, as well as drug plasma levels, the ultimate goal of antiretroviral therapy should always be borne in mind: To prolong the patient's life, while maintaining the best possible qualityn of health and life.

This means, that it is equally important to not only prevent opportunistic infections and malignancies, but also to minimize the side effects of therapy. Ideally, antiretroviral treatment should have as little influence as possible on daily life. Even if a high CD4 cell count and a low viral load are useful therapeutic goals, the patient's condition is at least as significant as the laboratory results! Patients, too, often lose focus on what really matters. The response to the doctor's query: "How are you?" is often accompanied by a glance toward the CD4 count result on the chart: "That's what I'd like you to tell me!"

It may therefore be useful for both patient and physician to reflect during the good times upon what one realistically aims to achieve. Treatment aimed only at improving laboratory values with little emphasis on the physical and mental well being of the patient cannot be successful. The patient has to be treated, not the viral load.

Success and failure of treatment

Success and failure of treatment can be evaluated using virological, immunological or clinical criteria. Although they are often associated with each other, they should be judged separately.

The earliest indicator is **virological** success or failure. This mainly means decrease, absence of decrease, or increase in viral load. This is followed, often a little later, by **immunological** treatment success, measured through the CD4 cells, or immunological treatment failure. **Clinical** treatment failure, if it occurs, usually only becomes apparent much later – first the lab values deteriorate, then the patient! Although the incidence of opportunistic infections after only three months on HAART is approximately halved, the clinical treatment success is not noticed by asymptomatic patients (Ledergerber 1999).

Virological treatment success and failure

Virological treatment success is generally a decrease in viral load to below the level of detection of 50 copies/ml. This is based on the experience that, the more rapid and greater the decrease in viral load, the longer the therapeutic effect (Kempf 1998, Powderly 1999).

In as early as the INCAS Trial, the relative risk of treatment failure (defined here as an increase to above 5,000 copies/ml) in patients who had reached a viral load below 20 copies/ml was 20 times lower than in those who had never reached a level

under 400 copies/ml (Raboud 1998). It is not completely clear whether the data obtained from the early HAART era are still valid.

On HAART, viral load declines in two phases. An initial, very rapid decrease in the first few weeks is followed by a slower phase, in which plasma viremia declines only slowly. A decay to below the level of detection should be reached after 3-4 months; in cases of very high baseline viral load, it may even take longer. However, a viral load above the level of detection after 6 months of treatment is almost always seen as failure. The same is true if a rebound in viral load is confirmed, in which - following fast confirmation – it should be considered what can be improved in the therapy (resorption, resistance, compliance?).

Virological treatment failure can be recognized quite early – therefore, initial monitoring even after four weeks is useful not only to the patient for psychological reasons ("less viruses, more helper cells"). If the viral load after 4 weeks is not at least substantially less than 5,000 copies/ml, failure of therapy is likely later (Maggiolo 2000). Of those patients, in whom the viral load is not below 500 copies/ml after 8 weeks or at least one log lower than baseline, only 9 % will reach less than 500 copies/ml at 24 weeks (Demeter 2001). According to a new prospective study, the response at 48 weeks can be predicted as early as 7 days (Haubrich 2007) – a control so early on is not part of the routine management.

The cut-off point of 50 copies/ml as the success criterion is arbitrary. It is based on the currently available assays for measurement of viral load. Whether 60 copies/ml are worse than 30 copies/ml indicating successful treatment is as yet not proven. At these low levels, methodological inaccuracies must also be considered. A single viral load rebound ("blip") to low levels is often irrelevant (see below). However, to distinguish them, blips are from lower, but still measurable viral loads (50-400 copies/ml). Resistances are frequently detectable in these patients – in one study this was so in 43 % of cases (Nettles 2004).

A viral load "below the level of detection" of 50 copies/ml means just that – no more, no less. Even so, numerous studies indicate that replication and therefore development of resistance can continue with an undetectable virus load. 50 viral copies/ml indicate that 5 liters of blood contain 250,000 viruses; in addition, even more actively replicating viruses are present in the lymphatic organs. Theoretically, a measurable viremia, even at very low levels, may possibly translate to a higher risk of resistance in the long-term. Perhaps there is indeed a relevant difference between 100 and 10 copies/ml with regard to the risk of developing resistance. But we just don't know yet.

The most important risk factors for virological treatment failure are antiretroviral treatment (pre-existing resistances) and poor compliance (review: Deeks 2000). It has still not been proven whether the CD4-cell count at the start of therapy plays an important role. In several cohorts, no association has been found (Cozzi Lepri 2001, Phillips 2001, Le Moing 2002). See also the discussion in the chapter "When to start HAART".

Many other factors that influence the success of therapy probably remain unknown. Pharmacogenetics is a new field, which, although still in the early phases, is starting to gain importance. It investigates individual genetic factors which influence the success of therapy. Until now, most factors that have been uncovered have predicted intolerance or allergies to, for example, abacavir or nevirapine (see relevant

section). But one day, tests will be available that will help antiretroviral therapy to be individualized and the success of therapy to be improved. These will range from individual dosing to tests, which predict results – eg. the CCR5 antagonists (Review: Haas 2006).

For the time being, the good news is: morbidity and mortality may be lowered significantly even if the virological success is not complete, i.e., the viral load is not decreased below the level of detection (Mezzaroma 1999, Deeks 2000, Grabar 2000). This is important in patients who have a limited number of treatment options. In such cases, it can sometimes be more sensible to temporarily abandon viral load as a measure of success (see also chapter on "Salvage Therapy"); and to make the stabilization of the CD4 cells the top priority. Patients often remain immunologically stable for relatively long periods of time, even with insufficient viral suppression. A cohort study has shown that CD4 cells do not drop as long as the viral load remains below 10,000 copies/ml or at least 1.5 logs below the individual set point (Lederberger 2004).

However, in comparison to a few years previously, more has become possible through new drugs and classes of drugs. In the age of T-20, tipranavir, darunavir, etravirine, maraviroc and raltegravir a repeat attempt should be made to reduce the viral load to below the level of detection, even in intensively pre-treated patients.

How long does virological treatment success last?

Little is known about how long treatments remain effective. The rumor that treatment success is limited to only a few years is still widespread. It originates from the early years of HAART. However, many patients at the time were still inadequately treated or had been pretreated with mono- or dual therapy, and had thus developed extensive resistance. In such patients, the effect of treatment was often limited, as even a single point mutation was often enough to topple a whole regimen. Today, especially in therapy-naïve patients without pre-existing mutations, the risk of treatment failure is much less.

After ten years of HAART, a surprisingly high number of patients still have viral loads below the level of detection. This is particularly true for patients who were adequately treated from the start, as judged by today's standards (starting with triple therapy and/or rapid switching of several drugs). One of the few trials with a longer follow-up period studied 336 antiretroviral-naïve patients who had reached a viral load below 50 copies/ml within 24 weeks (Phillips 2001). After 3.3 years, the risk of viral rebound seemed at first glance to be relatively high at 25.3 %. More detailed analysis showed that a large proportion of the patients experiencing viral rebound had actually interrupted HAART. True virological failure was only seen in 14 patients, which corresponds to a risk of 5.2 % after 3.3 years. Most importantly, the risk of virological failure decreased significantly with time. In the Phase II M97-720 Study, in which 100 patients were originally treated with d4T+3TC+lopinavir/r, 62 % still had less than 50 copies/ml after six years in the ITT analysis, compared to 98 % in the On-Treatment-Analysis (Gulick 2004). Real virological failure was very rare. In the Merck 035 subanalysis, patients on AZT+3TC+indinavir were also followed for six years. In the last ITT analysis, 58 % were still below the level of detection, despite the fact that these patients had been pre-treated with nucleoside analogs (Gulick 2003).

These studies clearly show that, providing treatment is not interrupted, viral load may remain below the level of detection for many years, perhaps even decades. Resistances are by no means unavoidable. This has been confirmed by cohort studies, in which virological treatment failure has become significantly less in the last few years (Lohase 2005, Lampe 2006). HAART is getting better and better. In 1996, only 58 % of patients had a viral load of less than 500 copies/ml; in 2003, it was 83 % (May 2006).

"Blips" – Do they mean virological failure?

Blips are thought to be transient and, almost always, small increases in viral load, so long as the viral load before and after the blip was below the borderline value of 50 copies/ml. At least three measurements of viral load are therefore required to be able to identify a blip. Blips are a frequent phenomenon of HIV patients on HAART and are observed in 20-40 % of patients on HAART (Sungkanuparph 2005). Blips often worry both patients and clinicians: do they signal treatment failure?

Although studies indicate that this is not the case in the medium term (Havlir 2001, Moore 2002, Sklar 2002, Mira 2003, Sungkanuparph 2005), the causes of blips have, to a large extent, not been investigated. There has been no association found with compliance. (Di Mascio 2003, Miller 2004). It is possible that blips are the result of immunological mechanisms. The earlier patients are treated in the course of infection, i.e., the higher the CD4 cell count at the start of therapy, the more seldom blips seem to occur (Di Mascio 2003+2004, Sungkanuparph 2005). There does not appear to be any association with particular antiretroviral combinations – in a large cohort (Sungkanuparph 2005), the frequency of blips on NNRTIs was 34 versus 33 % on PIs, and even the size of the blips were equivalent (median 140 and 144 copies/ml respectively). In both groups, the risk of virological failure at 2 years was approximately 8 %. One important observation was that the blips did not increase the risk of treatment failure, even with NNRTIs (Martinez 2005).

At the beginning of 2005, the study team led by Bob Siciliano set out to determine the meaning of "blips". In a labor-intensive study, 10 stalwart patients who had had a viral load of less than 50 copies/ml for at least six months, had blood samples taken every 2-3 days (!) over a period of 3-4 months (Nettles 2005). The obvious result: the more you look, the more you will find. During the observation time, at least one transient increase in the viral load was measurable above 50 copies/ml, in nine of the ten patients. Each blip was moderate, with a median value of 79 copies/ml, ranging from 51 to 201 copies/ml. The blips could not be associated with either specific clinical data, low plasma levels, or resistances. This observation led the authors to believe, that blips (with low, measurable values) mainly represent biological or statistical exceptions, and are not associatedwith treatment failure. In an estimated steady state level of viral load at around 20 copies/ml, the values are distributed randomly. However, 96 % of the randomly distributed measurements were less than 200 copies/ml.

It should be noted that other factors may also be responsible for intermittent viremia. In one large, retrospective analysis, 26 % were caused by intercurrent infections (Easterbrook 2002). For example, syphilis can cause a significant increase in

viral load and reduction of CD4 cells (Buchacz 2004). Viral load can also increase temporarily after immunizations (Kolber 2002).

Summary: Based on available data, HAART should not be changed, even after repetitive blips. However, caution should be executed for higher blips (> 200-500 copies/ml). Blips are distinguishable from low, repetitive, measurable plasma viremias, in that the risk of resistance is actually increased (Gunthard 1998, Nettlers 2004). Although there does not seem to be a relationship to compliance or drug levels, blips should raise the opportunity to talk to the patient about the subject of adherence. Compliance cannot be discussed often enough. Does the patient take his or her drugs regularly, or are doses occasionally missed? Are the dosing directions (on an empty stomach or with a meal) followed correctly?

Everything should be considered before changing a therapy. Each new therapy can cause new problems. Therefore, every suspected increase in the viral load should be controlled within a short interval, before treatment is prematurely changed.

Immunological treatment failure and success

Immunological treatment success is an increase in the CD4 cells - it is not defined more precisely. Depending on the study, increases *by* 50, 100 or 200 CD4 cells/µl or increases *to* above 200 or 500 CD4 cells/µl are defined as success. Failure is usually described as the absence of an increase or as a decrease in the CD4 count in patients receiving HAART.

It is difficult to individually predict the immunological success of therapy for patients on HAART, as it varies significantly from one person to another. As with the decrease in viral load, the increase in CD4 count also occurs in two phases. After a first, usually rapid increase over the first three to four months, further increases are considerably less pronounced. In a prospective study involving some 1,000 patients, the CD4-cell count increased during the first three months by a median of 21.2 CD4 cells/µl per month; in the following months the increase was only 5.5 CD4 cells/µl (Le Moing 2002). It is still under debate whether the immune system is restored continuously after a long period of viral suppression or whether a plateau is reached after three to four years (Smith 2004, Viard 2004). In our experience, both occurs: patients with CD4 cells that still increase only slowly after 5 or 6 years, and patients whose CD4 cells remain at relatively low level after just a relatively short period of time. The immunological success is not predictable in individual cases.

However, the lower the CD4 cell count at baseline, the less likely they are to normalize completely (Valdez 2002, Kaufmann 2003+2005). The immune system often does not recover completely. In the Swiss Cohort, only 39 % of 2,235 patients who had begun HAART in 1996-97 reached a CD4-cell count above 500/µl (Kaufmann 2003, see also below). The introduction of treatment within the first 3-6 months possibly provides certain clues as to how well the immune system will be restored (Kaufmann 2005).

Immunological treatment success is not necessarily linked to maximal viral suppression; even partial suppression can result in improved CD4-cell count (Kaufmann 1998, Mezzaroma 1999, Ledergerber 2004). The initial level of viral load is also not significant; what seems to be decisive is that the viral load remains lower than before treatment (Deeks 2002, Ledergerber 2004). In view of the many factors that occur, which are able to influence the success of therapy as well as the individ-

ual regeneration capacity (independent of HAART), it no longer makes sense to depend on the CD4-cell count as the deciding criterion for the success of HAART. Virological success is more appropriate for judging the efficacy of specific regimens.

Discordant response

A discordant response occurs when the therapeutic goals - clinical, immunological and virological - cannot all be achieved (see Table 4.1 for frequencies). So, the treatment may be virologically successful, with no visible immunological response; with the CD4 cells remaining on the low side despite undetectable viral load (Piketty 1998, Renaud 1999, Gabrar 2000, Piketty 2001). In contrast, a HAART regimen can bring about a considerable increase in CD4 cells, even when the viral load is detectable. This is sometimes seen in children (see Pediatric chapter).

Table 4.1: Treatment success in prospective cohort studies

Response to HAART	Piketty 2001 n = 150	Grabar 2000 n = 2,236	Moore 2005 n = 1,527
Virological and immunological	60 %	48 %	56 %
Discordant: only immunological	19 %	19 %	12 %
Discordant: only virological	9 %	17 %	15 %
No treatment response	12 %	16 %	17 %

Definition of immunological success: increase in CD4 cells > 100/µl after 30 months (Piketty 2001) or > 50/µl after 6 months (Grabar 2000) or at least once > 50/µl (Moore 2005)

Definition of virological success: continually > 1 log less than baseline or < 500 copies/ ml (Piketty 2001) or < 1,000 (Grabar 2000) or < 500 copies/ml (Moore 2005)

The reasons for the poor immunological treatment success despite good viral suppression are heterogeneous (Review: Aiuti 2006).

Low CD4 cells at baseline as well as low viral load before the start of therapy are just two of many factors (Florence 2003, Kaufmann 2005, Moore 2005, Wolbers 2007). Age also plays an important role: in older patients, immunological response is often only moderate in comparison to virological response. Several studies demonstrated that the probability of not achieving a rise in the CD4-cell count increases with patient age and with progressive decrease in thymus size as detected by computed tomography (Goetz 2001, Marimoutou 2001, Piketty 2001, Teixera 2001, Viard 2001, Wolbers 2007). Patients who are intravenous drug users also have relatively poor increases in CD4 cells (Dragstedt 2004). In the Swiss cohort, the CD4 cells increased more in women than in men (Wolbers 2007).

Other causes for a lack of immunological response may be immuno- or myelosuppressive concomitant therapies. We have seen patients, who have had a suppressed viral load below 50 CD4 cells/µl for years, who only experience significant immunological reconstitution when gancyclovir, cotrimoxazole or azathioprine are withdrawn. Concurrent illnesses such as various autoimmune diseases (Crohn's disease, Lupus erythmatosis) or liver cirrhosis can also have negative effects on the immune response.

There is also evidence that certain antiretroviral drugs have negative effects on immune reconstitution. On a combination of TDF+ddI (plus nevirapine) significant decreases in CD4 cells occur (Negredo 2004). The reason may lie in an unfavorable interaction between ddI and tenofovir. In two other studies, the CD4 cells increased significantly more on ABC+3TC, as well as on TDF+FTC, than on AZT+3TC, despite comparable virological success. However, it remains to be shown whether this is really a problem of myelotoxicity of AZT or a pure coincidence (DeJesus 2004, Pozniak 2006).

Practical considerations in dealing with viral load and CD4 cells

- Viral load is the most important parameter in treatment monitoring.
- If possible, use only one type of assay (in the same lab) – bear in mind that there is considerable methodological variability (up to half a log)!
- Virological success should be monitored one month after initiation or modification of HAART.
- Viral load should be below 50 copies/ml after 3-4 months (with high initial viral load, after 6 months at the latest) – if it is not, look for a cause!
- The greater the decrease in viral load, the more durable the response to treatment.
- Transient, low-level increases in viral load (blips) are usually insignificant – but VL should be monitored at short intervals (e.g. 2-4 weeks after such blips).
- The older the patient, the greater the risk of a discordant response (well-suppressed viral load with no significant increase in CD4 count).
- In contrast to viral load, increase in CD4 cells, i.e. immunological success, is difficult to influence.
- CD4 cells are probably better predictors of the individual risk of AIDS.
- Once CD4 count is good, it requires less frequent monitoring. Remember that with higher CD4 counts, values may vary considerably from one measurement to the next (which may mislead the patient to either a false sense of euphoria or unnecessary concern).

Clinical treatment success and failure

Clinical success is almost always evaluated on the reduction of clinical endpoints (AIDS-defining illnesses, death), although the improvement on HAART in a patient with considerable constitutional symptoms should also be seen as clinical success.

Clinical treatment success is not always easy to measure and is dependent on both virological and immunological treatment success.

Table 4.2: Morbidity and Mortality, based on virological or immunological treatment success. Definition see Table 4.1. 95 % confidence intervals are shown in parentheses

	Grabar 2000	Piketty 2001	Moore 2005
CD4 cells at baseline*	150	73	180-250
Treatment success:			
Complete = Reference	1	1	1
Only immunological, RR	1.6 (1.0-2.5)	6.5 (1.2-35.8)	1.9 (1.1-3.0)
Only virological, RR	2.0 (1.3-3.1)	9.7 (1.6-58.4)	2.5 (1.5-4.0)
None, RR	3.4 (2.3-5.0)	51.0 (11.3-229.8)	3.5 (2.3-5.3)

RR = relative risk *median.

Clinical endpoint: progression/death (Grabar 2000, Piketty 2001), death (Moore 2005).

In the Swiss cohort, out of those with a constantly undetectable viral load, the proportion of patients developing AIDS or dying was 6.6 % after 30 months. In contrast, this proportion was 9.0 % in patients with viral rebound and even 20.1 % if the viral load was never suppressed to undetectable levels (Ledergerber 1999). The importance of sustained virological treatment success for clinical success has also been reported by other cohorts (Salzberger 1999, Thiebaud 2000).

Clinical failure is usually defined as the development of an AIDS-associated condition or even death. Clinical failure, arising from a failing HAART regimen, has to be distinguished from clinical failure that can ascribed to simply starting HAART too late. This is particularly true, for example in immune reconstitution inflammatory syndrome (IRIS), where pre-existing, subclinical infections manifest themselves during the first weeks following initiation of antiretroviral therapy (see "AIDS" chapter). An OI in the presence of increasing CD4 cells does not necessarily indicate failure of HAART, but rather, simply put, that the immune system starts working again.

On the other hand, if a patient develops serious side effects or even dies, this should clearly be regarded as treatment failure. Luckily, this is rare. It should be noted that there might also be other causes. Many severe, life-threatening events that affect HIV infected patients on HAART today are associated neither with HAART nor AIDS (Reisler 2003).

What can be achieved?

Every HIV clinician sees the remarkable strides made possible by HAART reflected in his or her own patients (see example below). In many areas, the incidence of AIDS has been reduced to less than a tenth (Mocroft 2000). Some illnesses that occur only with severe immunodeficiencies are rarely seen today. CMV retinitis or MAC disease have become unusual.

Table 4.3: Patient case (female, 41 years) illustrating the success of HAART*

		CD4$^+$ T-cells	Viral load
Feb 95	AZT+ddC	23 (4 %)	NA
Nov 96	AIDS: Toxoplasmosis, MAC, Candida esophagitis	12 (1 %)	815,000
Feb 97	d4T+3TC+SQV	35 (8 %)	500
June 97	Treatment interruption due to polyneuropathy		
July 97	AZT+3TC+IDV	17 (4 %)	141,000
Mar 98		147 (22 %)	< 50
Mar 99	AZT+3TC+IDV/r+NVP	558 (24 %)	100
Mar 00		942 (31 %)	< 50
Apr 05	AZT+3TC+LPV/r+NVP	744 (30 %)	130
Jan 07		712 (38 %)	< 50

* Excellent immune reconstitution despite initial severe immunodeficiency and several AIDS-defining illnesses. All prophylaxis (MAC, Toxoplasmosis, PCP) has now been discontinued.

Today, AIDS cases occur mainly in patients who are not being treated with antiretroviral therapy – usually because they are unaware of their infection or do not want to acknowledge it. These so-called "late presenters" now make up a large proportion of AIDS cases. In patients who are continuously followed in specialized centers, AIDS has become a rare occurrence.

The mortality rate has continued to decline over time (Mocroft 2002).

In an investigation on 3,990 HIV patients in Denmark, compared with 380,000 individuals from the non-infected population, the average increase in life expectancy increased in a 25-year old HIV patient from 19.9 years between 1995-1999 to 32.5 years between 2000-2005; this increased to 38.9 years when patients with HCV were excluded, which was fairly close to the 51.1 years of the normal population (Lohse 2007).

Data from prospective, controlled studies on this dramatic change is still limited, however. So far, there have been few randomized trials with clinical endpoints (Hammer 1997, Cameron 1998, Stellbrink 2000).

The success of these studies was comparatively unassuming from a design point of view. In the ABT-247 trial, in which 1,090 clinically advanced patients received ritonavir liquid formulation or placebo in addition to their ongoing treatment, the probability of AIDS and death in the ritonavir arm after 29 weeks was 21.9 % and 37.5 % in the placebo arm (Cameron 1998).

Because studies of mono- or dual therapy are no longer ethically justifiable and the number of clinical endpoints that occur is now extremely low, controlled prospective trials, in which the clinical superiority of the treatment should be proven, simply last too long these days. Unrealistically large study populations would also now be required given the extremely low probability of progression, and therefore, such investigations will only rarely be undertaken in the future (Raffi 2001). One of the few to have underpinned the value of HAART on the basis of clinical endpoints is the SMART study (see chapter on treatment interruptions).

Due to the lack of randomized studies, data from the large cohorts, such as Euro-

SIDA, the Swiss cohort, and the American HOPS cohort, have to be relied upon to document the decline in AIDS mortality (see Table 4.4).

Table 4.4: Decline in morbidity and mortality in large cohorts

	Where? (n)	Patients (Period)	Mortality (/100 PY)	Morbidity (/100 PY)
Palella 1998	USA (1255)	< 100 $CD4^+$ T-cells/µl (1/94-6/97)	29.4 → 8.8	21.9 → 3.7*
Ledergerber 1999	Switzerland (2410)	6 months *before* versus 3 months *after* HAART (9/95-12/97)	NA	15.1 → 7.7
Mocroft 2000	Europe (7331)	All (94-98)	NA	30.7 → 2.5
Mocroft 2002	Europe (8556)	All (94-01)	15.6 → 2.7	NA
D'Arminio 2005	Worldwide (12,574)	The first 3 months *after* versus 3 years *after* HAART	NA	12.9 → 1.3

* MAC, PCP, CMV. Mortality/Morbidity each per 100 py = patient years

In the Swiss cohort, the effect of HAART increases over time – after more than two years on HAART, the risk of progression was only 4 % of the risk without HAART (Sterne 2005). However, a completely new analysis of several large cohorts (with over 20,000 patients) showed that in the recent years, the rates of AIDS and mortality have not decreased further – in 1997 as well as in 2003, the risk of AIDS was around 6 %. HAART is possibly being started too late in many cases. In the last few years, every second patient had just 200 CD4 cells at the start of treatment (May 2006).

The effect of HAART on the incidence of individual AIDS diseases is probably different: the most obvious is the decline of viral OIs, although this is not so pronounced for fungal OIs (D'Arminio 2005).

The effect of HAART is equally as apparent on the clinical course as it is on the incidence. Illnesses such as cryptosporidiosis or PML can be cured, while Kaposi's sarcoma can resolve completely without specific therapy. Prophylaxis of pneumocystis pneumonia, toxoplasmic encephalitis, CMV, or MAC infection can usually be safely withdrawn. These effects are discussed in more detail in the corresponding chapters.

Treatment aim: Cure

In a chapter on the aims of therapy, the possibility of a cure also has to be discussed. Whoever speaks of cure will eventually achieve it. Following the success of antiretroviral therapies in the last 20 years, which help most patients to control infection for decades, many now believe that the next 20 years should concentrate on cure as the main aim of therapy.

What is cure?

One important question is whether complete eradication is necessary for a cure. Does the last virus actually have to be removed from the body? Cure could also mean that the body is able to control the infection without the help of medication – analogous to other infections, such as herpes simplex or varicella zoster, in which only small amounts of the virus persist. A very few HIV patients, the so-called "elite controllers" have already succeeded in this. These patients, a few of which are found in every large centre, have normal CD4 cells for many years, and even more impressively, a viral load that remains below the level of detection of normal assays without antiretroviral therapy (Table 4.5). Only when the lymph nodes are examined with ultrasensitive methods, can the virus be detected in comparatively minute amounts. What makes the HIV-specific immune response of these patients so effective; what makes the virus in these people so "unfit"; which genetic changes are responsible? These questions are currently occupying many leading working groups worldwide.

Table 4.5: Example of an "elite controller" from our clinic

Date	(HA)ART	CD4 cells	Viral load
04/03	Acute HIV infection (Western blot: 5 bands)	203 (8 %)	> 1 Mill
04/03	Start with ART (AZT+3TC+IDV/r)	412 (12 %)	> 1 Mill
06/03		702 (51 %)	2,000
01/04	ART stopped after 8 months	838 (52 %)	< 50
06/04		467 (46 %)	< 25
05/05		1,288 (51 %)	44
01/07	Three years without antiviral therapy	841 (44 %)	< 25

Comment: It is unclear whether HAART had an effect during the acute infection. Such courses are also seen without treatment. In some cases, different VL tests were used. Notable are the initial very low and later very high percentages of CD4 cells.

The problem with latent reservoirs

At this point in time, eradication of HIV in the sense of a cure is still unrealistic. The main problem lies in the pool of latently HIV-infected cells, which probably comprise a lifelong reservoir (review: Saksena 2003). Even after years of sufficient viral suppression to below 20-50 copies/ml, cellular viral transcription still takes place in these cells (Finzi 1999, Furtado 1999, Zhang 1999, Sharkey 2000). This is particularly true for blood cells, but also applies to lymph nodes and sperm (Lafeuillade 2001, Nunnari 2002). Replication probably also takes place in the cells of the gastrointestinal tract long after there is no trace left in the blood.

How long does it take for the last latently infected cells to be removed? In a study on 62 patients, whose viral load had been successfully suppressed on HAART for seven years, a half-life of 44.2 months was calculated for the latently infected reservoir (Siciliano 2003). The calculated time to eradication of these reservoirs was 73.4 years. Even in a highly selected group of patients, without even a single viral blip measured during a minimum of three years of stable HAART, and with an

overall trend for a slightly more rapid decrease in infected cells, the time to eradication was 51.2 years.

Latently infected reservoirs consist of very heterogeneous cell populations, the stability of which is probably even independent of residual viral replication. Therefore, even complete inhibition of viral replication would probably be insufficient to eradicate HIV (Strain 2004).

Different methods have been used in the last few years to attempt to flush out these latent reservoirs (IL-2, hydroxyurea or OKT), but all have failed (Kulkosky 2002, Pomerantz 2002). In summer 2005, a pilot study on valproic acid, an antiepileptic treatment used worldwide, caused a stir as they discovered that valproic acid, an inhibitor of histon deacetylase-1 (HDAC1), caused a release of HIV from dormant T cells (Lehrman 2005). In three out of four HIV patients, the number of infected dormant T cells decreased significantly, and the half-life sank to 2-3 months –much less in comparison to other studies, which have reported 44.2 months under classical HAART (Siciliano 2003).

Summary: based on the currently available medication, eradication is still not possible. Washing out the reservoirs, or simply eliminating all infected memory cells is either unsuccessful, too toxic or much too dangerous. It remains to be seen whether valproic acid or other immune therapies given in addition to HAART, will provide a perspective. Due to the complexity of the immune system, which is only gradually beginning to be understood, a solution seems to be a long way off.

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5. When to start HAART

Christian Hoffmann and Fiona Mulcahy

"It's the most important question in HIV therapy" (A. Fauci)

The indication for antiretroviral therapy is based on the clinical assessment, CD4 cell count, and viral load. These factors determine whether therapy should be started or if it can still be deferred. At first glance, it appears straightforward: the lower the CD4 cell count and the higher the viral load, the higher the risk of AIDS (Mellors 1997, Lyles 2000), and the more urgent the indication for treatment.

But, how high is the individual risk really? The following table lists the (selected) risks of developing AIDS within six months, as identified in 3,326 patients from the pre-HAART era (Phillips 2004). The range of individual risk of progression varies widely – from 0 to almost 50 %. For a 55-year-old patient with a CD4 cell count of 50/µl and a viral load of 300,000 copies/ml, the risk of progressing to AIDS within the next 6 months was 44.8 %; for a 25-year-old patient with 500 CD4 cells/µl and a viral load of 3,000 copies/ml, the risk was only 0.3 %. This demonstrates the importance of these parameters for estimating the individual risk and indication for treatment (see Table 5.1). Surprisingly, the age of the patients, which according to these data significantly increases the risk of progression, has so far not been included in any of the guidelines.

Table 5.1: Predicted six-month percentage risk of developing AIDS, according to age, viral load and CD4 cell count (data from the pre-HAART era)

	100 CD4/µl	200 CD4/µl	350 CD4/µl
35 years			
Viral load 10,000	5.3	2.0	1.1
Viral load 100,000	10.6	4.1	2.3
55 years			
Viral load 10,000	10.7	4.6	1.8
Viral load 100,000	20.5	9.2	3.6

From: Phillips A, CASCADE Collaboration. AIDS 2004, 18:51-8. Link: http://amedeo.com/lit.php?id=15090829

The best time for initiation of therapy remains the subject of controversial debate. The risk of AIDS must be weighed against the risks of viral resistance and long-term toxicity. These risks and the realization that eradication cannot be achieved at present have led to the relaxation of treatmentb guidelines in recent years. In a large cohort of over 20,000 patients, the median CD4-cell count at the start of therapy has hovered at around 200/µl for the last few years, after being at 270/µl in 1998 (May 2006). The initial "hit hard and early" dogma of 1996, which recommended therapy from the earliest stages of infection, has been discarded. Instead, it has been replaced by the motto "hit hard but only when necessary". It is now no longer common practice to treat every patient with a viral load above 10,000 copies/ml, inde-

pendent of the CD4 cell count, as was still recommended in the 1997 US guidelines (Carpenter 1997). Lately, however, there has been a trend in the opposite direction: the pendulum is swinging back. In view of the constantly improving therapy, there is increasing pressure to start it earlier (Holmberg 2004, Schechter 2004). In addition, although the risk of AIDS is low with good CD4-cell counts, it is not nil. The "low" individual risk of AIDS of 1 to 2 % per year just a few years ago, has become relevant in these times when patients are treated for decades.

International treatment guidelines agree that all symptomatic patients and patients with less than 200 CD4 cells/µl have to be treated. The situation is less clear for asymptomatic patients with more than 200 CD4 cells/µl. Because of the lack of randomized trials, all the recommendations are based on cohort studies, meta-analyses, and the evaluation of large databanks. However, these data present problems, because they often exclude essential aspects such as compliance or possibly treatment experience, and consist of very heterogeneous patient populations. Consequently, they can be interpreted in different ways. Table 5.2 shows the latest recommendations from the USA, Great Britain and Germany on the start of treatment.

Table 5.2: Recommendations from various guidelines on when to initiate therapy

Clinical	CD4 cells/µl	Initiation of HAART is...
CDC B+C	All values	"recommended" (DHHS, GA, GB)
CDC A	< 200	"recommended" (DHHS, GA, GB)
CDC A	200-350	"should be offered" (DHSS)
		"generally advisable, independent of VL" (GA)
		"recommended for most patients, but should depend on individual factors"* (GB)
CDC A	> 350	"most experts recommend deferring with a VL > 100,000, some clinicians will treat; defer with a VL < 100,000" (DHHS)
		up to 500 CD4 cells "recommended by some experts with a VL 50,000 –100,000; most were hesitant to treat with a VL of 50,000", over 500 CD4 cells "generally avoid" (GA)
		"to be deferred" (GB)

*Individual factors: symptoms, patient wishes, expected adherence, potential toxicity, decline in CD4 cells, level of viral load and age. VL = viral load

DHHS: United States Centers for Disease Control and Prevention. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents, October 10, 2006. Link: http://aidsinfo.nih.gov/Guidelines

GA: German-Austrian Guidelines on Antiretroviral Therapy of HIV Infection (June 2005). http://www.daignet.de/edia/PDF_D_A_antiretroviral_06_05.pdf

GB: British HIV Association (BHIVA) guidelines for the treatment of HIV-infected adults with antiretroviral therapy, 2005. http://www.bhiva.org/guidelines/2005/BHIVA-guidelines/index.html

Guidelines merely provide points of reference and are not set in stone. Therapy may be started earlier; but in individual cases, can (or even should) be deferred. The following chapter discusses the relevant studies on initiation of therapy in chronic HIV infection. The special case of acute HIV infection is referred to in the corresponding chapter.

Experiences from practice

Even if the indication for HAART seems obvious, it should be clarified whether the patient is indeed ready to start treatment. The problem is not the initiation of HAART, but the continuity. The decision to initiate treatment is often made prematurely. It is usually unwise to prescribe antiretroviral medication to a patient in the first consultation. One should first attain an overall picture of the patient, and try to get to know something about his lifestyle and motives – why he has come to see a doctor, and what he expects.

In some cases, patients put themselves under pressure unnecessarily, or let others do so. A single lower CD4 count, a prolonged case of flu seeming to indicate a weakened immune system ("I never had anything like that before"), springtime lethargy, new study results, a promising new drug in the newspaper ("I've heard a lot about T-20"), a partner who has started therapy – none of these are therapeutic indications. It is often particularly difficult to inform people from other cultures that not every person with an HIV infection needs immediate therapy.

On the other hand, a patient's desire for one particular therapy also has to be respected. HAART should not be withheld from a patient that wishes to start antiretroviral therapy after extensive discussions, although the levels would still justify waiting. For many patients, treatment can be a psychological support. Not everyone can sleep peacefully in the knowledge that every day a few hundred million viruses are being produced and a huge number of helper cells destroyed within their body.

As a rule, as much time as is needed should be taken to make the decision to start therapy. This is usually possible. A well-informed patient complies better with treatment! We recommend that patients come for several consultations to prepare them emotionally for treatment. There are two exceptions: acute HIV infection, and severe immunodeficiency. However, even in the presence of most AIDS-defining conditions, the acute disease should often be treated first before initiating ART, as the potential for complications with PCP, toxoplasmosis or CMV therapies unnecessarily jeopardize treatment options. Not a single study to date has convincingly shown a benefit of commencing HAART simultaneously with OI therapy (however, there is also no study to show that starting HAART early causes harm).

If a vacation is planned, it is better to delay therapy so that treatment response and side effects can be adequately monitored. On the other hand, patients may sometimes find one reason after another (stress at work, exams, change of job, etc.) to delay initiation of treatment. Many patients are afraid of AIDS, but often just as afraid of HAART ("the pills are the beginning of the end!"). They may have irrational expectations of HAART and its consequences – starting therapy does not mean that one will be subjected to daily infusions and no longer able to work!

Therapy should be explained to every patient from the outset, even when treatment is still not necessary. It is also useful early on to define with patients the individual threshold values for the commencement of therapy, so that therapy is started only when these levels are reached. In our experience, patients are more motivated by this approach.

We also tend to start HAART earlier in older patients (above 50 years). Although the regenerative capacity of the immune system in older patients is significantly reduced (Ledermann 2002, Grabar 2004), this has not been acknowledged in any

guidelines to date. More importantly, the OI risk also depends on age (Phillips 2004). One example from the CASCADE Study (Table 5.1) exemplifies this: a 25 year-old patient with 100 CD4 cells/µl and a viral load of 100,000 copies/ml has a risk of approximately 10 % for developing AIDS within six months – at 55 years, this level of risk is reached at 150 CD4 cells/µl and 30,000 copies/ml!

It is also important that beside the absolute CD4 count, the percentage is also considered. In particular, when the absolute CD4 count is high, the CD4 percentage is the most important predictor of the AIDS risk. In one study, the risk of progression for patients with more than 350 CD4 cells/µl was increased approximately four fold, if the percentage was below 17 % (Hulgan 2005).

Finally, it should also not be forgotten that CD4 cells are actually surrogate markers. As a "surrogate", they are conceived as a replacement for clinical endpoints. Therefore, they are only a rough expression of the clinical reality. Although they usually do this supremely, and even though the CD4-cell count is one of the best surrogate markers in HIV medicine, the patient must also be examined!

Symptomatic patients

There is consensus that every patient with HIV-associated symptoms should receive antiretroviral therapy. This is mainly true for patients in CDC Stage C (with AIDS), but also for Stage B. Although this should be correct in most cases, it may be advisable to consider the situation more closely in individual cases. To avoid misunderstanding: all OIs, which only occur in severe immunodeficiency, such as CMV, MAC or PCP, and also AIDS malignancies (including the non-AIDS-defining Hodgkin's Disease), should therefore prompt rapid initiation of therapy, especially, as in the case of PML, if there is no specific treatment available. In these cases, rapid initiation of HAART is the only treatment option available.

However: Herpes zoster (Stage B) may occur even with a slight immune defect and does not necessarily indicate immunological deterioration. Thrombocytopenia or constitutional symptoms may also have other causes. A further example: tuberculosis (TB), which is an AIDS-defining illness and therefore an "urgent" indication for therapy, can occur as a facultative opportunistic infection, without or with only moderate immunodeficiency. Waiting with HAART can be justified in a TB patient with good CD4 cells (see example in Table 5.3).

Table 5.3: Case study, in which HIV treatment, if it had been given in accordance to the guidelines, could have led to almost eleven years of over-treatment. NA = not available

		CD4 (%)	Viral load
May 95	Pulmonary tuberculosis (= AIDS)	330 (27)	NA
Feb 96	End of tuberculosis treatment	437 (29)	NA
	Patient refuses (urgently recommended) HAART		
Oct 97	Patient refuses (urgently recommended) HAART	402 (33)	29,500
Oct 00	Patient refuses (recommended) HAART	520 (30)	12,500
Jun 02	Doctor does not want to start HAART	521 (29)	7,440
Oct 04	HAART is rarely discussed…	391 (26)	15,300
Nov 06	Nothing new. Will it change again?	336 (26)	11,200

In the British guidelines, pulmonary tuberculosis is considered to be a possible exception. On the other hand, typical marker-illnesses, such as oral candida or oral hairy leukoplakia, can be an indication that the immune system is impaired. They may often precede far more serious illnesses. In such cases, it is advisable to offer the patient therapy, even if the CD4 cell count is relatively stable.

The same applies to constitutional or cognitive disturbances. A patient who newly develops concentration deficits, could – if other causes have been ruled out – have developed the first cognitive deficiency associated with HIV. Neuropsychological changes are sometimes seen observed in otherwise asymptomatic patients (Review: McArthur 2005).

Asymptomatic patients – below 200 CD4 cells/µl

There is a clear indication for initiation of therapy in these patients. 200 CD4 cells/µl is the cut-off, and values should not drop below this level - the risk of severe complications increases significantly after this (Mellors 1997, Egger 2002). For patients with CD4 cells of 200/µl and a high viral load, the six-month risk for AIDS is sometimes greater than 10 % (Phillips 2004). It is therefore advisable not to let this happen: the first manifestation of AIDS may not be an easily treatable infection. If PML, CMV, or toxoplasmosis occurs, the result is often permanently damaging.

However, such considerations are redundant for many of the patients that present for the first time. At least one third have a CD4-cell count below 200/µl. Nevertheless, even here the point is not to start therapy within a matter of days, but rather whether HAART is to be started at all. Is the patient going to return? We have now made it our practice to start PCP prophylaxis in such patients, and use the first two weeks for diagnostic procedures (fundoscopy! thoracic x-ray, ultrasound) to provide informative counseling – as well as exploring whether the patient is eligible to enter a study - and to identify patients with psychosocial issues. Requirements with respect to pill burden and dosing schedules need to be raised. HAART is started only when these issues have been addressed.

The risk of AIDS remains elevated in these patients even after initiation of HAART. This is logical – severe immunodeficiency requires time to reconstitute, and patients therefore remain at risk during the initial months. However, this risk is relatively low: in an analysis of treatment-naïve patients with less than 200 CD4 cells/µl at the beginning of therapy, 8.3 new AIDS-defining illnesses per 100 patient years were observed - in patients with at least 350 CD4 cells/µl this value was 1.8/100 patient years. Similarly, mortality was slightly elevated at 2.9 versus 0.7/100 patient years (Phillips 2001).

Asymptomatic patients – 200-350 CD4 cells/µl

Even in these patients, most guidelines recommend starting treatment, although the risk of developing AIDS is rather low. In the MACS Cohort, frozen blood samples obtained in the years 1985-1988 were analyzed and correlated with the clinical course of disease in these patients (Phair 2002). Not a single patient with more than

200 CD4 cells/µl and a viral load below 20,000 copies/ml became ill with AIDS within the following year.

On the other hand, a long-term risk of AIDS, especially with a high viral load, cannot be completely excluded. One should not feel too secure. We have seen a few patients, who have developed Kaposi's sarcoma, PML or a lymphoma with 200-350 CD4 cells/µl. In EuroSIDA, the risk of developing PCP or esophageal thrush at more than 200 CD4 cells was 1.6 % (Podlekareva 2006). In times of well-tolerated HAART combinations, an annual AIDS risk of 1 or 2 % becomes relevant. What is really gained in quality of life if one waits and exposes patients to such a risk? What is actually saved in long-term toxicity in these 1, 2 or 3 therapy-free years, which can perhaps be "taken out"? It is clear that: the less worries one has about long-term side effects, the earlier HAART will be used in the future.

Individual factors, which also have to be considered in asymptomatic patients with good CD4 cell levels

- Is there a falling trend in the CD4 cells; how rapid is the decrease? → always check percentage, too. Check CD4/CD8-ratio; often the absolute values vary considerably
- How high is the viral load; does the picture fit? → "real" decreases in CD4 cells tend to be rare with lower viral loads (< 10,000 copies/ml)
- What are the usual values for the patient? → a patient that always has a CD4 cell level around 1,200, which then drops to 350, probably has a more severe immune defect than someone, who always has 450 CD4 cells
- How prepared is the patient for therapy, how well are they informed, how compliant is the patient? → the more reluctant and nervous the patient, the more time one has to take prior to initiating therapy.
- How old is the patient? The immunological regeneration capacity decreases with increasing age → the older the patient, the earlier treatment should be started
- Are symptoms present, which the patient has not yet noticed, or which he/she finds not worth mentioning → regular full examination! OHL, oral candidiasis, seborrhoeic dermatitis, mycoses, etc?

See also Practical Tips (below)

tients of the same group, who had either started ART immediately or waited until they had "dropped" into a lower group, were compared. This design eliminated a problem encountered in cohort studies, in that a patient's risk is usually only determined at the time when therapy is started ("lead time bias") - the clock was theoretically started at the same time point for all patients.

However, the methods of this study are not without criticism. For example, patients that had started mono or dual therapy were also included, and the first patients to enter the analysis were from 1994. With the treatment available today, a difference may not have been observed. The mortality risk was, however, low. New data from the HOPS cohort (Lichtenstein 2006) calculated that at 200-349 CD4 cells/µl it was 15.9/1,000 person years (350-500 CD4 cells/µl: 11.5; over 500: 7.5).

Why has no randomized study been performed so far to address this question? An editorial on the cohort described above provided calculations (Lane 2003): in order to design a randomized study with 80 % power on starting treatment above or below 250 CD4 cells/µl, 650 events would be required to detect a 20 % difference in mortality. With a probability for progression of 1 % per patient year, around 6,500 would have to be followed for 10 years.

Despite these logistical problems, a large, global randomized trial on the optimal treatment start is, according to many experts, urgently needed. It is currently being planned. Following the success of the SMART trial, in which 6,000 patients on treatment interruptions were investigated (see "Treatment interruptions"), this has now become realistic.

Practical tips for starting therapy in asymptomatic patients

- Below 200 CD4 cells/µl treatment should be started as soon as possible.
- "As soon as possible" does not mean "immediately": one should still take the time to get acquainted with the patient, give proper counseling, start prophylaxis - it's not usually a question of having to start within a few days!
- Above 200 CD4 cells/µl, there is even more time – the individual course of the CD4-cell count is important. Beware the percentage values!
- A decrease of more than 50-100 CD4 cells/µl per year is too much! Don't delay too long in such patients!
- Because of considerable variability, a single CD4 cell count should be repeated before starting therapy.
- Above 350 CD4 cells/µl: wait, but continue to monitor levels every three months.
- The higher the viral load, the more frequent checks of CD4 cell counts are necessary: > 100,000 copies/ml, at least every two months.
- Initiation of treatment may be justified at levels above 350 CD4 cells/µl – if viral load is very high, CD4 cell count is decreasing rapidly or the patient requests it (after careful counseling).
- Consider whether a patient is suitable for enrolment in a clinical trial!

Consequences for the further course of disease

In the discussion about the start of treatment, it is often argued that beginning later can have an unfavorable effect on the success of therapy. However, does the time point actually influence virological or immunological treatment success? Do the so-called late presenters really have a worse prognosis? The following is a summary of the data.

Virological treatment success with unfavorable starting points

At first glance, many cohort studies have clearly demonstrated that virological response was poorer if the CD4-cell count at initiation of treatment was low and the viral load high (Casado 1998, Mocroft 1998 + 2000, Miller 1999, Wit 1999, Deeks

1999, Chaisson 2000, Grabar 2000, Yamashita 2001, Palella 2003, Wood 2005). In a meta-analysis of 30 prospective studies, baseline CD4-cell count was important for viral load decline on treatment (Skowron 2001). It might appear straightforward: the higher the viral load and the lower the CD4-cell count, the less the virological success of HAART. Defenders of an early initiation of HAART, who often cite this data, forget three important points:

First, this is not true for a few cohorts in which only treatment-naïve patients were studied, or in which therapy-naïve and treatment-experienced patients are differentiated (Cozzi-Lepri 2001, Phillips 2001, Le Moing 2002). Previous NRTI therapy has been a risk factor for virological treatment failure in many cohorts (Casado 1998, Deeks 1999, Chaisson 2000, Grabar 2000, Le Moing 2002). In the HOPS Cohort, lack of prior therapy was predictive of long-term treatment success (Holmberg 2003). Pre-treatment with NRTI is a rarity today, and besides modern HAART regimens are so effective that even in patients with a high viremia, high success rates can be achieved.

Secondly, the relative risk of virological failure was often only increased in patients with substantial immunosuppression (below 50 CD4 cells/µl) or very high viral load (above 100,000 copies/ml). At levels above 200 CD4 cells/µl or a viral load of less than 100,000 copies/ml, differences could generally not be detected (see below).

Thirdly, only a few of these studies considered adherence. It is difficult to measure, but crucial for virological response (Le Moing 2002, Wood 2004). A patient who starts HAART under emergency conditions at 30 CD4 cells/µl (and who went to the physician only shortly before or even after clinical manifestation of AIDS) may have a different view on sickness and health, and may be less adherent than someone who seeks medical advice with a good CD4 cell count and begins HAART after thorough reflection. It seems clear that the benefit of HAART differs for such patients.

Summary: in these times of modern HAART regimens, it is questionable whether the viral load of a therapy-naïve, compliant patient with low CD4 cells and high viral load is actually more difficult to decrease than when a more favorable starting point is taken.

Immunological treatment success with unfavorable initial values

Multiple factors can influence the increase in CD4 cells: age, thymus size or extent of thymus degeneration (see chapter “Goals of Therapy”). But, do baseline CD4 cell levels at the initiation of therapy play a role? Several cohorts found no association (Cozzi-Lepri 2001, Pezzotto 2001, Yamashita 2001). In the Swiss Cohort, having a low CD4-cell count was a clear risk factor for not attaining 500 CD4 cells/µl after four years (Kaufmann 2005).

Furthermore, in our experience immune reconstitution is rarely complete if values were low initially; the more damaged the immune system, the less likely a complete recovery in the long run (Garcia 2004).

Another consequence of starting therapy later can be that antigen-specific immune reconstitution remains impaired, both against HIV and other opportunistic infections. Diverse studies suggest that qualitative immune reconstitution does not initially occur at the same pace as quantitative reconstitution (Gochorov 1998, Lange

2002). One can make the analogy with a patch of desert where weeds will grow before flowers. So, what are the clinical consequences of these lab data? Why does the risk of AIDS decrease so impressively and rapidly with a rising CD4 cell count? The weed does not appear to be so bad after all. Why can even severely immunodeficient patients discontinue their prophylaxis quite safely, once their CD4 cell count has risen to above 200/µl? The clinical observations – at least in the short term – are contradictory.

Clinical therapeutic success with unfavorable initial values

Most studies have found a clear correlation between CD4 cells at the start of treatment and rates of both AIDS and death (Hogg 2000, Grabar 2000, Cozzi-Lepri 2001, Kaplan 2001 + 2003, Phillips 2001, Egger 2002, Palella 2003, Sterling 2003). Above all, when starting therapy with less than 50 CD4 cells, the risk for developing AIDS remains permanently high (Hogg 2003). In other cohorts, the risk remained elevated even below 200 CD4 cells/µl (Phillips 2001, Sterling 2001, Kaplan 2003).

Data from the largest study to date (Egger 2002), in which almost 13,000 patients on HAART were analyzed, confirmed that the CD4-cell count at the start of treatment correlated highly with the probability later of AIDS or death. In comparison to the patients who started HAART with less than 50 CD4 cells/µl, the risks with higher levels of helper cells were significantly less (see Table 5.4). One should note the moderate difference between the groups above 200 CD4 cells/µl. Viral load at baseline was only relevant if it was at a very high level, i.e. above 100,000 copies/ml.

Table 5.4: Risk of progression in the ART Cohort Collaboration (Egger 2002)

Baseline CD4 cells/µl	Relative risk
50-99 versus < 50	0.74 (0.62-0.89)
100-199 versus < 50	0.52 (0.44-0.63)
200-349 versus < 50	0.24 (0.20-0.30)
> 350 versus < 50	0.18 (0.14-0.22)

Are there any differences between 200-350 and >350 CD4 cells/µl?

In the above-mentioned meta-analysis, the difference was minimal (Egger 2002). The AIDS rate was 2.3 versus 1.8; the mortality rate 1.0 versus 0.7 per 100 patient years. This means one case of AIDS in 200 patient years! Very large, randomized studies would probably be necessary to detect a difference between the two patient groups. Other cohort studies have also posed the question of whether there is a difference if patients first start at a CD4-cell count of 200-350 cells or earlier. So far, most have not been able to detect an advantage for starting treatment early (Table 5.5). However, the observation periods were usually relatively short. It is possible that differences may emerge in the longer term.will be found in the long term.

A problem of many cohort studies is that they do not consider the success of HAART on an individual level. In a complex analysis of almost 10,000 patients,

which considered the baseline values as well as the values after six months (Chene 2003), the response to HAART was predictive of decreased mortality and AIDS related morbidity irrespective of baseline CD4 counts.

Table 5.5: The influence of CD4-cell count on treatment success. Comparison between 200-350 CD4 cells/µl and > 350 CD4 cells/µl at initiation of HAART.

Study	Less AIDS, fewer deaths?	More pronounced increase in CD4 cells?	Improved virological response?
Canadian Cohort (Chaisson 2000, n=553)	**	**	No (trend)
ICONA Cohort, Italian (Cozzi-Lepri 2001, n=1,421)	No	No	No
CDC database, USA (Kaplan 2001, n=10,885)	No	**	**
John Hopkins Cohort (Sterling 2003, n=333)	No	**	No
Swiss, Frankfurt, EuroSIDA Cohorts (Phillips 2001, n=3,226)	No	**	No
Swiss Cohort (matched pair) (Opravil 2002, n=2x283)	Yes	**	**
MACS Cohort (Ahdieh-Grant 2003, n=349)	No	**	**
HOPS Cohort (Palella 2003, n=1,464)	Yes	**	Yes
Barcelona Cohort, single-center (Garcia 2004, n = 861)	No	No (trend)	**

** not specified

Finding the optimal time to start treatment is one of the most difficult decisions of HIV therapy. To conclude, here are a few typical arguments about the pros and cons of starting therapy.

Arguments for and against an EARLY start

Statement	Counter
"The lower the CD4 count, the longer the patient will remain at risk later."	"This statement applies mainly to patients with substantial immune defects, in whom therapy has to be started. The earlier one starts, the more long-term toxicities will occur!"
"A lower CD4 count often implies that only moderate immunological-virological treatment success is possible – at some stage, the destruction is irreversible."	"This is mainly true for patients with substantial immunosuppression. However, the virological response does not seem to be reduced in treatment-naïve patients."
"The longer one waits, the fitter the virus becomes via immune escape variants, and the more difficult it is to treat."	"Interesting laboratory hypothesis. But, where's the relevant clinical data?"
"The worse the condition of the patient, the worse the tolerability of HAART."	"Ancient medical wisdom. But, does it apply here? We are referring to asymptomatic patients…"
"HIV should be treated as early as possible, as should any other infectious disease."	"HIV is not akin to any other infectious disease. HIV cannot be cured like many bacterial infections. Herpes viruses, for which there is no cure, are also treated only as needed."
"It has been proven that patients are less infectious on treatment."	"And may be more prone to risk behavior. In addition, the risk of transmission of primary resistance mutations increases."

Arguments for and against a LATE start

Statement	Counter
"The earlier one starts, the sooner and more certain the side effects."	"The question is: does one more year without therapy, but with an increasing risk of AIDS, really make a difference?"
"The earlier one starts, the higher the risk for resistances."	"In compliant patients, the risk is very low with today's treatments."
"Even a bad immune system can regenerate; after all, prophylaxis can be safely stopped after a rise in CD4 count."	"This may be true for some patients, but not for all. There are indications that the qualitative response remains impaired."
"It is never too late to start therapy at 200 CD4 cells."	"Some AIDS diseases may occur even in this scenario; there is no certainty that PML or lymphoma might not develop."

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6. Which HAART to start with?

Christian Hoffmann and Fiona Mulcahy

Once the decision has been made that HAART is necessary, the next question is: what to start with? Because more than two dozen drugs are now available, the number of theoretically possible combinations at first sight seems to be very complex. In many guidelines, dozens of different combinations are recommendable or at least advisable.

Thus, it is preferable that every treatment-naïve patient participates in a clinical study, because only then can HAART be improved further. However, every now and then clinical trials are not possible. For these patients, the data available to date needs to be summarized.

Recommended initial regimens

Combinations that we currently recommend for first-line therapy (as of January 2007) are shown in Table 6.1.

Table 6.1: Combinations suitable for initial HIV therapy (not in order of preference!)

NRTIs		NNRTI/PI
*TDF + 3TC		Lopinavir/ritonavir
*TDF + FTC	plus either	Fosamprenavir/ritonavir
**ABC + 3TC		Efavirenz***
		Nevirapine****
Alternatives		Alternatives
AZT + 3TC		Saquinavir/ritonavir
AZT + FTC		

* Convincing data only on combination with efavirenz.
** Combination with NNRTIs without HLA typing, may be problematic due to allergies.
*** Caution should be taken in women of child-bearing age (teratogenicity)
**** Caution with high CD4-cell counts (women > 250/µl, men > 400/µl) because of hepatotoxicity.

Moreover, numerous other combinations are, of course, possible and licensed. These combinations are certainly not wrong, and may be acceptable in individual cases or in investigational studies, but general recommendations for their use cannot be given. Problematic combinations, that are not advisable for use, are listed at the end of this chapter.

Practical approach to the first regimen – important rules

All current initial regimens consist of two NRTIs, combined with either a boosted PI, an NNRTI or – with distinct restrictions - a third NRTI. No single combination has clearly been shown to be superior to another: there is no gold standard. When choosing primary therapy, many factors are involved, besides the antiviral potency and tolerability. Individual compliance, concurrent illnesses and concomitant medications, and the needs of the patient should be included in the decision. One should be aware that a primary therapy is of great significance and needs to be well prepared. It is at this time that the chance of viral suppression is greatest.

Practical tips for first-line therapy:

- The first regimen offers the patient the best chance. This means that the viral load must decrease to below detection levels within 3-6 months!
- Don't rush – the patient must be ready for HAART, no half-hearted start! If in doubt, wait and continue to monitor the levels.
- If possible, don't prescribe medication in the first consultation with a new patient. Do you know the patient well enough? Is he really motivated? Will he ever come back again?
- For every patient, only prescribe the ART he is able to take! Don't insist on theoretically superior combinations.
- The pros and cons (side effects) of different combinations should be discussed – there is usually enough time for this.
- The initial regimen should be taken no more then twice daily. Once-daily treatment should be considered if it is important for the patient.
- The toxicity profiles should not overlap, if possible – never use several allergenic drugs simultaneously.
- Ask about other medication (and drug consumption) – are relevant interactions to be expected?
- Concomitant illnesses should also be checked – what about the liver (hepatitis), kidneys?
- All drugs are started on the same day – no lead-in mono- or dual therapy!
- Be sure to check whether the patient would be eligible for a clinical study! All patients, especially if treatment-naïve, should be encouraged to participate in clinical trials!

What should be clarified beforehand?

Dosing issues

Can the patient really take drugs reliably? Is this realistic with regard to his individual, professional or social situation? How regular is the patient's living, sleeping, and eating routine? If in doubt, a simpler regimen is preferable. For example, it is often not realistic to expect intravenous drug users to take tablets several times a

day according to a strict protocol. There have been successful attempts at once-daily regimens for drug addicts (Staszewski 2000), which are also suitable for DOT (Directly Observed Therapy) together with methadone (a heroin substitute).

For many patients, the numbers of pills or requirements for food intake are important. The range of licensed and recommended initial regimens varies from 2 to 13 pills per day. Some find it unacceptable to have to take pills at certain times during the day with fatty foods. Patients today are more demanding than earlier – justifiably so. There are now alternatives. Even the size or consistency of tablets can be a problem. Such issues must be discussed *before* initiating therapy.

Concurrent illnesses

Before starting treatment, a possible concurrent illness must be identified as it may effect drug choice. (see Table 6.2). For example, a patient with diarrhea may not tolerate nelfinavir, fosamprenavir, or lopinavir. ddI is contraindicated in patients with a history of pancreatitis! Caution with tenofovir or indinavir in renal disease! Polyneuropathy requires that any d-drugs (ddI, d4T) be avoided; they are only used as exceptions in primary therapy. Non-insulin-dependent diabetes can become insulin-dependent for the first time on PI treatment.

The risk of developing severe hepatotoxicity on nevirapine or ritonavir is highest in patients with a history of liver disease and chronic hepatitis (Den Brinker 2000, Sulkowski 2000). Caution is also required with boosted PIs. However, one study conducted in over 1,000 patients found no difference between lopinavir/ritonavir and an unboosted PI such as nelfinavir in patients co-infected with hepatitis C (Sulkowski 2004). In co-infections with HBV, 3TC or FTC (not simultaneously!) in combination with tenofovir should ideally be used.

Table 6.2: Concurrent illnesses requiring caution with specific drugs. There are no absolute contraindications.

Illness	Caution with
Active hepatitis B	Nevirapine, boosted PIs (In contrast: 3TC, FTC, tenofovir are beneficial!)
Active hepatitis C	Nevirapine, boosted PIs
Active substance abuse, substitution	NNRTIs, ritonavir
Anemia	AZT, possibly also 3TC
Arterial hypertension	Indinavir
Chronic diarrhea, intestinal diseases	Nelfinavir, lopinavir, fosamprenavir
Diabetes mellitus	PIs (especially if a NIDDM is at risk of becoming an IDDM!)
Kidney disease	Indinavir, tenofovir
Myocardial infarction	PIs (potentially beneficial: nevirapine)
Pancreatitis	ddI
Polyneuropathy	d4T, ddI
Psychoses, other CNS illnesses	Efavirenz

Interactions with medications and drugs

Interactions are important in the choice of combination regimens. Whereas interactions between antiretroviral drugs are well known, interactions with other concomitant medications are often less well characterized (see "Interactions"). The urgent need for more research was demonstrated in a study investigating the interactions between HAART and statins. In healthy volunteers, the measurement of plasma levels showed that levels of simvastatin were elevated by 3.059 % after concurrent dosing with ritonavir or saquinavir (Fichtenbaum 2002). One fatal rhabdomyolysis on simvastatin and nelfinavir has been described (Hare 2002).

Many drugs should not be combined with particular antiretroviral drugs, as incalculable interactions may occur. These include certain contraceptives. Even drugs that seem unproblematic at first glance can have unfavorable effects: for example, the plasma levels of saquinavir can be reduced by half due to concurrent administration of garlic capsules (Piscitelli 2002). Even a seemingly harmless substance such as vitamin C can significantly lower indinavir levels (Slain 2005). Even warfarin can be a problem; ritonavir significantly lowers plasma levels (Llibre 2002). Further typical "problem drugs" include migraine remedies, prokinetic drugs and sedatives/hypnotics. One fatal case has been described with ergotamine and ritonavir (Pardo 2003). The simultaneous administration of HAART and PDE-5 inhibitors (sildenafil, vardenafil, tadalafil) can also be problematic (see "Sexual Dysfunction").

Drugs or alcohol can also interact with HAART. For those in substitution programs, the methadone requirement may be significantly increased by certain antiretroviral drugs such as nevirapine and efavirenz (Clarke 2001). To a lesser extent, this is also true for ritonavir and nelfinavir. There is inconsistent data on lopinavir, but it may also require dose adjustments (McCance-Katz 2003, Stevens 2003). Tenofovir does not seem to have significant interactions with methadone (Smith 2004).

Other interactions have even more dangerous consequences. Several deaths have been reported after simultaneous dosing with ritonavir and amphetamines or MDMA/ecstasy, or the popular narcotic gamma hydroxybutyric acid (GHB, Samsonit™ or "liquid ecstasy"; Henry 1998, Harrington 1999, Hales 2000). Ritonavir in particular inhibits the metabolism of amphetamines (speed or MDMA/ecstasy), ketamines or LSD (review in: Antoniou 2002). Clinician and patient are well advised to have an open conversation about drug use before starting therapy. Marijuana and THC appear to have a low potential for interactions (Kosel 2002). Amphetamines seem to be particularly dangerous and neurotoxic in HIV patients (Langford 2003).

Not every substance can be discussed here. Many are described in the respective drug chapters. It is always recommended to check the package insert. Initiation of HAART provides a good opportunity to re-evaluate existing prescribed medications.

Additive toxicities

Potential additive toxicities should also be considered in the choice of therapy.

If other myelotoxic drugs (valganciclovir!) are necessary, caution is required with AZT. The same is true for dapsone and co-trimoxazole. When treating hepatitis C

with interferon and ribavirin, ddI must be avoided, as well as AZT and d4T, where possible.

Lastly, it is not advisable during the primary therapy to start with potential allergy-inducing substances if anti-infectious prophylaxis with co-trimoxazole or other sulphonamides is necessary. Included in this are nevirapine, efavirenz, and abacavir (and possibly fosamprenavir). In order not to disturb the prophylaxis, it is better to avoid these antiretroviral drugs; after all, one does have a choice. Otherwise, it can be difficult to clearly identify the causative agent for a drug-induced exanthema.

Which drug classes are to be used?

The combinations currently used as initial regimens consist of two nucleoside analogs plus either a PI or an NNRTI. A third nucleoside analog is only used in exceptional cases. All three strategies reduce the risk of AIDS approximately equally (Olsen 2005). In contrast, other combinations are experimental or not justified for use outside the framework of clinical studies. Advantages and problems of these three strategies are outlined in Table 6.3.

Table 6.3: Combining drug classes: Advantages (↑) and disadvantages (↓)

2 NRTIs + PI	2 NRTIs + NNRTI	Triple Nuke
↑ a lot of data, including clinical endpoints and severely immunocompromised patients	↑ equivalent, perhaps even better suppression of viral load than with PIs	↑ low pill burden, easy dosing
↑ long-term data available	↑ low pill burden! once-daily may be possible	↑ leaves many options
↑ high genetic resistance barrier	↑ leaves PI options	↑ few interactions
↓ higher pill burden (for the older PIs), partly strict dosing requirements, most once-daily regimens not licensed	↓ clinical effect not proven (only surrogate marker studies)	↓ less potent, with higher viral load, especially with tenofovir-containing triple nuke therapy
↓ frequent drug interactions	↓ less data in severely immunocompromised patients	↓ once-daily with AZT not possible
↓ some PIs with cross-resistance, leaving limited options	↓ rapidly occurring complete cross-resistance	↓ no clinical endpoints, no long-term data
↓ long-term toxicity, lipodystrophy, dyslipidemia with most PIs	↓ strict monitoring required initially (esp. nevirapine), allergies frequent	↓ possible raised mitochondrial toxicity with three NRTIs

There are only a few studies that directly compare all three of these strategies. In addition, the most tested combination is no longer used so that the validity of these studies is limited. This applies, for example, to the ATLANTIC study (van Leeuwen 2003) or the CLASS trial (Bartlett 2004), as well as to a few others (Gerstoft 2003).

In 2006, a randomized trial on ACTG 5142 was published, in which the boosted PI lopinavir was tested against the NNRTI efavirenz (Riddler 2006) – two of the most used drugs at present. 753 therapy-naïve patients were included in this three-arm US study. Two groups were given two NRTIs (there was free choice and most received 3TC plus AZT, TDF or d4T-XR) and either lopinavir/r or efavirenz. The third group received an NRTI-free therapy with lopinavir/r and efavirenz.

Table 6.4: ACTG 5142 – essential results after 96 weeks (Riddler 2006)

Arm	No treatment failure*	Continuation of treatment	< 50 (< 200) copies/ml	CD4 increase
EFV + 2 NRTIs	76 %	60 %	89 % (93 %)	241
LPV/r + 2 NRTIs	67 %	54 %	77 % (86 %)	285
EFV + LPV/r	73 %	61 %	83 % (92 %)	268

* defined as a viral load > 200 copies/ml or a drop of < 1 log after 32 weeks or change of treatment due to side effects

The differences in the antiviral efficacy between EFV + NRTIs and LPV/r + NRTIs were significant; with less than 50 copies/ml after 96 weeks was approximately 12 %. The NRTI-free group was approximately in the middle of the other two groups. However, in the EFV + NRTI arm, the rate of virological failure was less – if the treatment did fail, resistance mutations in the LPV/r arms were more frequently seen, and the CD4 cells increased more on LPV/r than on EFV. The surprise was in the relatively good results of the NRTI-free arm. Thus, ACTG 5142 can still not provide a definitive answer and there remain pros and cons for each individual strtegy – the controversy about the best initial therapy persists.

In the following, various strategies of primary therapy are discussed in more detail. These include:

1. Two NRTIs plus a NNRTI
2. Two NRTIs plus a protease inhibitor
3. Three NRTIs ("triple nuke")
4. Once-daily combinations
5. Experimental combinations ("nuke sparing", intensive approaches)
6. Problematic primary therapies, which should be avoided

1. Two NRTIs plus a NNRTI

NNRTI-containing regimens have an at least equal, if not even better antiviral potency than PI combinations. NNRTIs have done well in numerous randomized studies. Efavirenz-based regimens were superior to indinavir, nelfinavir, amprenavir/r or triple nuke in studies such as 006, ACTG 384, ACTG 5095 or CLASS (Staszewski 1999, Robbins 2003, Gulick 2004, Bartlett 2004).

Newer studies, such as ACTG 5142 (see above) or FIRST seem to support the superiority of NNRTIs (MacArthur 2006, Riddler 2006). Nevirapine-based regimens in COMBINE or ATLANTIC were at least equal to nelfinavir or indinavir, and better than triple nuke (Podzamczer 2002, van Leeuwen 2003). In the 2NN trial, there was no significant difference between efavirenz and nevirapine (van Leth 2004).

Advantages of NNRTI-regimens include the low pill burden and good tolerability. In contrast to PIs, however, there is no study available with clinical endpoints. Neither is there any long-term data or studies on severely immunocompromised patients. Furthermore, a disadvantage of NNRTI combinations is the rapid development of cross-resistance. Allergies to NNRTIs are well described. Nevirapine, as it induces its own metabolism should be introduced in a phased increase over two weeks; with efavirenz, CNS disturbances are relatively common.

TDF+3TC/FTC plus efavirenz (or nevirapine)

In our opinion, this seems to be one of the preferable combination at present. In the double blind, randomized Gilead 903 Study, virological efficacy was equivalent to d4T+3TC (plus efavirenz), although tolerability was significantly better (Gallant 2004). Toxicity was reduced, and polyneuropathy, lipodystrophy and even dyslipidemia were significantly less frequent in the tenofovir arm. In the Gilead 934 Study, TDF+FTC plus efavirenz was more effective than AZT+3TC plus efavirenz after 48 weeks, because of tolerability (Gallant 2006). There is no reliable data on nevirapine in combination with TDF+3TC/FTC yet. For all TDF-containing combinations, care must be taken to monitor renal function on a monthly basis.

AZT+3TC plus efavirenz or nevirapine

These regimens were among those most frequently used and have been investigated in several large milestone trials (006, Combine, ACTG 384, 5095, 934). Side effects may occur during the first weeks, and normally trace back to AZT. In the 934 Study, anemia and gastrointestinal problems occurred frequently, which significantly compromised the efficacy of AZT+3TC in contrast to TDF+FTC (Gallant 2006, Pozniak 2006) More importantly it should be remembered that AZT has to be taken twice daily – once-daily dosing is not possible.

d4T+3TC plus efavirenz or nevirapine

Since the 903 Study (see above) and the ABCDE Study (Podzamczer 2006) the usefulness of d4T+3TC has become limited. This combination is only useful if renal problems or problems with hematopoiesis (anemia or thrombocytopenia) exist at the start of therapy. This applies, for example, to patients receiving chemotherapy or gancyclovir. In 2NN, d4T+3TC+efavirenz and d4T+3TC+nevirapine were approximately comparable (Van Leth 2004).

2. Two NRTIs plus a Protease Inhibitor

This combination is the only HAART for which efficacy has been based on clinical endpoints in randomized studies (Hammer 1997, Cameron 1998, Stellbrink 2000). Data is also available for extended time periods, with some studies running for five years or more (Gulick 2003, Hicks 2003). Many experts choose these combinations in patients with AIDS or high viral load, in view of the robustness of boosted PIs to viral resistance. Disadvantages of the PI-containing primary therapy are the, sometimes high, pill burden and frequent side effects, both of which make compliance difficult. The most common combinations are:

Two NRTIs plus lopinavir/r

These are categorized in many guidelines as a combination that should be used in preference to other regimens. Long-term efficacy is good (Hicks 2003). So far, practically no resistance has been described in primary therapy. The combination of d4T+3TC+lopinavir/r was significantly better than d4T+3TC+nelfinavir in the only comparative study described to date. After week 48, 67 versus 52 % of patients had a viral load below 50 copies/ml (Walmsley 2002). Following studies such as KLEAN and Gemini, however, it appears that lopinavir/r is not more effective for initial therapy than other boosted PIs (Eron 2006, Slim 2006). According to ACTG 5142, efavirenz may be superior to lopinavir/r (Riddler 2006, see above). The nuke backbone used in most studies is currently TDF+FTC (Johnson 2006).

ABC+3TC plus fosamprenavir/r

ABC+3TC, in the combination Kivexa™, have been shown in the NEAT and SOLO studies to have good efficacy in combination with fosamprenavir (Gathe 2004, Rodriguez-French 2004). In the KLEAN study, there was no difference between fosamprenavir/r and lopinavir/r.in either efficacy or tolerability. Severe diarrhea or raised cholesterol were no less frequent (Eron 2006). In the ALERT study, fosamprenavir/r was approximately as effective as atazanavir/r with a backbone of TDF+FTC (Smith 2006).

Two NRTIs plus saquinavir/r

AZT+ddC+saquinavir was the first PI combination for which a survival advantage was shown (Stellbrink 2000). Nevertheless, saquinavir is still given with other NRTIs, rather than with AZT+ddC, and more importantly still, only in its boosted form (saquinavir/r 1,000/100 bid). Tolerability is probably better than for indinavir/r (Dragstedt 2003). More data is available for the AZT-containing nuke backbones than for those containing TDF. However, in the relatively small GEMINI trial, saquinavir/r with a TDF+FTC backbone did not appear to be much worse than lopinavir (Slim 2006).

Two NRTIs plus nelfinavir

Nelfinavir combinations were previously among the most frequently used ART regimens. The licensing studies mainly combined nelfinavir with AZT+3TC (Saag 2001, Gartland 2001). In Combine, there was a trend for nelfinavir to be slightly weaker than nevirapine (Podczamczer 2002); in INITIO it was clearly weaker than efavirenz (Yeni 2006). Even in direct comparison to boosted PIs such as lopinavir/r or fosamprenavir/r, nelfinavir is less potent (Walmsley 2002, Gathe 2004, Rodriguez-French 2004). Due to the high pill burden and the often substantial diarrhea, nelfinavir is generally no longer recommended for first-line therapy.

3. Three NRTIs – "Triple Nuke"

Triple nuke therapies have advantages: few pills, few interactions, no side effects typical of PIs or NNRTIs, and the fact that all other drug classes can be spared for later. A big disadvantage is that triple nukes are virologically less potent than other combinations from several drug classes. With the growing knowledge about mitochondrial toxicity of NRTIs, some of the attractiveness of their use has been lost.

AZT+3TC+ABC

This combination in a single tablet of Trizivir™ (twice daily) is the classic triple nuke therapy. Trizivir™ is not as potent as other combinations from other drug classes. Initially, the combination with two NRTIs plus either unboosted PIs such as nelfinavir, atazanavir (Matheron 2003, Kumar 2006) or indinavir (Staszewski 2001, Vibhagool 2004) was accepted, but since ACTG 5095, Trizivir™ is no longer valid as a primary therapy (Gulick 2004). In this double blind, randomized study, 1,147 treatment-naïve patients received either AZT+3TC+ABC, AZT+3TC plus efavirenz, or AZT+3TC+ABC plus efavirenz. The endpoint was a viral load above 200 copies/ml after 16 weeks or later. After 32 study weeks, 21 % of patients in the Trizivir™ arm had a viral load above 200 copies/ml – in contrast to just 11 % in the other two arms. These differences were significant, and the triple nuke arm with AZT+3TC+ABC was discontinued. Trizivir™ is generally well tolerated – however, counseling on the abacavir hypersensitivity reaction is necessary. With respect to the AZT dose, the same applies for Trizivir™ as for Combivir™: it may be too high for some patients.

TDF+3TC+ABC/ddI

This combination should be avoided (Jemsek 2004, Gallant 2005, Khanlou 2005). There is a risk of treatment failure in up to 49 % of patients, probably due to a low genetic resistance barrier (Landman 2005). This also applies to treatment-experienced patients, who simplify HAART with this combination (Hoogewerf 2003, Perez-Elias 2005).

TDF+AZT+3TC (+ABC)

In retrospect, we ourselves have had good experience with TDF+AZT+3TC (Mauss 2005). Obviously, the thymidine analog of AZT is protective against tenofovir-associated mutations due to the various resistance pathways (Rey 2006, see also "Resistances").

Pilot studies have reported low viral failure rates on a quadruple therapy with TDF+AZT+3TC+ABC (Moyle 2006, Elion 2006); however, nothing is yet known about long-term toxicity and efficacy.

Besides those involving Trizivir™ and tenofovir, a number of other triple nuke therapies have been tested, mostly with d4T and ddI (Gerstoft 2003, Van Leeuwen 2003, Bartlett 2004). They do not play any role in practice today.

Summary: It is difficult for triple nukes to continue to carry the flag in primary therapy.. This option is only useful for patients with compliance problems or co-medications with the potential for interactions (tuberculosis or MAC therapy, marcumar) and low viral load. Triple nuke therapy also remains under consideration for maintenance therapy (see following chapter).

4. Once-daily combinations

In recent years, many drugs have been licensed for administration once a day ("once-daily", OD; see Table 6.5). As a result, many once-daily options for primary therapy have emerged, such as TDF+FTC(3TC)+EFV (Saag 2004, Gallant 2006), ABC+3TC+EFV (Moyle 2005), and TDF+FTC+LPV/r (Johnson 2006).

Table 6.4: Antiretroviral drugs and their usage in once-daily regimens (OD)

Trade name	Abbr. drugs	OD?	Comment
Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs)			
Combivir™	AZT+3TC	No	Not possible due to AZT
Emtriva™	FTC	Yes	
Epivir™	3TC	Yes	
Kivexa/Epzicom™	3TC+ABC	Yes	
Retrovir™	AZT	No	Not possible
Trizivir™	AZT+3TC+ABC	No	Not possible due to AZT
Truvada™	FTC+TDF	Yes	
Videx™	ddI	Yes	Must be taken on an empty stomach
Viread™	TDF	Yes	
Zerit™	d4T	No	d4T-XR is no longer coming
Ziagen™	ABC	Yes	
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)			
Rescriptor™	DLV	No	Not possible
Sustiva/Stocrin™	EFV	Yes	
Viramune™	NVP	Possibly	A lot of data, OD-license planned NVP XR
Protease inhibitors			
Aptivus™	TPV/r	No	Not possible
Crixivan™	IDV/r	No	Little data available
Darunavir™	DRV/r	Possibly	Studies are underway
Invirase 500™	SQV/r	Possibly	Studies are underway
Kaletra™	LPV/r	Yes	Licensed in the USA, not in Europe
Reyataz™	ATV/r	Yes	Also unboosted in the USA
Telzir/Lexiva™	FPV/r	Yes	Licensed in the USA, not in Europe
Viracept™	NFV	No	Hardly any data available
Fusion inhibitors			
Fuzeon™	T-20	No	OD not possible

In theory, some experts still fear that once-daily regimens are unfavorable with respect to the development of resistance. If one dose is forgotten, a whole day of treatment is lost at once. These OD-regimens may therefore be problematic particularly in patients with poor compliance. However, if given within DOT programs (directly observed therapy), OD-regimens can be very helpful in this patient group (Staszewski 2000, Mitty 2005 + 2006). But, in the ACTG 5073 trial, DOT with a combination of lopinavir/r+FTC+d4T-XR produced no advantage, in fact the once-daily administration was less effective (Mildvan 2007).

It is not yet clear whether once-daily dosing increases the compliance per se through such programs. In our experience, the step from three doses to two is bigger than from two to one. A meta-analysis (Claxton 2001) showed that the compliance

was better on once-daily than on three or four-times daily dosing, but not better than twice-daily dosing (BID). There appears to be no difference between OD and BID if the BID regimens are simple and well tolerated (Stone 2004). Patients often would like to have once-daily regimens, but only when there are no dietary restrictions and the number of pills is low (Moyle 2003). Because of the quantity of tablets alone, despite the fairly good data available, several OD PI-combinations with saquinavir/r or lopinavir/r will never become popular (Mildvan 2007).

The higher peak levels may also reduce the tolerability, as suggested by several studies. In the 418 Study, for example, once-daily lopinavir led to significantly more diarrhea than twice-daily doses (Johnson 2006). But, once-daily regimens not only affect the peak levels – the lengthened interval between doses also causes the trough levels to sink, especially with boosted PIs (Gibbons 2005). This can be relevant in treatment-experienced patients (Elston 2004, la Porte 2005), but should not be a problem in primary therapy.

Summary: There is certainly no requirement for all patients to be treated with OD regimens. The wish of the patient should be considered. In particular, it may be difficult for individuals in employment with shift work, or with irregular lifestyles to take medication twice a day at set times. However, even these patients must be advised that it is just as important in once-daily regimens to take the medication on time.

Experimental Combinations

HAART has to become simpler and more tolerable. However, there is not always time to wait for new drugs to be developed! As a result, two approaches are currently being investigated: combinations without any NRTIs (nuke sparing), and so-called induction therapies, comprised of intensive combinations using more than three active drugs or drugs from three different classes.

"Nuke sparing"

Classical HAART regimens include a "backbone" consisting of two NRTIs (nuke backbone). This mainly has historical reasons: NRTIs were the first drugs on the market, and by the time NNRTIs and PIs were in development, treatment with two NRTIs was standard. With growing knowledge of the mitochondrial toxicity of NRTIs, nuke sparing, i.e. omission of NRTIs, even from the primary therapy, is being investigated more and more (see Table 6.6). A few studies on pre-treated patients have already tested nuke sparing successfully (see "When to change HAART"), and salvage therapy with double PI combinations is also being investigated.

But for primary therapy? Since an NRTI-free combination of indinavir+efavirenz fared quite badly in the 006 Study (Staszewski 1999), nuke sparing initially seemed to be a thing of the past. But the pressure on NRTIs is increasing. The first large study to produce convincing data on nuke sparing was ACTG 5142 (Riddler 2006, see above). It showed that a combination of lopinavir/r and efavirenz was not worse than two NRTIs with either lopinavir/r or efavirenz. ACTG 5142 will definitely lead to further studies, and potentially in the mid-term to giving nuke sparing a firmer role in primary therapy than it has so far had.

Apart from ACTG 5142 and 006, there have only been a few randomized studies to date. In EASIER, patients received indinavir/r and efavirenz with or without d4T. After 48 weeks, there were comparable effects with respect to the surrogate markers – and d4T did not have any additional effects. However, this study was compromised by the relatively high dropout rate (Stek 2003). Two small, randomized studies also found no significant difference between nuke sparing and standard regimens (Harris 2005, Cameron 2005).

It is still unclear whether side effects really improve with nuke sparing. In HIVNAT009 it was reported that lipoatrophy resolved (Boyd 2003b); in CTN 177, nuke sparing had a favorable effect on lactate (Harris 2005). In ACTG 5142, the rate of lipoatrophy was reduced, but otherwise the tolerability was no better than on conventional regimens. Dyslipidemia was actually seen more frequently (Riddler 2006, Haubrich 2007). In view of the current data, it is still too early to recommend nuke sparing as an equally good approach.

Table 6.6: Prospective studies on nuke sparing in treatment-naïve patients and patients with little prior treatment experience (intent-to-treat analyses)

	n (naïve)	Combination (Study name)	Proportion viral load < 50 copies/ml
Staszewski 1999	148 (126)*	EFV+IDV (006 Study)	47 % at 48 weeks
Gisolf 2000	104 (104)	SQV+RTV (Prometheus)	63 % at 48 weeks (< 400)
Lopez-Cortez 2003	42 (0)**	EFV+SQV/r	71 % at 52 weeks
Stek 2003	47 (na)*	EFV+IDV/r (EASIER)	53 % at 48 weeks
Boyd 2003	61 (0)*	EFV+IDV/r (HIVNAT 009)	69 % at 96 weeks
Hellinger 2005	20 (4)*	SQV+LPV/r (PIN)	70 % at 48 weeks
Cameron 2005	16 (16)	SQV+LPV/r (ACTG 384)	63 % at 48 weeks
Allavena 2005	86 (65)*	EFV+LPV/r (BIKS)	73 % at 48 weeks (< 400)
Harris 2005	14 (14)	NVP+LPV/r (CTN 177)	78 % at 48 weeks
Ward 2006	63 (63)	EFV+ATV/r (BMS 121)	63 % at 48 weeks
Riddler 2006	253 (253)	EFV+LPV/r (ACTG 5142)	83 % at 96 weeks

*All PI-naïve. **22/42 less than 50 copies/ml at the time of switch. na = not available.

Monotherapies, alternating therapies

Does it get any easier? In the summer of 2003, an avant-garde concept was presented: monotherapy with boosted PIs. In view of the high resistance barrier of PIs, the success was, in part, promising (see "How to Change HAART"). Because of the always greater number of well-tolerated drugs, it is difficult to find sensible reasons for monotherapy in primary therapy.

Another new approach is alternating therapy. In the SWATCH study, a total of 161 patients were randomized to a regimen of d4T+ddI+efavirenz or AZT+3TC+nelfinavir (Martinez-Picado 2003). A third arm changed between the two regimens every three months, as soon as the viral load was below the level of detection. After 48 weeks, virological failure in the alternating arm was significantly reduced. There was no difference for other parameters (CD4 cells, side ef-

fects). However, the good tolerability of other treatments has meant that such alternating therapies, which can confuse the patients completely, have lost their significance.

More intensive (induction-) treatment with 4-5 drugs

Over and over again, the question is brought up as to whether more intensive approaches than triple therapy combinations are necessary in patients with a high viral load. Due to a growing concern about the rapid development of resistance, some clinicians are starting to treat these patients with an "induction" of four or even five drugs, which are then simplified to a triple combination once the viral load has been well suppressed. This concept has not yet been validated, and is only based on theoretical hypotheses or smaller proof-of-concept studies in which it has been shown that the viral load sinks faster under intensive combinations than under standard therapies (Ramratnam 2004).

Approaches in which multiple individual drugs are given have to be distinguished from approaches in which three instead of two classes of drugs are used.

Multiple individual drugs: really have no advantages. Giving two PIs instead of one PI, or two instead of one NNRTI sometimes produced even negative results (Moyle 2000, Katzenstein 2000, van Leth 2004). There is also no argument in favor of giving three instead of two NRTIs (Staszewski 2003, Orkin 2004). In ACTG 5095, there was clearly no difference between Combivir™+efavirenz and Trizivir™+efavirenz; not even in highly viremic patients (Gulick 2005).

More drug classes: The data on whether to use three or two drug classes is not so clear.

ACTG 388: 517 relatively advanced HIV patients received indinavir, indinavir+efavirenz, or indinavir+nelfinavir (Fischl 2003). After two years, virological failure on indinavir+efavirenz was lower than in the other arms. The poorest results came from indinavir+nelfinavir. Thus, ACTG 388 showed an advantage of triple- over two-class therapy. However, some patients were treatment-experienced and around 10 % already had resistance mutations at baseline.

ACTG 384: 980 patients were distributed between six treatment arms (Robbins 2003, Shafer 2003): either AZT+3TC or d4T+ddI combined with efavirenz, nelfinavir or efavirenz+nelfinavir. The NRTIs were blinded; the rest were given openly. Preliminary data after a follow-up of 28 months is confusing: AZT+3TC were more effective than d4T+ddI, but only in combination with efavirenz, not with nelfinavir. Conversely, efavirenz was superior to nelfinavir, but only with AZT+3TC as a backbone. The quadruple arm was better than all triple regimen arms combined, but not in comparison to the single most effective arm of AZT+3TC+efavirenz.

INITIO: 911 patients received efavirenz, nelfinavir or efavirenz+nelfinavir, each with a backbone of d4T+ddI, in an open-label design. No difference was seen between the triple and quadruple arms (Yeni 2006). The main disadvantage of this long-term study was that the treatment regimens being studied became somewhat outdated, and dropout rates were correspondingly high as a result.

ANRS 081: tested a triple-class regimen consisting of d4T+nevirapine+indinavir compared to a conventional d4T+3TC+indinavir regimen in 145 patients who were

either treatment-naïve or had only little prior treatment experience. The triple-class arm fared worse. At week 72, 52 versus 79 % had a viral load below 20 copies/ml. 43 % discontinued the nevirapine therapy (Launay 2002).

FIRST (CPCRA 058): 1,397 patients were given two NRTIs together with either a PI, a NNRTI, or a PI plus a NNRTI. Because the trial started more than five years ago, the most frequently-used PI was nelfinavir, and boosted PI regimens were rare. Despite the limited predictive strength, the NNRTIs were found to be superior (MacArthur 2006).

Summary: in the studies cited, improved efficacy could not be demonstrated and increased side effects of the intensified regmens negatively impacted on adherence. Indeed, there is the risk of scaring patients away with the higher number of pills and side effects. It is still unclear whether in patients who first start with HAART at an advanced stage of their disease ("late presenters") such intensification of therapy is useful.

6. Unfavorable Primary Therapies

Combinations considered to be suboptimal include all forms of mono- and dual therapy, especially two NRTIs. Even one NRTI plus one NNRTI is not good, as shown by the INCAS Trial (Montaner 1998). When using NRTIs, it is important to make sure that they are not competing for the same bases. Combinations of thymidine analogs (AZT+d4T) or cytidine analogs (FTC+3TC) make no sense. The thymidine analogs AZT and d4T are even antagonistic (Havlir 2000, Pollard 2002). ddC (HIVID™), saquinavir-SGC (Fortovase™) and amprenavir (Agenerase™), which have partially been taken off the market, should be avoided. T-20, darunavir, and tipranavir as well as delavirdine and atazanavir (in some countries) are not licensed for use in primary therapy. Ritonavir in full dose (not as boosting) can be rejected, as the tolerability is so poor. The much-used combination d4T+ddI, is also not recommended because of mitochondrial toxicity.

Abacavir plus NNRTIs simultaneously: a new ABC-containing combination should not include a new NNRTI. Both can cause allergies, which are often difficult to distinguish from one another. In the case of abacavir, even a suspected allergy rules out re-exposure, so that an important drug may be unnecessarily and permanently lost. In CNA30024, 9 % of patients developed a hypersensitivity reaction on ABC+3TC+efavirenz (DeJesus 2004).

NNRTI combinations: NNRTIs act non-competitively at the same site, and furthermore all can cause a rash, making differential diagnosis difficult. Efavirenz levels seem to be lowered considerably with nevirapine (Veldkamp 2001). In the wake of the 2NN Study, it finally seems clear that the combination of efavirenz and nevirapine should be avoided. The study arm with this combination fared worse than the other arms, mainly due to toxicity (Van Leth 2004).

TDF-triple nuke: Tenofovir should not be administered as part of a triple nuke regimen. Too many studies have reported poor response rates, particularly in combination with ABC+3TC (Hoogewerf 2003, Jemsek 2004, Khanlou 2005, Gallant 2005). See "Triple Nuke".

TDF+ddI: It is rare that a combination is discarded within only a few months with such a data collection: at least five trials, which tested TDF+ddI plus a NNRTI, resulted in a high failure rate of therapy, and some were stopped prematurely (Leon 2005, Podzamczer 2005, Maitland 2005, van Lunzen 2005, Torti 2005). The worst efficacy was observed in patients with a significant immune defect and high viral load. The company BMS even sent a warning letter concerning TDF+ddI. Meanwhile, there have also been reports of unfavorable effects on the CD4 cells, despite a good virological response. (Kakuda 2004, Barrios 2005). The reasons for this effect have not been fully explained. Reports of higher toxicity and in particular pancreatitis (Blanchard 2003, Martinez 2004, Masia 2005, Crane 2006), have been described and therefore the combination of TDF+ddI is no longer recommended.

Starting gradually: All drugs should be started simultaneously. In several studies, significant differences were shown between patients who were started on three drugs simultaneously and those who were started on only two drugs (Gulick 1998, Ait-Khaled 2002). The risk of a virological treatment failure is doubled even after years if dual therapy is given for just a few weeks (Phillips 2002). There is no doubt: the "cautious approach", as is sometimes practiced due to concern over too many side effects, is unnecessary and dangerous. This also applies to the dosing – starting therapy should always be with the full dose (exception: nevirapine! See corresponding section).

Avoidable mistakes in primary therapy

- Mono- or dual therapy (except in controlled trials), as well as a slow introduction – always start with a complete HAART regimen!
- Lowering the doses at the beginning (with the exception of nevirapine!)
- T-20, delavirdine, tipranavir (not licensed for primary therapy)
- ddC (HIVID™), SQV-SGC (Fortovase™), amprenavir (Agenerase™) – distribution has been partially stopped
- Ritonavir (not tolerated – only for use as booster)
- AZT+d4T and 3TC+FTC (antagonistic effects)
- TDF+ddI (diverse reasons), d4T+ddI (too toxic)
- TDF in triple nuke therapy (especially without thymidine analogs)
- Simultaneous introduction of ABC and NNRTIs (allergy potential)
- Efavirenz+nevirapine (too toxic)

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7. When to change HAART

Christian Hoffmann and Fiona Mulcahy

Antiretroviral therapy is frequently modified. This occurs in up to 50% of patients within the first year of therapy (Mocroft 2001, Fätkenheuer 2001). The most important reasons are discussed below. These are:

1. Acute side effects
2. Long-term toxicity (or concern regarding this)
3. Virological treatment failure

7.1 Change due to acute side effects

Not every acute side effect requires immediate modification or complete cessation of therapy. Mild nausea or diarrhea can occur in the beginning and should be tolerated. Gastrointestinal side effects that occur during the first weeks are not dangerous, are treated easily (see "Side Effects"), and often improve spontaneously. The same is true for mild CNS disorders on efavirenz or mild allergies. However, certain adverse drug events (see box) almost always require immediate alteration of HAART, as they could seriously endanger the patient.

Side effects that almost always require alteration of HAART

- Severe diarrhea, which persists despite loperamide even after several weeks (usually due to nelfinavir, lopinavir, fosamprenavir)
- Severe nausea, which persists despite metoclopramide, which requires continuous treatment or leads to significant weight loss (usually AZT, ddI)
- Polyneuropathy (d4T, ddI, possibly also 3TC – often resolves very slowly, therefore change treatment quickly!)
- Severe anemia (AZT)
- Severe, progressive muscular weakness (d4T!, ddI!)
- Pancreatitis (ddI, ddI+TDF!, d4T+ddI+HU! In rare cases lopinavir/r)
- Lactic acidosis (most often d4T+ddI, but also all other NRTIs)
- Severe allergies with involvement of mucous membranes, fever (typically abacavir, NNRTIs, more rarely fosamprenavir)
- Renal failure (tenofovir, indinavir)
- Nephrolithiasis (indinavir)
- Hepatotoxicity with transaminases > 5 x normal values (nevirapine, tipranavir)
- Jaundice (nevirapine, atazanavir, indinavir, tipranavir)
- Severe repetitive onychitis (indinavir, possibly also 3TC)
- Psychosis (efavirenz, possibly also AZT)

7.2 Change due to long-term toxicity

In the last few years, many clinicians have changed virologically successful combinations to minimize cumulative long-term toxicities (especially lipodystrophy and dyslipidemia). In particular, PIs and d4T are replaced with NNRTIs or other NRTIs. The most important studies are discussed below.

PI replacement

Replacement of PIs by NNRTIs or NRTIs is virologically safe, if the viral load is well suppressed (Table 7.1). It seems to work reasonably effectively on the lipid levels, but the effect on lipodystrophy is much weaker. Lipid levels are most likely to improve after switching to abacavir, and are least likely to do so on efavirenz. Quality of life improved significantly in the switch arms of most studies, probably due to the reduced pill burden. Previous NRTI experience increases the risk of virological failure following the switch to abacavir.

Finally, there is also the potential side effects of the new medications, which have been introduced, have to be heeded: a rash or hepatotoxicity can be expected with nevirapine, CNS disturbances with efavirenz. The hypersensitivity reaction with abacavir is a threat, which had a frequency of 10 % in the TRIZAL study (Katlama 2003). A meta-analysis also showed that the change to a PI free regimen is associated with a lower rise in CD4 cells (Owen 2004).

It is possible that the PI does not always have to be replaced by another class. With dyslipidemia, a change to atazanavir can be considered (Wood 2004, Gatell 2006), although in our experience it has little effect on lipodystrophy.

Table 7.1: Randomized studies on switching from PIs to other drugs

Source	N	Wk	Viral load Effect	Effect of switch on lipids (L) or lipodystrophy (LD)
PI → NVP				
Barreiro 2000	138	24	Advantage	L unchanged, LD better
Ruiz 2001	106	48	n.s.	L better, LD unchanged
Arranz-Caso 2005	160	48	n.s.	L better, LD better
PI → EFV				
Becker 2001	346	48	Advantage	L unchanged
Molina 2005	355	48	Advantage	L/LD n.a., side effects similar
PI → ABC				
Clumeck 2001	211	24	Advantage	L better, LD subjectively better
Opravil 2002	163	84	Disadv. (trend)	L better, LD unchanged
Katlama 2003	209*	48	n.s.	L better, LD better
Keiser 2005	104	28	n.s.	L better
PI → EFV v NVP				
Negredo 2002	77	48	n.s.	L only better on NVP, LD unchanged
Calza 2005	130	48	n.s.	L actually worse, if the PI-arm contained lipid reducer
PI → EFV v NVP v ABC				
Martinez 2003	460	48	Trend against ABC	L only better on ABC. LD probably unchanged

All studies (except Martinez 2003), were openly randomized against the continuation of PIs. All patients had been on PIs for several months at the time of the switch, with undetectable viral load. Viral load in the switch arm versus the continuing arm. Wk = weeks, LD = lipodystrophy, L = lipids, n.a. = not available, n.s. = not significant.

*Only 62 % were taking a PI, the rest were on NNRTIs or triple nuke.

d4T replacement

The thymidine analog d4T, which plays a leading role in mitochondrial toxicity (see corresponding section), is also frequently replaced with other NRTIs. The switch studies were mainly smaller, however, and sometimes the PIs were replaced at the same time (see Table 7.2).

Table 7.2: Randomized studies on switching from d4T to other drugs

Source	N	Switch	Wk	Effect of switch
Carr 2002 Martin 2004	106	ABC instead of d4T or AZT	104	LA better, lipids unchanged
John 2003	37	AZT instead of d4T and ABC instead of PI	48	LA of limbs slightly better, lipids and abdominal fat unchanged
Moyle 2003	30	ABC instead of d4T or PI/NNRTI, or AZT+ABC instead of d4T+PI	48	LA better (when replacing d4T) Lipids better (when replacing PI)
McComsey 2004*	118	AZT or ABC instead of d4T	48	LA better, lactate better
Milinkovic 2005	56	TDF or d4T-reduction to 30 mg instead of d4T	24	LA, lipids better (TDF effects stronger than d4T reduction)
Moyle 2006	105	TDF or ABC instead of d4T or AZT	48	LA better, lipids better on TDF
Murphy 2006	101	ABC or nuke sparing instead of d4T or AZT	48	LA better

No study showed any difference with respect to virological failure. Wk = weeks, LA = lipoatrophy. McComsey 2004/Moyle 2005: only patients with LA were investigated. * The study was not randomized.

Despite the heterogeneity of these studies, they clearly demonstrated that lipoatrophy improves if d4T is replaced. In particular, the subcutaneous fat of the limbs increases, although at first the improvement is often unrecognizable clinically and can only be detected in DEXA scans (Martin 2004). Histological investigations have shown that the elevated rate of apoptosis in adipocytes normalizes when d4T has been replaced (Cherry 2005, McComsey 2005).

It therefore seems to be advisable to replace d4T with another NRTI. With abacavir, however, the HSR remains a problem, occurring in 10 % of patients in the Mitox Study (Carr 2002). It should also be noted that it is never certain whether the viral suppression will persist under a new regimen. Particular caution has to be taken when there has been long-term pretreatment.

One example of what could happen with a strategic change is shown in Table 7.3. This case also shows how carefully one has to approach changes if there has been inadequate dual-therapy in the past. The ice is thin!

Table 7.3: Example of what could happen on switching drugs. (n.k. = not known)

Date	(HA)ART	CD4 cells	Viral load
1996-98	AZT+ddC	n.k.	n.k.
Since 1998	AZT+3TC+NFV (always under the detection limit)	n.k.	n.k.
Nov. 2002	Findings: significant lipoatrophy. Decision to switch	688	< 50
Feb. 2003	**ABC**+3TC+NFV*	788	< 50
Apr. 2003	ABC+**TDF+NVP** (= planned ART, see notes)	871	< 50
May 2003	Severe rash, ALT/AST > 500 U/l	n.k.	< 50
Jun. 2003	ABC+TDF+**3TC**		
Aug. 2003	Resistance: M41L+D67N+M184V+L210W+T215Y	679	37,400
Sep. 2003	**AZT**+3TC+**NFV**	n.k.	59,100
Oct. 2004		743	< 50

*On account of lipodystrophy, the combination of ABC+TDF+NVP was planned in February 2003, but due to potential allergic reactions to ABC and NVP, it was changed in two steps. Rash with hepatic involvement did indeed occur on NVP in April 2003, so that NVP was replaced by 3TC – triple nuke! The resistances that were then detected were almost certainly present under AZT+ddC, but sufficiently suppressed by PI therapy. Surprising is the good reaction after the reintroduction of the former therapy.

Switching to tenofovir

In studies on therapy-naïve patients, tenofovir had considerably lower mitochondrial toxicity than d4T or AZT. In the 903 Study tenofovir was tolerated significantly better than d4T (Gallant 2004, 2006). Switching to tenofovir can also help to reduce side effects (Domingo 2004). In the 903 Study, lipids improved when d4T was switched to tenofovir (Suleiman 2004). In a retrospective study, both lipids and liver enzymes improved (Schewe 2006). The mitochondrial DNA that was depleted by d4T seems to improve (Ribera 2003).

However, only a few randomized studies have been performed on switching thymidine analogs to tenofovir. In 105 patients with lipoatrophy, who had the thymidine analog replaced by either tenofovir or abacavir, the clinical changes after 48 weeks were the same, but lipids improved more significantly on tenofovir (Moyle 2006).

In view of the poor efficacy of TDF-containing triple nuke combinations (see corresponding section), one should avoid these wherever possible (Hoogewerf 2003, Perez-Elias 2005). One example is shown in Table 7.3.

In practice, changes are often made, which go further than PI and/or d4T/AZT simply due to concerns over long-term toxicity. This (e.g. abacavir or tenofovir instead of ddI) is based on laboratory studies showing a hierarchy with respect to mitochondrial toxicity (see also section on mitochondrial toxicity). In addition, there are reports on simplification of therapy, in which mono- or nuke-sparing strategies are used (see below). There is so far no evidence of a clinical benefit. Therefore, it is currently advisable to wait for the results of the corresponding clinical studies.

Switch to nuke sparing

Some studies have also tried to avoid NRTIs altogether. These “nuke sparing” strategies have even been tested on therapy-naïve patients, too (see previous chapter) and following the results of the ACTG 5142 study, could play a role in the fu-

ture (Riddler 2006). In ACTG 5142, nuke sparing was virologically effective and beneficial with respect to lipoatrophy; however, the tolerability was no better than in conventional regimens. In fact, dyslipidemia was observed more frequently (Riddler 2006). In the largest study to date, ACTG 5116 (Fischl 2007) in 236 patients on an effective HAART, the change to lopinavir/r plus efavirenz in comparison to efavirenz plus 2 NRTIs led to an increased rate of discontinuation, due as much to virological failure as to side effects. The results of this study are in contrast to several other studies (see Table 7.4) and to the results of lopinavir/r plus efavirenz in therapy-naïve patients (Riddler 2006). At present, it seems to be too early to recommend nuke sparing as a switch strategy. Of course, this also applies to the monotherapy with boosted PIs (see next chapter).

Table 7.4: Studies of switching to nuke sparing with PI plus NNRTI

Source	n	Switch	Wk	Effect of the switch
Lopez-Corles 2003	42*	SQV/r + EFV	48	Virologically good
Tebas 2005 (ACTG 5125)	62	LPV/r + EFV	48	Diverse metabolic disturbances, lipoatrophy better
Negredo 2005 (NEKA)	16*	LPV/r + NVP	48	Virologically good, lipids and mitochondrial DNA better
Boyd 2005 (HIVNAT 009)	26*	IDV/r + EFV	48	Virologically good, but many SE from IDV, LA possibly somewhat better
Fischl 2007 (ACTG 5116)	118*	LPV/r + EFV	110	Trend to more virological failure, more SE
Murphy 2006 (ACTG 5110)	101	LPV/r + NVP	48	Virologically safe, lipodystrophy better

LA = Lipoatrophy, SE = side effects * im Switch-Arm

7.3. Switch for virological treatment failure

The change in treatment due to virological failure requires a certain degree of finesse, but also decisiveness! There is a great potential for mistakes to be made. It is important to explain to the, often skeptical, patient ("Shouldn't I save other drugs for later?") when and why changes have to be made.

HAART should be rapidly changed in the case of insufficient viral suppression and/or after an increase in plasma viremia, otherwise there is a risk of new resistance mutations, which may eliminate future treatment options. First-line therapy with AZT+3TC+indinavir is a good example. If this regimen fails but the patient continues this regimen, the virus accumulates further mutations (including TAMs) such as 41L, 67N, 210W, 215F, 184V, 82T, 84V, 46L, 90M – and this eliminates all other currently available drugs with the exception of NNRTIs and ddI (and T-20). If an NNRTI is added, most options disappear. Even individual mutations can be a problem: K65R, which very frequently occurs on failing tenofovir-containing triple nuke therapies, leads to considerable loss of efficacy for ABC, 3TC, FTC and probably ddI.

Viral replication in the presence of insufficient plasma levels is ideal for the development of resistance mutations. In the case of clear virological failure, action must be taken without delay – the longer one waits, the more difficult things become. Insufficient viral suppression means a viral load above the level of detection of 50 copies/ml. Some clinicians, however, tolerate values up to 500 or even 1,000 copies/ml. In patients with good options for subsequent regimens and good compliance, we consider this delay unwise, with a few exceptions.

Currently, several trials are underway to investigate two randomized strategies in patients, in whom several HAART combinations have failed: either change immediately, or when the viral load reaches a certain level ("early versus deferred switch"). The preliminary results indicate that even in such cases, one can wait a short time (Nasta 2006, Riddler 2006).

Arguments for rapid management of virological treatment failure	**Argument for waiting with virological treatment failure**
The virus will take the opportunity to generate further resistances	New therapies always carry the risk of new toxicities/intolerabilities, which can necessitate interruption of treatment
Options are preserved	With low viremia, most patients are immunologically stable for a long time (at least clinically)
The less resistances that are present, the more successful the switch	The replicative fitness is often reduced, and this often remains under therapy
The lower the viral load by the switch, the better the effect of the new therapy	With a lower viral load, resistance testing is often not possible; although resistance mutations are already present, one makes the switch "blind"
The new regimen is often no more complex than the actual one – sometimes, it is possible to simplify it (once daily, d4T/ddI out, etc.)	It is often difficult to convince patients to change a well-tolerated simple regimen

In cases of clinical treatment failure (AIDS) or immunological failure (stagnation or decrease in the level of CD4 cells), in which the viral load is below 50 copies/ml, the value of a change in therapy is uncertain. Some combinations such as TDF+ddI, however, are rather unfavorable for immunological reconstitution; such combinations should be changed. Otherwise, by switching HAART alone, one hardly improves anything.

It is important that when virological failure occurs, the individual situation of the patient is carefully analyzed. In particular, several questions need to be addressed:

What are the reasons for the measurable viral load?

A viral load above 50 copies/ml does not necessarily mean that resistance mutations have developed. The plasma drug levels may be insufficient (measure the plasma levels!) - which, in turn may be due to: drug malabsorption, drug interactions or insufficient dosing (e.g. in very big, heavy patients). Compliance is also critical. Any possible difficulties associated with the taking of the drugs should be openly addressed: Is it the number of pills? Do restrictions in food intake cause problems? Would once-daily treatment be better? Are there other reasons, such as depression? The risks of resistance developing as a result of non-compliance should be reiter-

ated. If plasma levels are sufficient and viral load remains detectable (monitor blips occurring within a few weeks!), treatment should be changed as soon as possible.

How vulnerable is the present combination?

NNRTI regimens are very sensitive, as cross-resistance can develop particularly rapidly for the whole class. Thus, a prompt change in therapy is even more vital than with the other drug classes. Delaying this by even a few days or weeks may be too long! Rapid development of resistance can also be expected with 3TC (and FTC). A PI-containing regimen without an NNRTI may allow a little more time, but the credo still applies: the higher the viral load at the time of modification, the lower the chances of success. One should not wait too long.

What options does the patient have, and what are the consequences of the change in therapy?

The more options that remain available, the sooner they should be utilized. Therapy can often be intensified quite easily (e.g. adding abacavir plus an NNRTI). In such cases, the decision to change or intensify a regimen is less difficult.

On the other hand, it may be advisable to continue therapy in a patient with three NRTIs, even if the plasma viremia is not completely suppressed. Often, the viral load does not rise above the baseline value, and the CD4 cells remain stable or even increase. Some experts advocate waiting in these cases. Resistances to nucleoside analogs are to be expected, and therefore NNRTIs and PIs can be saved from the start. Even when multiple resistances are already present, one is probably able to wait initially (see above).

In all cases, it has to be clarified beforehand whether the patient is eligible for an intensification of therapy. A patient on triple-class therapy as well as extensive pre-treatment usually has few options left. These are often reduced even further by side effects. In such cases, the goal of achieving a viral load below the level of detection may have to be abandoned (see also “Salvage Therapy”).

References

See at the end of the next chapter.

8. How to change HAART

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A switch because of side effects of an otherwise successful therapy is usually straightforward. The suspected drug is replaced with another drug of the same class. Difficulties can arise if alternate drugs are contraindicated because of potential toxicity or if resistance mutations against some of these drugs are suspected. In such cases, changes have to be individualized according to the situation of the patient.

This chapter discusses two other important reasons for switching: changing due to virological failure, and change to simplify the HAART regimen. Switching out of concern for lipodystrophy has been discussed in previous chapters.

Change due to virological failure

The same principles apply as when initiating therapy: compliance, dosing issues, concurrent diseases, co-medications and drug interactions. It is also essential to consider treatment history and possible existing resistance mutations. Although desirable before any change in treatment, resistance tests are not always practical. It is therefore useful to become familiar with the most important resistance mutations, particularly for nucleoside analogs (see Table 8.1). The basic principles for changing therapy in cases of virological failure apply: the faster the change, the better; the virus should be given as little time as possible to generate more resistance mutations. In addition: the more drugs that are changed, the higher the likelihood of success for the new regimen.

Table 8.1: Expected resistance mutations with different nuke backbones

Failing nuke backbone	Mutations
AZT/d4T+3TC AZT+3TC+ABC	M184V and then successive TAMs, the longer one waits
TDF+3TC/FTC	K65R and/or M184V
ABC+3TC	L74V > K65R and/or M184V
AZT/d4T+ddI	TAMs, Q151M, T69ins
TDF+ABC/ddI	K65R

The situation with NNRTIs is more straightforward: there is usually complete cross-resistance. Continuation in the presence of these resistance mutations is of no use, as they have no impact on the replicative fitness of the virus.

There are also relevant cross-resistance mutations for PIs. Resistance testing is therefore recommended here. At the latest after the second PI, the area of salvage begins, which is discussed in more detail in the next chapter.

Table 8.2 provides a rough guide on how to proceed without knowledge of resistance mutations.

Table 8.2: Changing first-line therapy without knowledge of resistance mutations*

Failing initial therapy	Potentially successful change	
3 Nukes	2 new nukes plus NNRTI or PI 2 new nukes plus NNRTI plus PI	possibly also: with high viral load
2 Nukes + 1 NNRTI	2 new nukes plus PI	
PI + NNRTI	2 nukes + PI	
2 Nukes + 1 PI	2 new nukes plus NNRTI plus possibly new boosted PI, or boost present PI, if this was not already the case	

* Note: there is insufficient data available on all these changes. In individual cases, other modifications or simply waiting may be advisable. Apart from nelfinavir, all PIs should be boosted.

If the increase in viral load is minimal, treatment success may also be achieved with simple changes – if one acts quickly. In the case of two NRTIs plus an NNRTI, for example, treatment may possibly be intensified simply by the addition of abacavir (Degen 2000, Katlama 2001 Rozenbaum 2001). In a placebo-controlled study, 41 % of patients on stable ART with a viral load between 400 and 5,000 copies/ml achieved a viral load below 400 copies/ml at 48 weeks after addition of abacavir alone (Katlama 2001). Such results could possibly be even better with "more rigorous" entry levels (for example, not waiting to change therapy until 5,000 copies/ml are reached, but acting already at 500 copies/ml).

Addition of tenofovir also seems possible in certain cases (Khanlou 2005). Tenofovir reduced the viral load under stable HAART by 0.62 log (Schooley 2002). Our experience with this approach has been good in cases with minimal increases in the viral load (up to 500 copies/ml) and in the absence of TAMs.

In patients who have been treated exclusively (and over a prolonged period) with nukes, this strategy is not promising. Extensive resistance mutations usually exist, so that a complete change of HAART is necessary. At least two randomized studies (some blinded) have shown that most benefit is achieved by switching to an NNRTI plus a PI plus at least one new NRTI. This has been shown for both nelfinavir plus efavirenz and indinavir plus efavirenz (Albrecht 2001, Haas 2001). In patients previously treated with NRTIs or NNRTIs, a boosted PI must be used.

Change to simplify – do "maintenance therapies" work?

Can HIV infection be treated in a similar fashion to some hematological diseases or tuberculosis, with a sequence of intense induction therapy, which is then followed by less toxic (and less expensive) maintenance therapy? The idea is appealing, and has circulated almost since the beginning of HAART. Before 2003, the answer was clearly that maintenance therapies did not work. By 1998, three randomized studies (Trilège, ADAM, ACTG 343) had already destroyed all hope that HAART might be reduced to two or even one drug.

In the French Trilège Trial, 279 patients adequately treated with HAART were randomized to three arms of different intensity (Pialoux 1998, Flander 2002). At 18 months, the viral load had increased to above 500 copies/ml in 83 patients – 10 on AZT+3TC+indinavir, but 46 on AZT+3TC and 27 on AZT+indinavir. However, temporary dual therapy had no negative consequences, and resistance did not develop (Descamps 2000). In the ADAM Trial (Reijers 1998), patients who had been treated with d4T+3TC plus saquinavir+nelfinavir for several months either stopped

or continued their nucleoside analogs. The study was already doomed at interim analysis: in 9/14 (64 %) patients, simplifying therapy already had a detectable viral load at 12 weeks, versus 1/11 (9 %) of those continuing on the previous regimen. The third study, finally led to the end of the notion of maintenance therapy was ACTG 343. 316 patients, with a viral load below 200 copies/ml for at least two years, either continued to take AZT+3TC+indinavir or a simplified regimen of AZT+3TC or indinavir. The failure rate (viral load above 200 copies/ml) was 23 % versus 4 % on continued therapy (Havlir 1998).

In the last few years, newer better drugs have been licensed. In particular, lopinavir with its antiviral potency and concurrent high resistance barrier casts the negative image of maintenance therapies in a different light. Other boosted PIs have also been tried, and several smaller studies on the simplification of therapy have been conducted with "PI/r monotherapy" (see Table 8.3).

Table 8.3: Newer studies on changing to "maintenance therapies"

Source	n	"Maintenance"	Week	Less than 50 copies?
LPV/r-mono				
Arribas 2005 (OK04 Study)	198	LPV/r versus 2 NRTIs+LPV/r	48	81 versus 95 % (ITT). Failure mainly due to poor adherence
Delfraissy 2006 (MONARK)	136	LPV/r versus CBV+EFV	48	71 versus 75 % (ITT), 84 versus 98 % (OT), lower viremia in mono-arm
Cameron 2006 (M03-613)	155	LPV/r versus CBV+EFV	24	50 versus 61 % (ITT), lower viremia in mono-arm
Nunez 2006 (KalMo)	60	LPV/r versus 2 NRTIs+LPV/r	48	83 versus 87 % (ITT, VL<80)
Other "mono"				
Kahlert 2004	12	IDV/r	48	92 %, 1 dropout, no failure
Vernazza 2006 (ATARITMO)	28	ATV/r	24	92 %, no resistance or failure
Swindells 2006 (ACTG 5201)	34	ATV/r	24	91 %, no resistance
Karlstrom 2006	15	ATV/r	16	33 % treatment failure, study interrupted
Other				
Girard 2006 (COOL Trial)	143	EFV+TDF versus EFV+3TC+TDF	24	82 versus 97 %

OT = on treatment; ITT = intention to treat

They show that in most cases virological suppression is maintained when there is a switch to PI/r monotherapy. In one study with lopinavir/r, lipoatrophy was even reduced (Cameron 2007). Resistances seldom occurred (Arribas 2007). However, in a few patients, low viremia was observed, especially with low CD4-cell counts or, not unexpectedly with reduced compliance (Campo 2007). Overall, monotherapy with lopinavir/r seems to be somewhat less potent than the earlier triple combinations.

There is much less data available for the other PIs than there is for lopinavir/r. A pilot study with atazanavir was interrupted after 5/15 patients demonstrated virological failure (Karlstrom 2006). In the Prometheus Study, PI- and d4T-naïve (including some completely treatment-naïve) patients were randomized to a regimen of saquinavir/r plus/minus d4T. After 48 weeks, 88 versus 91 % of patients in the on-treatment analysis were below 400 copies/ml. However, patients with high viral loads were not stable on this treatment (Gisolf 2000).

In the French COOL Study, 143 patients were randomized to TDF+3TC+efavirenz or TDF+efavirenz for 48 weeks. Inclusion criterion was HAART with a viral load below 50 copies/ml for at least three months; patients with prior treatment failure were excluded. There were no restrictions on CD4 counts. A recently presented appraisal showed a significantly poorer response under double- compared to triple-therapy. It was also important that there was no difference in the toxicity in both arms – the additional administration of 3TC obviously had a very important effect on viral suppression, but did not increase the frequency of side effects (Girard 2006).

Conversion in order to simplify – triple nuke revisited

Triple nuke therapy, though now fairly obsolete for first-line therapy (see "Which HAART to start with"), may be an option for maintenance therapy. At least three randomized studies could not detect any virological disadvantage (Katlama 2003, Bonjoch 2005, Markowitz 2005).

In the ESS40013 Study, 448 patients were treated with AZT+3TC+ABC plus efavirenz. After 36 or 44 weeks, 282 patients with undetectable viral load at this time were randomized to continue with the same therapy or to stop efavirenz. After 96 weeks, 79 versus 77 % of patients were still below 50 copies/ml, proving that triple nuke was not inferior (Markowitz 2005).

In a Spanish study, 134 patients with an undetectable viral load for at least 24 weeks were randomized to receive either Trizivir™ or Combivir™ plus nevirapine (Bonjoch 2005). After 48 weeks, the viral load in both arms often remained undetectable (71 versus 73 % in the ITT analysis). Similar results were also seen in the TRIZAL study, in which 209 patients were randomized (Katlama 2003).

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9. Salvage therapy

Christian Hoffmann and Fiona Mulcahy

The term "salvage therapy" is not clearly defined in HIV medicine. It is currently used to refer to varying situations. Some speak of salvage only if all drug classes have failed, whereas for others it applies to second-line therapy onwards. No consensus on a definition has been reached at multiple conferences. Here, we define salvage as the therapeutic approach when at least one PI-containing regimen has failed. Moreover, the concept is constantly being shifted further back in the therapy career of patients. Today, many clinicians talk about salvage when there is resistance to at least two or three antiretroviral drug classes. Viruses with multiple resistances are in turn termed MDR ("multi-drug resistant") viruses.

In the last few years, significant progress has been made for these patients. T-20, tipranavir, darunavir, maraviroc, raltegravir and etravirine are also still effective in the presence of numerous resistances (see also "HAART 2007/2008"). This provides hope for the future. In addition, it changes the aim of therapy. These days, even in intensively pre-treated patients, an attempt should be made to reduce the viral load to below the level of detection (Youle 2006).

Nevertheless, there are many problems. Salvage studies are becoming increasingly more difficult as patients with MDR viruses are becoming less frequent (Lohse 2005). Homogenous patient populations are scarce as each one has an individual history of therapy, a different distribution of resistances and therefore varying prerequisites. In large HIV centers, often more than 50 different combinations are used. This makes it difficult to test new salvage substances in Phase II/III trials. It is also hard to find the correct study design: as the single use of an experimental drug in a failing regimen is ethically questionable, the appropriate ART must always be optimized (=OBT, optimized background therapy). If the OBT is too good, the effect of the new drug may be hidden, as many patients achieve a good viral suppression just on OBT. If the OBT is too poor, the effect of the new drug may only be temporary or too weak – the window through which the efficacy of a new salvage drug can be seen is small.

Background

First: it should not be forgotten that patients with MDR viruses, who often have a long therapeutic history, and who now presumably find themselves once again on a precipice, need encouragement. It is important not to deny anyone hope. Although some studies have shown that patients with MDR viruses have a worse prognosis than patients without resistances (Hogg 2005, Zaccarelli 2005), data are not unequivocal. In the GART Study, the risk of progression for patients with more than six resistance mutations was not increased in contrast to patients with less than twomutations, (Lucas 2004). Despite MDR viruses, the risk of developing AIDS with good CD4-cell counts is relatively small (Ledergerber 2004). MDR viruses have a weaker ability to replicate and are probably less aggressive (Prado 2005).

Furthermore, progress is continuing. New classes of drugs will arrive. So, for MDR, simply - be patient!

Until then, one should accept that even today there are patients in whom one has to say goodbye to the primary aim of therapy of reducing the viral load to undetectable levels – especially if despite better compliance the only response to intensification of therapy is more side effects. Sometimes it is better to step back and wait for new options (see below). If possible, these patients should be managed in large centers, in which the new possibilities are usually available sooner, and where there is more experience with complex salvage regimens. A single new medication should ideally not be used alone - use as many effective substances as possible!

It usually takes years to progress from virological to immunological, and finally to clinical treatment failure (see also "Principles of Therapy").

It is, however, important that patients with MDR viruses are very carefully observed and undergo regular (monthly) full body examination – something that is often neglected today in the long discussions about blood values and resistance testing for many HIV patients. Loss of weight, B-symptoms, oral candidiasis, OHL, and cognitive worsening are early signs of disease progression that should not be missed.

The following is a discussion about a few salvage therapy strategies, which when used alone or in combination, are promising.

- Salvage with lopinavir/r, tipranavir/r, darunavir/r and T-20
- Double PI regimens
- Mega-HAART, with or without treatment interruptions
- Utilizing NNRTI "hypersusceptibility"
- Salvage through recycling
- Just waiting, and even simplifying ART
- Experimental salvage drugs

Salvage with lopinavir/r, tipranavir/r, darunavir/r and T-20

The three boosted PIs lopinavir (Kaletra™), tipranavir (Aptivus™) and darunavir (Prezista™) have significantly improved salvage therapy. The resistance barriers are high, so that the response rates, even in the presence of multiple PI resistance is often still good. Although the occurrence of dyslipidemia is sometimes disturbing, the three substances should be considered following failure of the first PI.

Lopinavir/r: was, in 2001, the first important salvage drug. At least 5-7 mutations are necessary for failure of lopinavir/r (Kempf 2001, Masquelier 2002). In 70 patients on a failing PI regimen, the viral load fell by 1.4 logs after two weeks following the substitution of the PI with lopinavir/r (Benson 2002). However, two large studies have shown that the virological effect on PI-resistant viruses is only marginally better than other boosted PIs such as atazanavir/r and fosamprenavir/r – a difference could only, if at all, be seen when multiple PI resistances were present (Elston 2004, Johnson 2006).

Table 9.1: Patient example of the success of lopinavir/r in salvage therapy

Date	(HA)ART	CD4+ T-cells	Viral load
Mar 1993	AZT (later +ddC)	320	N/A
May 1996	AZT+3TC+SQV	97	N/A
Feb 1997	d4T+3TC+IDV	198	126,500
Aug 1997	d4T+3TC+NFV	165	39,500
Mar 1998	d4T+ddI+SQV/RTV+HU	262	166,000
Sep 1998		238	44,000
Jul 2000	AZT+3TC+NVP+LPV/r	210	186,000
Oct 2000		385	< 50
Oct 2004		569	< 50

Note the insufficient responses to new regimens after failure of the first PI; insufficient viral suppression over two years with surprisingly stable CD4-cell levels; and finally a durable response to lopinavir/r – after more than four years of suboptimal PI-treatment! NNRTI hypersusceptibility may have possibly been present in this case (see below). On switching to lopinavir/r, genotypic and phenotypic resistance to various NRTIs and PIs were present.

Tipranavir/r: In the RESIST studies, 1,483 intensively pre-treated patients with optimized therapy received either tipranavir/r or a boosted comparison PI (Hicks 2006). The patients had a viral load of more than 1,000 copies/ml and at least one primary PI mutation. After 48 weeks, tipranavir was immunologically and virologically superior to the comparison PI. However, the difference actually also occurred because some patients had already been pre-treated with lopinavir/r – when this was not the case, there was no longer a significant benefit. In other words, if lopinavir/r is still effective, tipranavir/r is not much better, but when the lopinavir/r card has been played, it can still be effective.

Darunavir/r: two large Phase IIb studies, POWER-1 and -2, led to the licensing in the USA in 2006. Almost 600 intensively pre-treated patients were included. In the 600 mg group (600/100 darunavir/ritonavir bid) the viral load in 46 % remained at less than 50 copies/ml after 48 weeks (Lazzarin 2006) - a significantly better result than the control PI (10 %), and a result that had so far never been seen in a patient group with extremely limited options. The effect of darunavir is of course not limitless. A total of 11 resistance mutations have been identified; above 3 mutations, the efficacy decreases significantly (DeMeyer 2006).

All three PIs are more successful, the greater the number of additional active substances available. In the RESIST- and POWER-studies, the proportion of patients, who had a viral load below the level of detection increased when T-20 was given in addition to tipranavir or darunavir (Lazzarin 2006, Hicks 2006). If tipranavir or darunavir are being considered, T-20 should therefore always be contemplated, too.

Double PI salvage regimens

Not only lopinavir but also other PIs can be boosted with low doses of ritonavir. With the introduction of new substances, these double PI strategies have lost some of their standing. They do, however, need to be briefly discussed as etravirin, maraviroc or raltegravir are not available everywhere.

Lopinavir/r + saquinavir/r: in vitro they have synergistic effects (Molla 2002). There do not seem to be any unfavorable interactions (Ribera 2004). In the LopSaq Study, for various reasons (resistance, toxicity), 128 intensively pre-treated patients received a nuke-free combination consisting of lopinavir/r (400/100 mg bid) plus saquinavir (1,000 mg bid). At week 48, 61 % had achieved a viral load of less than 40 copies/ml. However, the response in the presence of numerous PI resistance mutations and low CD4 counts was poor (Staszewski 2006).

Atazanavir/r + saquinavir/r: under 300 mg atazanavir, 100 mg ritonavir and 1,600 mg saquinavir, not only the trough levels, but also the intracellular levels of saquinavir increase significantly (Boffito 2004, Ford 2006). In the ATSAQ study (Rottmann 2004), 40 heavily treatment-experienced patients were treated with a nuke-free combination of 300 mg atazanavir, 100 mg ritonavir and 2 x 1,000 mg saquinavir. After 32 weeks, 85 % had reached a viral load below 400 copies/ml.

Three further studies are currently underway. Despite the fact that saquinavir levels are elevated by atazanavir, ritonavir is also required. The unboosted combination is relatively weak (Haas 2003, Johnson 2005).

Saquinavir/r + fosamprenavir: was one of the first PI combinations (Eron 2001) and is still interesting due to its partially overlapping resistance profile. Fosamprenavir reduces saquinavir levels somewhat, but this is compensated by the administration of 200 mg ritonavir bid (Boffito 2004).

Lopinavir/r + indinavir: in vitro, there is synergy. The combination has been tested in different doses (Staszewski 2003, Isaac 2004). But, in view of the considerable tolerability and the improved salvage options available today, indinavir is rarely used. . However the data is not completely clear-cut, and case numbers are fairly low. An additional ritonavir dose is possibly necessary, and TDM is recommended. Indinavir and lopinavir do not usually seem to require dose adjustment.

Other double PI combinations: initial pilot studies have shown that advantageous interactions seem to exist between atazanavir and fosamprenavir (Zilly 2005, Khanlou 2006). This also applies to lopinavir + atazanavir (Langmann 2005), a combination that is currently under investigation in the LORAN study.

Unfavorable double PI combinations: atazanavir + indinavir should be avoided as both drugs cause hyperbilirubinemia. Severe diarrhea is to be expected when combining lopinavir/r + nelfinavir, and the lopinavir levels also decrease (Klein 2003). Indinavir + nelfinavir have relatively weak activity (Riddler 2003).

Unfavorable interactions exist between tipranavir and other PIs. The levels of lopinavir, saquinavir and amprenavir are reduced (Walmsley 2004). Even the combination of lopinavir/r + fosamprenavir, which has a very promising resistance profile, cannot be considered because of the unfavorable PK data – possibly the plasma levels of both drugs are significantly reduced through a complex interaction (Mauss 2002, Kashuba 2005). It should be noted that increasing the dose of ritonavir does not change anything (Mauss 2004, Taburet 2004).

Double PI combinations are not routine treatments. They should only be considered in salvage patients who are suffering from NRTI side effects (mitochondrial toxicity), and should be administered by experienced clinicians with access to therapeutic drug monitoring, so that dose adjustment is possible if required.

Table 9.2: Double PI combinations with sufficient supporting data

Combination	Daily Dose/comment	Source
More favorable		
Lopinavir/r + saquinavir	800/200/2,000	Staszewski 2006
Atazanavir/r + saquinavir	300/200/2,000	Boffito 2004 + 2006
Lopinavir/r + atazanavir	800/200/300	Langmann 2005
Saquinavir/r + fosamprenavir	2,000/200/1,400 bid	Boffito 2004
Lopinavir/r + indinavir	800/200/1,600 bid	Staszewski 2003
Less favorable		
Lopinavir/r + fosamprenavir	Poor PK data	Kashuba 2005
Atazanavir + saquinavir	Poor activity	Johnson 2005
Tipranavir + LPV/APV/SQV	Poor PK data	Walmsley 2004
Lopinavir/r + nelfinavir	Poor PK data, diarrhea	Klein 2003
Atazanavir + indinavir	Elevated bilirubin	
Indinavir + nelfinavir	Relatively poor activity	Riddler 2002

Mega-HAART with and without treatment interruptions

Intensified treatment combinations with five or more drugs – described as "mega"- or "giga"-HAART – may indeed be effective. However, only well-informed and motivated patients can be considered for mega-HAART regimens. Potential drug interactions are often difficult to predict. Nevertheless, mega-HAART will become less important with the introduction of new drugs and new drug classes.

So, do treatment interruptions produce any effect? In the GIGHAART Study, 68 heavily treatment-experienced patients were randomly allocated to eight weeks of treatment interruption or not (Katlama 2004). All patients were subsequently switched to a combination of 7-8 drugs: 3-4 NRTIs, hydroxyurea, 1 NNRTI and 3 PIs. In the treatment interruption group, efficacy after 24 weeks was significantly better, and viral load dropped by 1.08 versus 0.29 logs. The helper cells also increased significantly. These effects were still visible after 48 weeks, although less marked.

However, the results of the GIGHAART Study have not remained uncontradicted, and these days, there are a greater number of studies that have found treatment interruptions to have unfavorable effects. In CPRC064, in which treatment was interrupted for four months prior to the salvage regimen, no differences were found between patients with or without a treatment interruption (Lawrence 2003). However, it was disconcerting to see that patients who interrupted treatment not only had worse CD4-cell counts, but also a higher frequency of severe clinical events.

Other randomized studies did not find any virological benefit in interrupting treatment prior to a salvage regimen (Haubrich 2003, Ruiz 2003, Beatty 2006, Benson 2006), so that this strategy cannot be recommended at present (see "Treatment interruptions").

Utilizing NNRTI "hypersusceptibility"

Treatment-experienced but NNRTI-naïve patients often still respond surprisingly well to NNRTIs. In 56 patients in a small, randomized study, the proportion of patients with less than 200 copies/ml after 36 weeks increased from 22 to 52 %, as long as two new NRTIs and nelfinavir were given in addition to nevirapine (Jensen-Fangel 2001). In ACTG 359, delavirdine increased the virological response rate to a new PI from 18 to 40 % (Gulick 2002). "NNRTI hypersusceptibility" may be responsible for this. Viral strains, in which the IC50 (50 % inhibitory concentration) is lower than that of the wild-type in phenotypic resistance tests, are considered "hypersusceptible". This phenomenon, which was first described in January 2000 (Whitcomb 2000), and for which the biochemical correlate is still the subject of debate (Delgrado 2005), very rarely occurs with NRTIs, but quite frequently with NNRTIs – in particular in viruses that have developed resistance mutations against NRTIs.

NRTI hypersusceptibility has been described in several prospective studies (Albrecht 2001, Haubrich 2002, Katzenstein 2002, Mellors 2002). In an analysis of more than 17,000 blood samples, the prevalence in NRTI-naïve patients to, efavirenz and nevirapine was 9 and 11 %; in NRTI-experienced patients, it was notably 26 and 21 % (Whitcomb 2002). In particular, mutations on the codons 215, 208, and 118 are associated with NRTI hypersusceptibility (Schulman 2004).

There is some evidence that patients with NNRTI hypersusceptibility have better responses to treatment. Of 177 treatment-experienced (but NNRTI-naïve) patients, 29 % exhibited this type of lowered IC50 for one or several NNRTIs (Haubrich 2002). Of the 109 patients who received a NNRTI-containing regimen, the viral load in NNRTI hypersusceptibility was significantly lower after 12 months, and the CD4-cell count was much higher.

The replicative fitness does not seem to be important here (Schulman 2006). Even if the real significance and molecular correlate for NNRTI hypersusceptibility remain uncertain, the consequence is clear: patients with NRTI mutations and without NNRTI resistance should always receive a NNRTI in their new regimen if at all possible.

Salvage through recycling of older drugs

One can occasionally also make use of drugs that have already been used in the past as, for example, in the Jaguar Study (Molina 2003). 168 patients with more than 1,000 copies/ml and a median 4 NRTI mutations on stable HAART received either ddI or placebo. The viral load was reduced by 0.60 logs after 4 weeks. 68 % of patients had previously received ddI, and even in these patients, viral load was still reduced by 0.48 logs.

New salvage therapies should not only contain as many new active substances as possible, but should also contain drugs that force the virus to preserve the resistance mutations, which at the same time inhibits the replicative fitness. Thus, it may be reasonable to conserving the M184V mutation by continuing with 3TC or FTC (see below and section on resistances).

"Watch and wait" or even simplifying ART

Sometimes even the most intensified salvage protocol is not effective. Despite the use of T-20, darunavir and other antiretroviral drugs, viral load cannot be suppressed to undetectable levels. What should be done with such patients? The answer is: keep going, as long as the patient tolerates therapy! Multidrug-resistant viruses are typically slightly less aggressive than the wild-type, at least for a certain period of time. Therefore, 3TC for example still has a positive effect on the viral load even in the presence of a confirmed M184V resistance. In a small study, in which 6 patients with MDR viruses stopped only 3TC, the viral load increased 0.6 logs (Campbell 2005).

For this reason, very immunocompromised patients who are at risk of developing opportunistic infections should not stop HAART completely. In fact, all efforts should be made, particularly in such cases, to at least partially control the virus. Just "waiting" even on a suboptimal regimen is therefore a strategy that can be used to gain valuable time until new drugs become available.

HAART is not being taken by these patients without good reason: suboptimal HAART is better than none at all, and some viral suppression is still better than none. Patients benefit even with only a slight reduction in viral load (Deeks 2000). In a randomized study, patients with a viral load of at least 2,500 copies/ml on HAART either interrupted or continued their therapy for 12 weeks. It showed a significant CD4-cell benefit in those who remained on the failing HAART – the CD4 cells fell by merely 15 versus 128/µl in the interrupted group (Deeks 2001).

In a large cohort, CD4-cell counts did not drop, as long as the viral load remained below 10,000 copies/ml, or at least 1.5 logs below the individual set point (Lederberger 2004).

How intensive does the treatment have to be whilst in the waiting period? Some drugs can certainly be discontinued. The NNRTIs such as nevirapine or efavirenz should in principle be stopped if resistance mutations have been found, because replicative fitness is not influenced by the NNRTI mutations (Piketty 2004), and the occurrence of further NNRTI mutations, which would compromise future second generation NNRTIs such as etravirine, should be avoided.

Following the results of a pilot study, this probably also applies to the removal of PIs when resistances arise. 18 patients, in whom the viral load remained high despite more than 6 months on HAART (good compliance, appropriate efficacy), had the PIs removed from their respective therapies, whilst the NRTIs were continued (Deeks 2005). Within the first two weeks, none of the patients had an increase of more than 0.5 logs, and even after 16 weeks, no increase was observed in most patients (in only 5/18 patients, there was an increase of between 0.5 and 1.0 logs; in the others, there was no increase, or even a fall). A negative moderate immunological effect was only seen in a few patients. Repeated resistance tests showed that all PI mutations persisted in all patients for the first 12 weeks, in the absense of PIs. One retrospective study in HIV-infected children, in which the PIs had been discontinued. Here, but NRTI therapy continued, demonstrated an increase in viral load only after a long period of time (LeGrand 2005).

The course of one patient, in whom this approach has been successful for years, is shown in Table 9.3. Resistance tests showed that there were no changes in the MDR

virus. The approach of "watch and wait" on a simple NRTI regimen thus seems feasible in some patients for a certain period of time. The reasons for this phenomenon, however, are still not understood. It is of note that with PI therapy alone, this does not appear to be effective – in 5/5 patients, in whom only the nucleoside analog was stopped, the viral load significantly rapidly increased (Deeks 2005).

Table 9.3: Example of a successful "wait and watch"-strategy over three years

Date	(HA)ART	CD4+ T cells	Viral load
until 1997	AZT, AZT+ddC, AZT+ddI	40 (nadir)	107,000
Mar 97	AZT+3TC+SQV-HGC	84	259,000
Oct 97	d4T+3TC+SQV+NFV	211	67,000
Jun 98	d4T+3TC+NVP+IDV/r	406	1,200
Jan 00	AZT+3TC+ABC+NVP+IDV/r	370	1,030
Mar 02	AZT+3TC+ABC+TDF+NVP+IDV/r	429	3,350
Sep 02	d4T+ddI+3TC+NVP+LPV/r	283	5,000
Nov 02*		348	7,600
Jan 03		315	16,400
Feb 03	AZT+3TC+ABC	379	6,640
May 03		241	2,400
Dec 04	AZT+3TC+ABC+TDF**	298	4,200
Jan 06		323	5,800

*Resistance testing showed a total of 20 mutations, with genotypic resistance against all drugs tested. Compliance of the patient is very good, and plasma levels were always adequate. **TDF was added because of chronic hepatitis B infection.

An Italian study took another innovative approach (Castagna 2004). 50 patients with a viral load of at least 1,000 copies/ml on a 3TC-containing regimen, a M184V mutation and at least 500 CD4 cells/µl either completely interrupted treatment or continued with 3TC alone. The rationale: the M184V mutation reduces the replicative fitness of HIV. And in reality – patients on 3TC had a lesser increase in viral load (0.6 versus 1.2 logs) and lost less CD4 cells (73 versus 153/µl) over 24 weeks. The M184V mutation was maintained in all patients on 3TC, and no other mutations accumulated. In contrast, a shift to wild-type was observed in all patients without 3TC. The advantageous effect of 3TC could be observed over a period of up to 144 weeks (Castagna 2007).

As patient numbers are still very small in the data presented to date, some questions remain. How long and in which patients can these strategies remain successful? It is advisable to monitor CD4 cells at short intervals. Nevertheless, if such approaches could be confirmed in larger studies, they would be very attractive. In addition to better tolerability and simpler dosing, the approach with NRTI therapy alone would have the advantage of removing the selective pressure from the virus so that it does not generate further PI or NNRTI mutations – new drugs, which do not have unlimited efficacy for salvage, would not be compromised.

Specific New Salvage Drugs

Integrase inhibitors as well as CCR5-antagonists, attachment- or maturation inhibitors are the new classes of drugs that have already been shown to decrease the viral load in HIV patients.

In addition, new NRTIs and second generation NNRTIs such as SPD-754, etravirine or rilpivirine, are relatively far in their development (see "HAART 2007/2008"). In 2007, three Expanded Access Programs will be run: included are the second generation NNRTI etravirine, the integrase inhibitor raltegravir and the CCR5 antagonist maraviroc. Other substances are being tested in Phase III studies.

Where possible, patients with MDR viruses should be included in these studies. However, the problem is that it is only possible to take part in either a study or an EAP. Cooperation between firms is an exception, as each company only tests its preparation with licensed drugs. It would be ideal if at least two new active substances were used in salvage therapy.

Practical tips for therapy of MDR viruses

1. First question: which previous treatment has been used, with what level of success and for how long?
2. Choose as many new (active) substances as possible.
3. Don't wait too long, thus giving the virus the opportunity to develop further resistance mutations – the higher the viral load at the time of switch, the lower the chance of success.
4. Use lopinavir/r, tipranavir/r or darunavir/r! In addition, simultaneous therapy with T-20 should be considered.
5. Has the patient ever taken an NNRTI? If not, it's high time! If so, stop the NNRTI if there is resistance!
6. Don't demand too much from the patient! Not everyone is suitable for mega-HAART.
7. Don't exploit a single new drug – if the clinical condition and the CD4 cells allow, try and wait for a second active drug.
8. Endeavor for EAP (maraviroc, etravirine, raltegravir) or introduce the patient to a larger center.
9. Encourage the patient! There is no such thing as having no more therapeutic options. A "watch and wait" approach is often possible.
10. Don't allow reversion to wild-type virus – even in the absence of further options, a "failing" regimen should be continued.

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10. When to stop HAART

A current review of treatment interruption

Christian Hoffmann and Fiona Mulcahy

No other topic in the field of HIV medicine has evoked more heated discussions in the last years than the topic of treatment interruption. However, in the discussion over possible risks (AIDS, resistance) or advantages (reduction of toxicity and costs), many issues are confused. A distinction should be drawn between structured treatment interruptions (STIs), which are made with the knowledge of the treating physician , and unstructured "drug holidays" which the patient elects to take.The reasons for interruption of treatment can differ greatly.

- At the patient's request
- To improve compliance and psyche ("life sentence" removed)
- To reduce long-term toxicity
- For immunological reasons
- As a salvage strategy

Many treatment interruptions occur without the clinician's knowledge. For this reason alone, treatment interruptions are an important constituent of antiretroviral therapies, whether, as a clinician, one approves of them or not. To oppose them means to disregard the realities of treatment. The following chapter provides an overview of the current knowledge in this area. It is limited to patients with chronic HIV infection; (for recommendations on acutely infected patients see the chapter on "Acute HIV Infection").

Viral load and CD4 cells during treatment interruption

Almost all patients who stop treatment experience a "rebound" in viral load within a few weeks, even patients in whom this has been undetectable for several years (Davey 1999, Chun 2000). Viral load is usually detectable again within 10-20 days (Davey 1999, Harrigan 1999, Garcia 1999), and its doubling time in the blood is around 1.6 – 2.0 days. The viral load in compartments such as the CNS, as well as the semen and vaginal fluids, changes in parallel to that in the plasma (Garcia 1999, Neumann 1999). The patients should therefore be informed about the higher risk of transmitting HIV.

Frequently, an initial overshooting rebound is observed (De Jong 1997, Birk 2001), and only after a few weeks does the viral load settle to its original, pre-treatment level (Hatano 2000). The rebounding virus evidently does not originate from latent reservoirs; other cell populations must exist, from which these new viruses can be produced so quickly (Chun 2000, Ho 2000, Imamichi 2001).

Treatment interruptions can have serious immunological consequences. Often, CD4-cell counts drop within a short time to pre-treatment levels. The ground that has been gained on HAART is rapidly lost again. The drop is biphasic, and the reduction maximum in the first few months (Fagard 2005, Wit 2005, Skiest 2006).

CD4-cell losses vary greatly between patients but may reach 200 or 300/µl within a few weeks. The higher and faster the CD4 cells increased on HAART, the more rapid their decline (Tebas 2002). The CD4 nadir is also important. The lower it was, the more rapidly the cell count drops again (Maggiolo 2004, Skiest 2006). Age is also important – the older the patient, the more extensive the immunological deterioration. The loss of CD4 cells during an interruption may not be regained as quickly. In a prospective study, we saw a significant disadvantage for patients undergoing treatment interruptions. After a follow up of 18 months, CD4 cells were more than 120/µl less in these patients than in matched patients who had not interrupted treatment (Wolf 2005).

The risks: resistance, clinical problems, AIDS

Viral resistance always has to be anticipated whenever there is viral replication in the presence of suboptimal drug levels, and thereby resistant mutants gain a selective advantage over the wild-type virus. As a result, there are concerns that resistances could develop both during the washout phase of medication (increasing viral replication with insufficient plasma levels) and on re-initiation of treatment (continued replication despite sufficient plasma levels).

However, in the case of single treatment interruptions, the probability of this does not appear to be particularly high, as shown in 1999 by the small French COMET Study, one of the first studies on treatment interruption (Neumann 1999). But, there is no certainty as to whether interruptions might not eventually lead to development of resistant isolates, which merely require more time until they are able to dominate the wild-type. Mathematical models show that this risk – at least theoretically – is not low, especially if viral load rises to high levels (Dorman 2000, Bonhoeffer 2000).

The risk of resistance is probably higher for repeated treatment interruptions. In several studies, these have led particularly to NNRTI- or 3TC-resistance (Martinez-Picado 2002, Schweighardt 2002, Ruiz 2005). The risk seems particularly high for strategies involving stopping and starting of HAART at fixed intervals (see below).

Table 10.1 describes the example of a patient who was clinically well and who interrupted treatment. It was probably the repeated stopping and starting of HAART that ultimately led to resistance in this case.

The sharp increase in viral load that may often occur can present as a retroviral syndrome. The symptoms are similar to acute HIV infection, with lymphadenopathy, fever, asthenia and malaise (Colven 2000, Kilby 2000, Zeller 2001, Ruiz 2004). Thrombocytopenia has also been described during interruptions (Ananworanich 2003). The blood count needs to be monitored, especially in patients with a previous history of thrombocytopenia. Finally, attention should also be paid to patients who are co-infected with hepatitis B virus. If the HBV treatment with 3TC, FTC or tenofovir is interrupted, HBV rebound can result in fulminant and life-threatening hepatitis (Sellier 2004). It is therefore advisable to look after these patients very carefully and monitor the liver enzymes at least every two weeks.

Table 10.1: Example of the development of resistance due to repeated treatment interruptions*

Date	HAART/comments	CD4 cells	Viral load
Jun 97	AZT+3TC+SQV	288	67,000
Oct 99	HAART stopped, patient feeling well	540	< 50
Dec 99	Diagnosis of autoimmune hyperthyroidism	400	63,000
Jan 00	AZT+3TC+NVP (+ carbimazole)	260	74,000
Feb 00	Diagnosis of anemia (Hb 7.3 g/dl)	347	1,500
	HAART stopped again		
Mar 00	d4T+3TC+NVP (+ carbimazole)		
Apr 00	Resistance mutations K103N, M184V	360	2,400

*During the first treatment interruption the patient developed autoimmune hyperthyroidism, the treatment of which led to anemia after re-initiation of HAART, so that HAART was interrupted again. As a result, resistance developed against NNRTIs and 3TC. Autoimmune phenomena in the context of treatment interruption as seen in this patient have not previously been described.

The risk of AIDS seems to be low for single interruptions provided the immune defect is only moderate. In the Swiss Cohort, the risk of progression was not increased (Taffe 2002). In 133 patients who interrupted treatment, we observed no increased risk of AIDS after 24 months, compared to 262 matched controls (Wolf 2005). However, almost all patients in this study were immunologically stable throughout. The risk is probably higher in patients with severe immunodeficiency (Deeks 2001, Lawrence 2003). The CPRC064 Study in which 270 patients with MDR viruses and mostly distinct immunodeficiency (median 144 CD4 cells/µl) were randomized before a salvage regimen either to a four-month treatment interruption or not, was stopped because of a high risk of progression. In comparison with the control group, a significantly higher number of AIDS illnesses (17 versus 5) occurred in the group interrupting therapy. In a multivariate analysis, two factors were predictive for death or progression: treatment interruption and the CD4-cell count at the time of interruption. The risk increased by 1.4 with every drop of 50 CD4 cells, demonstrating that severely immunocompromised patients are particularly at risk of developing AIDS during long treatment interruptions of several months. Treatment interruptions should be avoided in such patients. Newer data from the SMART Study, however, show that even with higher CD4 cells, treatment interruptions can lead to the development of AIDS (see below).

STI at the patient's wish, and for reduction of toxicity

Interruption of therapy can have psychological advantages (Tuldra 2001). Quality of life improves (Moreno 2003), and many patients are relieved of the burden of continuous, "lifelong" therapy. Clinicians should take the wish for treatment interruption seriously. Presumably most patients expressing such a wish will interrupt sooner or later anyway; so the interruption may as well be structured and controlled. However, the psychological benefit of treatment interruption has not been confirmed by studies – in fact it is striking how few studies have been based on this theme.

Increased transaminases or lipid levels drop quite rapidly after stopping treatment (Hatano 2000, Wolf 2005). It is still not clear whether this is relevant in reducing the risk of cardiovascular disease. In SMART, the risk of cardiovascular and metabolic complications during STIs was actually increased (El Sadr 2006, see below).

What about lipodystrophy and mitochondrial toxicity? At least two studies have shown that, after a few months, mitochondrial DNA can regenerate itself during a treatment break (Cote 2002, Mussini 2005). In contrast, another study showed no effect (Negredo 2006). Whether or not a clinically manifested lipodystrophy improves, remains to be proven. At least short treatment interruptions have not had any effect on morphological changes (Hatano 2000). Resolution of lipodystrophy even after longer interruptions is by no means certain; we have a patient who was treated during seroconversion and developed a "buffalo hump" after one and a half years, which has not resolved even after almost five years of treatment interruption.

Summary: although treatment interruption, is theoretically useful to limit long-term toxicity on HAART, to date, a convincing argument has not been provided by the data.

STI – for immunological reasons

Hardly any patient has become as famous as the acutely infected homosexual man treated in a Berlin private practice a few years ago who, with a viral load of approximately 80,000 copies/ml, began a HAART regimen consisting of didanosine, indinavir and hydroxyurea. The virus rapidly became undetectable. After several problems – and two short treatment interruptions – HAART was completely stopped after 176 days. Surprisingly, even without drugs, plasma viremia has remained below the level of detection for more than five years. Although virus was still detectable in lymph nodes, thus excluding eradication, the immune system in this case – referred to as the Berlin Patient among experts in the field (Lisziewicz 1999) – was obviously capable of durable control of infection. But why? Was it the early initiation of therapy, the hydroxyurea, or the treatment interruptions? No one knows the answer, even today. There may be a completely different explanation: it is possible that certain host factors in this patients which have not yet been investigated influenced the course of disease – completely independently of HAART, STI or hydroxyurea. Nevertheless, STI has been extensively investigated in acutely infected patients (see "Acute HIV infection").

Attempts to improve HIV-specific immune responses with treatment interruptions in chronically infected patients have been unsuccessful. The theory of "endogenous vaccination" seems plausible: transient increases in viral load could strengthen HIV-specific immune responses, which decline with increasing viral suppression on HAART.

In several pilot studies from 2000/2001, successive interruptions seemed to indeed prolong the time to viral rebound or decrease the rate of rebound, and, in parallel, there were measurable improvements in HIV-specific CD4+ or CD8+ T-cell immune responses (Haslett 2000, Garcia 2001, Lori 2000, Ortiz 1999, Papasavvas 2000, Ruiz 2000). However, almost none of these studies included more than 2-6 patients, and a control group was usually missing. Was this wishful thinking?

STI was finally "put to the test" in the Spanish-Swiss SSITT Study (Oxenius 2002, Fagard 2003): 133 patients were monitored throughout for ten-week treatment cycles, each consisting of eight weeks HAART and two weeks of treatment interruption. After this, HAART was permanently interrupted. Treatment success – defined as a viral load below 5,000 copies/ml without HAART after 52 weeks – occurred in 21/99 patients. However, 5/21 patients had a low viral load even before the initiation of HAART. Most importantly, none of the 32 patients with a pre-HAART viral load above 60,000 copies/ml achieved a viral load of less than 5,000 copies/ml. The viral load set point is lowered in only a few patients, usually those with low initial viral load, despite repeated STIs. In contrast to acute infection, improvement of HIV-specific immune response seems unlikely in the setting of chronic HIV infection. SSITT clearly showed that treatment interruptions on immunological grounds alone are not justified and are dangerous.

In addition, approaches with immunomodulatory drugs, such as hydroxyurea (Foli 2004), mycophenolat (Garcia 2004) or steroids (Ulmer 2005), exist to lengthen the period of STIs. These approaches, whose benefits seem questionable, are still in the experimental phases and are not justified outside studies.

STI as a salvage strategy for MDR viruses

In most patients with MDR viruses, treatment interruption leads to a gradual shift back to the wild-type virus and a loss of resistance. Therefore, resistance testing during treatment interruption is often of little use since mutations disappear from the blood as early as two weeks after treatment interruption (Devereux 1999). In modestly immunosuppressed patients, this shift is observed more frequently and quickly. In more advanced stages of disease and with a longer duration of treatment, it lasts longer (Miller 2000, Izopet 2000), and sometimes after a longer interruption of therapy, no shift can be seen (Halfon 2005). PI mutations are the first to disappear, while NNRTI mutations are more protracted because they minimally affect the viral fitness (Deeks 2001, Birk 2001). It is assumed that the wild type merely dominates the resistant mutants. Special PCR methods are still able to detect low quantities of resistant viruses during STI (Izopet 2000), and after treatment is restarted, resistance mutations rapidly dominate again (Delaugerre 2001). Only a few cases have been described in which resistance mutations were apparently flushed out completely. One such patient, from Germany, has been described (Walter 2002), who was not able to attain sufficient viral suppression despite intensified HAART, and who then interrupted treatment. During the following seven months of treatment interruption, there was a gradual reversion to the wild-type virus, and after re-starting HAART (which, according to previous resistance testing, should have had no effect) the viral load has now been successfully suppressed for several years.

Can patients with multi-resistant viruses improve the effect of the salvage regimen, if they have had a previous interruption of treatment? At least two studies to date have shown that the shift resulting from treatment interruptions can be beneficial for salvage strategies. In the Frankfurt Cohort, a shift was associated with improved response to the salvage regimen (Miller 2000). In the GIGHAART Study, there was still evidence of antiviral efficacy after one year in patients who had interrupted treatment before starting a salvage regimen (Katlama 2004). However, this data is

in contrast to that of numerous other studies in which an increased risk of AIDS was seen during treatment interruptions (Lawrence 2003, Ruiz 2003, see above). At the end of 2005, a further work, the Reserve Study, was published, which brought the concept of STI in multiresistance under more scrutiny than previously (Ghosn 2005). A total of 23 patients with MDR viruses, on long-term therapy and severely immunosuppressed, interrupted their HAART until at least two drugs became effective again according to genotypic resistance tests. The interval lasted 24 weeks on average, after which an intensive salvage regimen was started (usually at least 6 drugs). The results were sobering: nothing changed during the interruption. After 12 weeks on the salvage regimen, the viral load was practically unchanged in comparison to the baseline value. An even more disturbing side effect: in 15/23 (65 %) of the patients, AIDS illnesses occurred, sometimes even after the interruption.

Summary: in view of the risk of AIDS and the lack of evidence regarding the benefits, treatment interruptions are not justified as salvage strategies outside clinical studies, at least in severely immunosuppressed patients.

Structured intermittent treatment, fixed intervals

In the initial phase following interruption of HAART, the viral load usually continues to be very low. Plasma viremia only reaches pre-treatment levels after about four, sometimes even six weeks. The risk of developing resistance is presumably small at lower levels of viral replication (Bonhoeffer 2000). Does this indicate that ultra-short treatment interruptions could be utilized to reduce drugs, costs and long-term toxicity?

In an NIH pilot study on SIT (structured intermittent treatment), 10 chronically infected patients with more than 300 CD4 cells/µl and a viral load below 50 copies/ml were switched to a combination of d4T+3TC+indinavir/r. This combination was administered as seven days of treatment and seven days interruption (7-on-7-off) for a period of at least 44 weeks. The result: neither the viral load nor the proviral DNA increased. CD4 cells and HIV-specific immune responses remained unchanged, suggesting that the immune system is probably unaffected by such ultra-short breaks in treatment. A significant reduction in lipid levels did, however, occur (Dybul 2001). Some patients experienced several blips (temporary increases in viral load) to above 100 copies/ml. The same group has recently reported successful use of the same strategy in eight patients using ddI+3TC+efavirenz. Seven of eight patients have now been followed for more than 60-84 weeks (Dybul 2004). Nevertheless: at this time, it is impossible to predict whether this treatment strategy might result in a higher risk of resistance in the long term. There are still no larger studies, and it has become suspiciously quiet in this area. In addition, patients in the NIH pilot studies were carefully selected, with good immune status and many years of viral suppression. This strategy is probably only applicable to a few patients. A three-armed study from Thailand has already gathered more negative experience with the 7-on-7-off approach (Cardiello 2005). In this study, 19 of 36 patients experienced virological treatment failure within a short period of time, and this treatment arm was consequently stopped prematurely. The main reason for these poor results appears to lie in the fact that the majority of patients were NRTI-experienced. This means: if nucleoside analogs are unstable, such on-off strategies are problematic.

ART only on weekdays? This approach was taken by the FOTO Study ("Five On, Two Off"), in which HAART was only taken from Monday to Friday and stopped at the weekends (i.e. sparing 28 %). This study enrolled patients on a HAART regimen, who had an undetectable viral load for at least three months. After 48 weeks only one of the 17 NNRTI-treated patients had an increase in viral load, although 2 of 9 PI-treated patients did (Cohen 2005). The authors speculate that the long half-life of efavirenz (none of the 9 patients on efavirenz demonstrated an increase) could be the reason for this difference. Further studies have to be conducted, before such an approach can be recommended.

In contrast, longer interruptions, over several weeks, with fixed intermittent treatment seem to be unfavorable. Results from a randomized NIH study with fixed intervals (each with one month of STI, two months of treatment) were disconcerting (Dybul 2003). The SIT arm contained significantly more patients with virological treatment failure. Resistance mutations developed particularly against NNRTIs and 3TC, so that the study was stopped early. In the Spanish-Swiss SSITT Study (2 weeks STI, 2 months HAART) some resistance was seen (Yerli 2003), likewise in an Italian study (Palmisano 2006). Even though the French WINDOW Study (two months each of STI and therapy) showed no increase in the number of resistance mutations. (Marchou 2006), the studies that indicate fixed interruptions as being susceptible to the development of resistance mutations prevail.

CD4-driven interruptions: SMART and the consequences

Beside fixed intervals, whether short or long, there is another approach, whereby interruptions are individualized and based on CD4-cell count. In other words, in patients with a good CD4 cell count, HAART is interrupted until the CD4 cell count drops below an immunological cut-off, and only then is it restarted. Over the last few years, many non-randomized studies with differing cut-off points and very heterogeneous patient populations came to the conclusion that this approach is safe and allows for a considerable reduction in drug exposure (Moreno 2003, Boschi 2004, Maggiolo 2004, Skiest 2004, Fernandez 2005, Mussini 2005). In the meantime, a few randomized studies compare such CD4-driven intervals with continuous administration of HAART.

The relevant data and results of these studies are given in Table 10.2.

It is clear that the results of these randomized studies differ considerably in part. Whilst TIBET, Staccato or ACTG 5170 produced the verdict that CD4-driven interruptions are safe, two other studies, Trivacan and SMART came to other conclusions.

Table 10.2: Randomized studies in which therapy was continued or interrupted based on CD4 cell count

Source	n	CD4 cells at entry	CD4 cells at restart	Results based on clinical findings in STIs
Ruiz 2005 TIBET	201	> 500 > 6 Mo	< 350 or VL > 100,000	6 % ARS, otherwise STIs clinically safe. Average STI-duration 44 weeks. de novo NNRTI resistances.
El Sadr 2006 SMART	5472	350	< 250	Morbidity and mortality risk low, but significantly raised! See Table 10.3.
Danel 2006 Trivacan	326	> 350	< 250	Morbidity significantly raised (double), due to invasive bacterial infections.
Ananworanich 2006 Staccato	430	> 350	< 350	After 484 PY: clinically safe (slightly more side effects in HAART arm; more candidiasis in STI arm). No evidence of resistances.
Skiest 2006 ACTG 5170	167	> 350	< 250	In general, safe, with risks only elevated when CD4 nadir was low.

ARS = acute retroviral syndrome; FU = follow up; Mo = months; PY = patient years

In particular, the results of the SMART Study, which started in 2002, caused a sensation. In this, the largest randomized HIV study of all time, the cut off levels for stopping HAART were at least 350 cells/µl, and 250 cells/µl for re-instating it. This study was very successful worldwide. In the end, 318 centers in 53 countries had recruited a total of 5,472 patients (90 % of the planned 6,000 patients) were included. In January 2006, following an intermediate evaluation, an independent data safety monitoring board concluded that therapeutic interruptions result in an increased risk of AIDS – in the interruption arm, approximately twice as many AIDS illnesses were observed at follow-up, over an average of 15 months. This included severe opportunistic infections as well as malignant tumors. In fact, the overall risk was low, but so significantly elevated that the unusual and far-reaching decision was made to abort the study. In addition, it was surprisingly observed that cardiovascular incidents in the interruption arm did not (as was hoped) become less frequent, but actually increased. The clinical incidents in SMART (details on the SMART website: http:/www.smart-trial.org/news.htm) are shown in the following table.

Table 10.3. Incidents occurring in SMART, for every 100 patient years (El Sadr 2006)

	STI (n)	Control (n)	Hazard ratio
Progression of disease or death	3.7 (120)	1.3 (47)	2.6 (1.9-3.7)*
Death	1.5 (55)	0.8 (30)	1.8 (1.2-2.9)*
Cardiovasc./renal/hepatic events	1.8 (65)	1.1 (39)	1.7 (1.1-2.5)*
Grade IV toxicity	5.0 (173)	4.2 (148)	1.2 (1.0-1.5)*

*Significant difference.

At present, the cause of these surprising results can only be speculated. What was conspicuous, however, was that the risk of disease was increased mainly in those patients whose viral load was below the borderline level at the time of interruption.

In contrast, an increased risk of AIDS or death was not associated with CD4-cell count at the start of the study. Even the CD4 nadir or a previous diagnosis of AIDS (approximately 24 % of the patients) surpisingly was not predictive. Severe events such as AIDS or death also occurred with good CD4-cell counts.

For many experts, SMART laid to rest the concept of interrupting therapy as a method of treatment. However, some points of criticism remain. Much of SMART has not yet been evaluated, and the type of clinical events and patients have to be evualated more closely. Despite the increased risk of progression, it is important not to lose sight of the proportions. Overall, the risk of becoming ill was low, and in SMART an essential point for stopping and restarting HAART was not noted: the CD4-cell percentage. Only the absolute CD4-cell counts were used as criteria, although the percentage values have been required to be included in therapeutic decisions for many years (Goicoechea 2005, Hulgan 2005). In our opinion, it is still too early to completely dismiss the concept of CD4-driven treatment interruptions. In the first instance SMART has shown that treatment interruptions *such as these, and in this design* are not beneficial.

Practical tips for treatment interruptions

- Don't try to convince patients to interrupt therapy – if there are no problems with HAART, there is no reason to stop it.
- To reverse resistance or for immunological reasons – i.e., as a "strategy"– STIs are not useful.
- A positive effect on cardiovascular incidents or lipodystrophy has not been confirmed. Following the SMART Study, this is highly unlikely.
- Nevertheless, the patient's wish for a break should be respected! The interruption will be made anyway, whether the clinician agrees with it or not.
- A supervised treatment interruption is still always better than one undertaken without the awareness of the clinician.
- Beforehand, information should be provided on clinical (retroviral syndrome, AIDS), immunological (loss of CD4 cells) and virological (resistance) consequences.
- Patients must be aware that the risk of infection increases – even after a longer suppression, viral load returns to initial levels after 4-6 weeks without HAART.
- Beware HBV co-infection (danger of hepatitis flaring up again)!
- CD4 cells (including percentage), viral load, and blood count (thrombocytes!) should be monitored monthly during interruptions.
- Risk of resistance is possibly higher with NNRTIs (choose robust regimens and stop NNRTIs several days earlier if possible – consider the half-life of the drugs).
- Patients who started HAART "too early" according to current standards can probably interrupt quite safely.
- Resistance testing during treatment interruptions is not useful – it usually only identifies wild-type virus.
- Start with HAART again, in good time after the treatment interruption!

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11. Monitoring

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Which parameters should be included in routine laboratory monitoring of HIV patients? What can be expected from the results? This section deals briefly with viral load, CD4 cells, routine checks, and plasma levels. Resistance tests are the subject of a separate chapter ("HIV Resistance Testing"). For tests which should be performed on initial presentation see the appropriate chapter.

Viral load

"Viral load" is the amount of viral copies in the blood. Alongside the CD4-cell count, viral load has become the most important surrogate marker for HIV infection (Hughes 1997, Mellors 1997, Lyles 2000, Ghani 2001, Phillips 2004). It provides both valuable information on the level of risk of disease progression and whether antiretroviral therapy is indicated; it is the critical value in determining the success of therapy. Other surrogate markers used frequently in the past, such as p24, neopterin or $ß_2$-microglobulin, are now superfluous and can be avoided, as they do not provide any additional information.

Viral load assays measure the amount of HIV RNA (viral genetic material). The units are viral copies/ml (or genome equivalents). This is reported either as a direct, whole number, or as a logarithmic number. A change of one or more "logs" refers to the change in viral load by one or more decimal powers.

Number of copies	Log_{10}
10	1.0
50	1.7
100	2.0
500	2.7
1,000	3.0
10,000	4.0
50,000	4.7
100,000	5.0
1,000,000	6.0

Assessment

The higher the viral load, the higher the risk of a decrease in CD4 cells, with subsequent disease progression or occurrence of AIDS-related illnesses (Mellors 1997, Lyles 2000, Phillips 2004). A viral load above 100,000 copies/ml, i.e. 5.0 logs (sometimes even above 50,000 copies/ml), is generally considered to be high; a value below 10,000 copies/ml (sometimes less than 5,000 copies/ml), low. However, these thresholds are not absolute and can only provide points of reference.

The level of the plasma viremia can have very different effects on the immune status of individuals. There are some patients whose CD4 cells remain stable for relatively long periods despite having a high viral load, while others experience a

rapid drop, although the viral load is relatively low. Viral load is probably lower overall in women than in men. In a meta-analysis, the difference was 41 % or 0.23 logs (95 % confidence interval 0.16-0.31 logs) (Napravnik 2002). The reason for this phenomenon remains unclear and whether it should have an impact on the indication for treatment, is still the subject of discussion.

Methods

Three methods or assays are currently used to measure viral load: Reverse Transcription Polymerase Chain Reaction (RT-PCR); branched-chain DNA (b-DNA); and, occasionally, Nucleic Acid Sequence-Based Amplification (NASBA). These methods differ both in levels of detection and in the linear range within which measurement is reliable or reproducible (see Table 11.1 below). In all methods, the minute amount of viral RNA must first be amplified to enable measurement. In the case of PCR and NASBA, the viral RNA is transformed in several enzymatic steps and then amplified to measurable amounts. B-DNA does not require this enzymatic step; signal amplification occurs via binding of branched DNA fragments to viral RNA. The actual procedure of PCR is based on real-time detection (TagMan-PCR, Roche) and possess a linear scale from 40-10,000,000 RNA copies/ml. Thus, replacing the ultrasensitive method, which was necessary in the earlier PCR versions (for example Cobas Amplicor).

Although intra-assay variability is good for all three methods and one can expect reproducible values, variations in measurements should be carefully considered. Differences of less than 0.5 logs are not considered significant. A decrease from 4.3 to 3.9 logs, for example (corresponding to a decrease from approximately 20,000 to 8,000 viral copies/ml), does not necessarily signify a drop in viral load. The same holds for increases in viral load. Changes of up to threefold can therefore be irrelevant! Patients who, after hearing mere numbers, frequently worry unnecessarily or become falsely optimistic should be made aware of this.

Considerable differences exist between the results of the three methods (Coste 1996). It is therefore not favorable to change from one method to another. The results obtained by b-DNA are often lower than the PCR by a factor of 2. Different subtypes are also detected with varying success according to the method employed (Parekh 1999); one should be particularly cautious in patients from Africa and Asia with non-B subtypes, for example, in whom the viral load at first presentation can be unexpectedly low. In such cases, use of a different assay may actually be indicated. However, newer versions with improved primers are superior in sensitively measuring even unusual HIV subtypes. All assays have a linear dynamic range, outside of which precise numbers are not possible.

The following rule applies: one method, one laboratory! The laboratory should be experienced and routinely perform a sufficiently large number of tests. Measurement should take place as soon as possible after blood withdrawal, and correct collection and shipping of centrifuged plasma is also important (contact the laboratory ahead of time on these issues).

Table 11.1: Methods of measurement, linear range and level of detection should be clearly indicated for the clinician on every test result

Company	Roche/Abbott	Bayer Siemens	Organon
Method	RT-PCR	b-DNAn	NucliSens HIV-1 QT
Linear range of assay	40 – 10,000,000	75 – 500,000	40 – 10,000,000
Comparability	Values possibly higher than b-DNA	Values possibly lower than PCR values	Values approx. same as PCR
Advantages	Higher specificity, possibly less false positive results than b-DNA (subtypes A-F)	Equally good for all subtypes (A-G), technically relatively simple	Equally good for all subtypes (A-G), large linear range

Influencing factors

Apart from methodological variability, a host of other factors may influence levels of viral load, including for example vaccinations and concurrent infections. During active opportunistic infections, viral load is often particularly high. One study showed a 5- to 160-fold elevation during active tuberculosis (Goletti 1996). Viral load can also increase significantly during syphilis (Buchacz 2004). In these situations, determining the viral load does not make much sense. Following immunization for influenza (O'Brien 1995) or pneumococcus (Farber 1996), the viral load may be transiently elevated (Kolber 2002). As the peak occurs one to three weeks after immunization, routine measurements of viral load should be avoided for up to four weeks following immunization. It should be noted that not every increase is indicative of virological treatment failure and resistance. Slight transient increases, called blips, are usually of no consequence (see "Goals and Principles of Therapy"). The possibility of mixing up samples always has to be considered. Unexpected results should be double-checked with the laboratory in the first instance, and if no cause is found there, then they should be repeated – people make mistakes.

Viral kinetics on HAART

The introduction of viral load measurement in 1996-1997 fundamentally changed HIV therapy. The breakthrough studies by David Ho and his group showed that HIV infection has significant dynamics (Ho 1995, Perelson 1996). The changes in viral load on antiretroviral therapy clearly reflect the dynamics of the process of viral production and elimination. The concentration of HIV-1 in plasma is usually already reduced by 99 % after two weeks (Perelson 1997). In one large cohort, the viral load in 84 % of patients was already below 1,000 copies/ml after four weeks. The decrease follows biphasic kinetics. In the first phase, within the first three to six weeks, an extremely rapid drop occurs, followed by a longer phase during which the viral load decreases slowly (Wu 1999).

The higher the viral load at initiation of therapy, the longer it takes to drop below the level of detection. In one study, the range was between 15 days with a baseline viral load of 1,000 and 113 days with a baseline of 1 million viral copies/ml (Rizzardi 2000). The following figure shows a typical biphasic decrease in viral load after initial high levels.

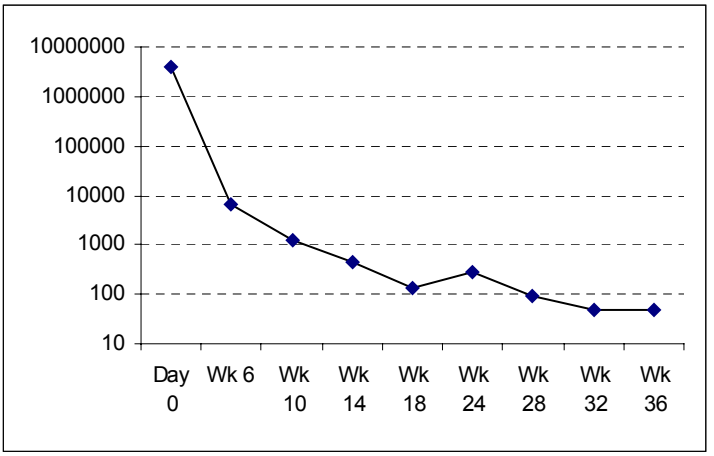

Figure 1: Typical biphasic decrease in viral load on HAART. Viral load was initially very high, and reached a level below 50 copies/ml only at week 32. Note the temporary increase at week 24, which is possibly due to methodological variability. HAART was not changed.

Numerous studies have focused on whether durable treatment success can be predicted early in treatment (Demeter 2001, Kitchen 2001, Lepri 2001, Thiabaut 2000). In a study on 124 patients, a decrease of less than 0.72 logs after one week was predictive of virological treatment failure in more than 99 % of patients (Polis 2001). However, this has little clinical relevance, and in our opinion, it is pointless to start measurement of viral load only one or two weeks after initiation of therapy.

In the first few months, we measure viral load every four weeks until it has dropped below the level of detection – the most important goal! After this, viral load can be measured every three months. In case of rebound, closer monitoring becomes necessary. Following initiation of therapy, viral load should be below 5,000 copies/ml after one month. Higher values are predictive of failure to reach levels below detection (Maggiolo 2000). Viral load can also be measured in body fluids other than blood or plasma (for example cerebrospinal, vaginal or seminal fluid). However, such tests are usually performed for scientific purposes and are not routine.

Practical tips for dealing with viral load (see "Goals and Principles")

- Use only one assay, if possible.
- Use only one experienced laboratory, if possible, no home-brewed assays.
- Watch for assay variability (up to half a log) and explain this to the patient!
- Monitor viral load every 4 weeks with new HAART, until the viral load is below the level of detection.
- Then measure viral loads on successful HAART 3 monthly .
- Without HAART, measurement every three months is also sufficient.
- Don't measure shortly after vaccinations or with concurrent infections.
- Unexpected results should be rechecked after 2-4 weeks.
- Remember differences between HIV subtypes (in some cases it may be useful to use another method).

CD4 cells

CD4 cells are T lymphocytes that express the CD4 receptor on their surface. This lymphocyte subpopulation is also referred to as "T helper cells". Alongside viral load, measurement of the CD4-cell level is the most important parameter or surrogate marker in HIV medicine. It allows for a reliable estimation of the individual risk of developing AIDS. Every HIV patient should have had a CD4-cell measurement within the last six months! Two reference values are generally accepted: above 400-500 CD4 cells/µl, severe AIDS-related diseases are very rare; below 200 CD4 cells/µl, the risk of AIDS-related morbidity increases significantly with increased duration of immunosuppression. However, most AIDS-related illnesses only occur below 100 CD4 cells/µl.

Several points should be considered when measuring CD4 cells (usually by flow cytometry). Blood samples should be processed within 18 hours. The lower normal values are between 400 and 500 cells/µl, depending on the laboratory. Samples should always be sent to only one (experienced) laboratory. The same applies to viral load as to CD4 cells: the higher the level, the greater the variability. Differences of 50-100 cells/µl are not unusual. In one study, the 95 % confidence intervals with a real value of 500 cells/µl were between 297 and 841 cells/µl. At 200 CD4 cells/µl, the 95 % confidence interval was between 118 and 337 cells/µl (Hoover 1993).

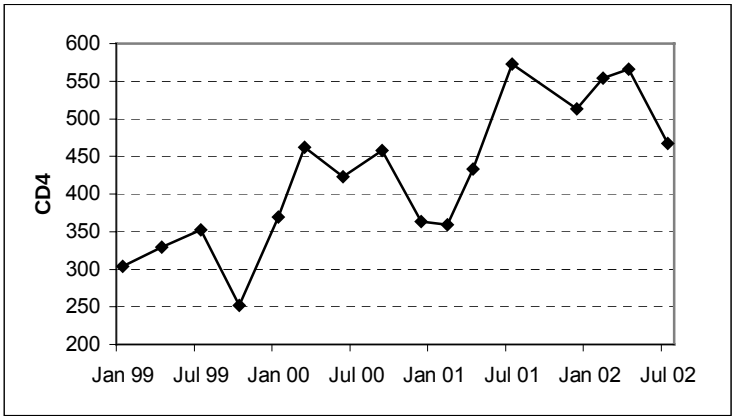

Figure 2. Example of variations in absolute CD4 cells/µl over a period of four years. The viral load was continuously below 50 copies/ml; HAART remained unchanged.

Measurement of CD4 cells should only be repeated in the case of highly implausible values. As long as the viral load remains below the level of detection, there is no need to be concerned, even with greater decreases in CD4 cells. In such cases, the relative values (CD4 percentages) and the CD4/CD8 ratio (ratio of CD4 to CD8 cells) should be referred to; these are usually more robust and less prone to fluctuation. As a general point of reference: with values above 500 CD4 cells/µl, more than 29 % is to be expected, with less than 200 CD4 cells/µl less than 14 %. Individual laboratories may define the normal ranges for the relative values and the ratio differently. If there are considerable discrepancies between absolute and relative CD4 cells, any decisions involving treatment should be carefully considered –

if in doubt, it is better to check the values one more time! The remaining differential blood count should also be scrutinized carefully: is leucopenia or leukocytosis present?

Clinicians sometimes forget that the result of the CD4-cell count is of great importance to the patient.and oftens associated with a great deal of stress for many patients. Insensitively informing the patient of a supposedly bad result can lead to reactive depression. From the start, patients must be informed about the possible physiological and method-related variability of laboratory tests. A drop from 1,200 to 900 cells/µl is often of no importance, but for the patient, this information can be a "disaster!"

In the case of unexpectedly good results, every effort should be made to contain euphoria. In the long run, this saves time and discussions, and the patient is spared unnecessary ups and downs. We do not consider it advisable for non-physician personnel (without extensive HIV experience) to inform patients of results.

In our opinion,. once CD4-cell counts are within the normal range with adequate viral suppression, half-yearly measurements are adequate. Indeed, in such cases, the probability of CD4 cells dropping to values below 350/µl is extremely low (Phillips 2003).

Influencing factors

Several other factors influence CD4 counts apart from laboratory-related variables. These include concurrent infections, leucopenia of varying etiology, spleenectomy and steroids or other immunosuppressive therapies. Extreme exertion, surgical procedures or pregnancy can also lead to lower values. Even diurnal variation occurs; CD4 cells are lower at noon, and highest in the evening around 8 p.m. (Malone 1990). Psychological stress seems to play a negligible role, even though patients often assume the contrary.

Kinetics of CD4 cells on HAART

Similarly to viral load, a biphasic increase in CD4 cells occurs following the initiation of HAART (Renaud 1999, Le Moing 2002), with a rapid increase within the first three to four months and a much slower rise thereafter. In a study of almost 1,000 patients, the CD4 cell count increased by 21/µl per month during the first three months. In the following 21 months, this rate was only 5.5 CD4 cells/µl per month (Le Moing 2002). The initial rapid increase in CD4 cells is probably due to redistribution, which is followed by the new production of naïve T-cells (Pakker 1998). Diminished apoptosis may also play a role (Roger 2002).

It is still being debated whether the immune system steadily continues its recovery even after a long period of viral load suppression, or whether a plateau is reached after three to four years, beyond which there is no further improvement (Smith 2004, Viard 2004).

Several factors can influence the extent of immune reconstitution during HAART. The degree of viral suppression is crucial – the lower the viral load, the more pronounced the effect (Le Moing 2002). The absolute increase is higher if CD4-cell counts were high at the start of HAART (Kaufmann 2000). Naïve T cells still present at initiation of therapy are a particularly important factor for long-term immune reconstitution (Notermans 1999). Age is also important (Grabar 2004). The larger

the thymus and the more active the process of thymopoiesis, the more significant the rise in CD4 cells is likely to be (Kolte 2002)., CD4 cells in older patients do not increase as much as those in younger ones, due to age-related degeneration of the thymus (Viard 2001). However, we have seen both 20-year-old patients with very poor CD4-cell count recovery and 60-year-old patients with very good, above average increases in CD4 cells. The regenerative capacity of the human immune system seems to vary considerably, and no method to date has been capable of reliably predicting this capacity.

It is possible that some antiretroviral therapies such as the ddI+tenofovir combination are associated with less immune reconstitution than others. Immunosuppressive concurrent medications should also be considered (see "Goals and Principles of Therapy").

Beyond the measurement of the CD4-cell count and lymphocyte subpopulations, a number of other assays allow detailed testing of the qualitative or functional capacity of the immune system, for example in response to specific antigens (Gorochov 1998, Lederman 2001, Lange 2002, review in Telenti 2002). These, often cumbersome, methods are not currently necessary for routine diagnostics, and their use remains questionable. However, they could one day help to better describe individual immune status and, for example, identify those (few) patients, who are at risk of developing opportunistic infections despite good CD4 counts.

Practical tips for dealing with CD4-cell counts

- As with viral load: use only one (experienced) laboratory.
- The higher the values, the greater the variability (consider numerous factors) – compare the relative (percentage) values and CD4/CD8 ratio with previous results!
- Do not disconcert the patient when there are apparent decreases – if viral suppression is sufficient, the drop is usually not HIV-related! Only highly implausible results should be repeated.
- If the viral load is below the level of detection, three-monthly measurements of CD4 cells are sufficient.
- In the presence of good viral suppression, CD4 cells (not viral load!) may also be checked less frequently.
- CD4-cell count and viral load should be discussed with the physician. Do not leave patients alone with their results.

Other routine checks – what else should be monitored?

Besides the CD4-cell count and viral load, several other parameters should be monitored in the HIV patient. The following recommendations apply to clinically asymptomatic patients with normal results on routine laboratory evaluation, who have been on stable treatment for several months, or who are not taking antiretroviral therapy. Of course, if treatment is started or changed, or if the patient develops complaints, more frequent and, depending on the problem, further investigations are

required. Additional tests may also be necessary. A complete physical examination should be performed regularly, and this often leads to the discovery of important findings such as Kaposi lesions, condyloma or mycoses (thrush!). The lower the CD4 cell count, the more frequently patients should be examined.

Table 11.2: Minimal evaluations per year in stable asymptomatic patients

	Patient on ART per year	Untreated per year
Blood count, LDH, ALT, AST, creatinine, bilirubin, AP, lipase, γGT, glucose	4-6 x	2-4 x
Viral load	4 x	2-4 x
CD4 cells	2-4 x	2-4 x
Lipids	1-2 x	1 x
Physical examination	2-4 x	1-2 x
Gynecological examination	1 x	1 x
Fundoscopy if CD4 cells < 200/µl	2-4 x	4 x

In patients with less than 200 CD4 cells/µl, we recommend fundoscopy every three to six months to exclude CMV retinitis. Close cooperation with an HIV-experienced ophthalmologist is important. The better the CD4 cells, the less often fundoscopy is requiredy – in our opinion, when CD4 counts have normalized, these can be stopped completely. In contrast, regular gynecological examinations with PAP smears are recommended, regardless of CD4 count (see also the European guidelines: http://hiv.net/link.php?id=185). Many experts now also recommend rectal examination (including proctoscopy) for the early detection of precancerous lesions and anal cancer.

However, such guidelines or recommendations are interpreted very differently. In our experience, in cases of good immune status, unless there is a specific suspicion, routine X-rays, ultrasound examinations (exception: patients with chronic hepatitis, as hepatocellular carcinoma is not rare in such cases!), multiple serologies or lactate measurements are not necessary.

An annual ECG is only indicated in our view in patients with a specific risk profile (see also “HIV and Cardiac Disease”). The tuberculin test (the Mendel-Mantoux skin test with 5 IE once a year) should only be repeated if it is negative initially.

Therapeutic drug monitoring (TDM)

Individual plasma levels of many antiretroviral drugs may vary considerably for differing reasons (e.g. compliance, metabolism, absorption). But, sufficient plasma levels are essential for success of virological treatment (Acosta 2000). In the VIRADAPT Study, adequate PI-concentrations were even more crucial than knowledge of resistance mutations (Durant 2000). The importance of sufficient plasma levels has also been shown for NNRTIs (Marzolini 2001, Veldkamp 2001).

On the other hand, very high plasma levels correlate with a higher rate of side effects. Reported renal problems with indinavir (Dielemann 1999), gastrointestinal disturbances with ritonavir (Gatti 1999), hepatotoxicity with nevirapine (Gonzalez

2002), or CNS problems with efavirenz (Marzolini 2001) were all associated with high plasma levels.

The measurement of drug concentrations in serum or plasma (therapeutic drug monitoring, TDM) has therefore become an important tool for monitoring therapy. The best reviews are to be found in Back 2002, Burger 2002, and Clevenbergh 2004. Due to the increasing complexities of antiretroviral combinations, TDM of protease inhibitors and NNRTIs will probably become more important in the future.

Several problems associated with TDM are limiting its broader use. The measurement of nucleoside analogs, for example, is senseless since they are converted to the active metabolites only intracellularly. Intracellular measurements are difficult and will not be available in routine clinical practice.

Measuring NNRTIs or PIs may therefore currently determine levels of only one component of a (failing) combination. Further problems include not only viral strains with different levels of resistance, different inhibitory concentrations, variable protein binding, and time-dependent variability of plasma levels, but also methodological problems with the assays, as well as the lack of clearly defined limits. Many uncertainties thus remain in the assessment of therapeutic drug plasma levels. Until data from randomized studies are available, proving the clinical value of TDM, both the measurement and interpretation of the results should be left to specialized centers.

TDM is currently recommended in the following situations:

- Complex drug combinations
- Concomitant medications that could lead to interactions or reduced efficacy
- Suspected absorption problems
- Pregnancy

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12. Costs, Prevention, Compliance

Christian Hoffmann and Fiona Mulcahy

The following discusses some aspects of HAART that have so far not been touched upon.

Costs

Antiretroviral drugs are expensive. For example, in Germany individual drugs cost between 290 Euro (Epivir™) and almost 2,000 Euro (Fuzeon™) per month. Even within drug classes, astonishing differences exist. Notable differences are also to be found within the drug classes. The boosted PI Crixivan™, at 350 Euro per month, is relatively cheap in comparison to Aptivus™, which at 1,054 Euro per month, is three times as expensive. A combination regimen can quickly add up to at least 2,000 Euro per month. As a healthcare provider, it is therefore important to have an idea of costs.

The pricing policy of the pharmaceutical industry is difficult to comprehend. For example, Combivir™ costs no more than AZT and 3TC, but Trizivir™ costs significantly more than the individual substances, with the difference lying at around 1,000 Euro/year! Why does the leap from 200 to 250 mg capsules of Videx™ make a difference of 1,500 Euro/year, but between 250 and 400 mg capsules it is only 73 Euro? The reason why directly concurrent preparations (nevirapine and efavirenz or 3TC and FTC) cost almost exactly the same, whilst other substances from the same drug class are approximately 300 % more expensive, cannot be explained through development costs alone.

There is no question about it: a lot of money is made from ART and the market has strong competition. One example is the price politics of the firm Abbott over Norvir™. When the sales figures of the competitor PI Reyataz™ (which needs Norvir™ as a booster) threatened to come close to those of the Abbott flagship Kaletra™, withdrawal of Norvir™ tablets from the market was seriously considered. Only after public demonstrations was it retained with a 400 % price increase…

Despite all criticism and discussion of costs, two things should not be forgotten: firstly the enormous costs of developing new drugs, which can sometimes amount to a billion dollars or more. By far the majority of new substances never reach the market. It is even questionable whether even a licensed drug such as T-20 will recuperate the development costs. According to Roche, the development cost 600 million dollars. In order to cover these high production costs, many thousands of patients worldwide would have to be treated with T-20 over several years – an unrealistic scenario.

Secondly, US estimates assume an expenditure of between $13,000 and $23,000 per additional QUALY (quality-adjusted year of life; Freedberg 2001) which is cheap in comparison to many other therapies. HAART reduces the cost of treatment of opportunistic infections, inpatient and outpatient care. In the Hannover cohort, between 1997 and 2001, total annual outgoings per patient decreased from 35,865 Euro to 24,482 Euro (Stoll 2002). Many patients are able to work again, resulting in an overall economic gain for society (Sendi 1999).

Nevertheless, the fact remains, that HAART is expensive. It is important that initially only one packet is prescribed, even if the standard dose of Retrovir™ 250 mg it is still just enough for 20 days – almost 20 years after its introduction! In this way, one avoids sitting on a mountain of pills if intolerability occurs. Prescription of more than three months supply of medication should also be avoided. Due to the payment obligation for each packet, many patients refuse it anyway.

In the future, it will certainly become more and more important to be informed about the costs of HAART.

Prevention

The following discusses the preventative effect of HAART on the AIDS epidemic as well as other medical prevention strategies with the exclusion of the ABC (abstinence, be faithful, condom use) rule that is propagated by governments.

HAART - makes an exceptionally important contribution to prevention, which is usually underestimated (Hosseinipour 2002). The lower the viral load, the lower the infectivity. A prospective study of 415 HIV-discordant couples in Uganda showed that of 90 new infections over a period of 30 months, none occurred from an infected partner with a viral load below 1,500 copies/ml. The risk of infection increased with every log by a factor of 2.45 (Quinn 2000). In a study from Thailand on 493 patients, this factor was 1.81. Not one single case of infection was observed below 1,094 copies/ml (Tovanabutra 2002). In the San Francisco Cohort, infectiousness in the HAART era dropped by 60 %, based on the probability of transmission per couple (Porco 2004); a study from Spain on heterosexual pairs calculated as much as 80 % (Castilla 2005).

Most patients are interested in knowing: “Do I still need to use a condom?” The answer is: “Yes” Studies have shown that the decrease of viral load in plasma and seminal fluid is roughly parallel and that a decrease of several logs in plasma after several months may also be seen in semen (Liuzzi 1999). Although the same seems to be true for the vaginal and anorectal mucosa, individual risk remains difficult to estimate (Cu-Uvin 2000). Furthermore, viral load levels in blood and other body fluids do not always correlate with one another.

Safe sex is still advisable, even if both partners are infected. HIV-infected patients are not protected from superinfections with new viral strains; and infections with several subtypes are often associated with accelerated disease progression (Gottlieb 2004). Transmission of resistant strains is also possible (Yang 2005).

There has also been concern that the preventive effects of HAART lead to an increase in risk behavior. Calculations have shown that an increase in risk behavior of only 10 % would offset the effects of HAART (Blower 2001, Law 2001). However, one meta-analysis concluded that HAART does not increase risk behavior of patients, even if viral load is undetectable (Crepaz 2004). The gladly circulated scenario of the irresponsible HIV patient, who sets his desires loose again in the age of HAART, putting innocent people at risk, is just a rumor.

On the other hand, with the decreasing interest in AIDS in the media and politics, a reduced awareness of the risks have been observed. In the French PRIMO Cohort, so-called risk contacts of patients increased from 5 to 21 % between 1998 and 2001 (Desquilbet 2002). In 2005, the number of new infections in homosexual men in Germany rose by 20 %– an all time high! Small syphilis endemics among HIV-

infected individuals are being reported in every major city in the US and Europe. Of equal concern is the data on transmission of multiresistant viruses. A case, such as that of the New York patient, who became infected with a multidrug-resistant virus and underwent rapid progression within a few months (Markowitz 2005), showed how important protection and "safer sex" remains.

Circumcision – circumcision of the male foreskin reduces the risk of infection from diverse sources through unprotected intercourse (overview: Weiss 2006). This is probably also true for HIV (Siegfried 2006). A randomized controlled study on 3,274 men in South Africa produced a notable result (Auvert 2005). After 18 months of observation, 20 infections occurred in the circumcision group 0.85 infections in 100 person years), in contrast to 49 in the control group (2.1/100). This corresponded to a reduction in the transmission risk of 61 %. Likewise, in a large randomized study in Uganda on 4,966 men, the risk of infection with HIV decreased from 1.33 to 0.66/100 person years (Gray 2007).

This effect is explained by the presence in the male foreskin of CD4-positive Langerhans cells, which act as the primary target cell for the HIV infection. It has been estimated that in Africa alone circumcision could prevent approximately 2 million HIV infections in the next few years (Williams 2006). However, the results of these pilot studies need to be confirmed, as some questions still remain open. Sexual behavior following circumcision, surgical complications, ethical and logistical problems are just a few aspects (Lie 2006). Further large, randomized studies are currently underway. It is also clear that circumcision is no substitute for safe sex – the risk is still there.

Microbicides are chemical substances, which are usually applied topically as vaginal gels, in order to kill or immobilize HIV and other germs. Currently, very heterogeneous mechanisms are being investigated. These include inactivated substances, which disrupt the viral structures, as well as those which bind to the target cell and inhibit them or antiretroviral drugs such as tenofovir or the nucleoside analog stampidine (overview: Stone 2006). Ideally, microbicides would also be active against sexually transmitted diseases, as these significantly increase the risk of HIV transmission (Schwebke 2005).

It should not be forgotten that so far, no microbicide has demonstrated a protective effect in clinical studies. In addition, investigations crop up every so often, in which the HIV-transmission risk increases on a microbicide, as for example with nonoxynol-9 (Van Damme 2002). In January 2007, there was once again a serious setback. In a randomized study of the Contraceptive Research and Development Program (CONRAD), a non-profit-making research organization, 1,333 women in South Africa, Benin, and Uganda received either a placebo preparation or a microbicide of cellulose sulfate gel. This locally applied gel (Ushercell™) from Polydex, Toronto, proved to be very promising in earlier studies (El-Sadr 2006). However, an interim analysis of CONRAD showed that the users of the cellulose sulfate gel had an increased risk of HIV transmission, and the study was prematurely stopped (http://www.conrad.org). Although the reasons for the increased risk are still unclear, another trial on cellulose sulfate in Nigeria was also terminated. It is questionable whether there is really a future for microbicides after these sobering results. Methodical and ethical problems of randomized studies make the development of effective microbicides very difficult.

PREP (pre-exposure prophylaxis) – includes the prophylactic administration of antiretroviral drugs. PREP approaches in high-risk groups (in particular prostitutes) has mainly been with tenofovir, or sometimes with tenofovir and emtricitabine. However, these studies are not without criticism. Under pressure from activists and diverse organizations, a trial sponsored by NIH and the Gates Foundation was stopped in 2004; and the same happened in 2005 in Cameroon and Nigeria (Cohen 2004, Sing 2005). Usually, the investigators and pharmaceutical firms are accused of neglecting the informed consent to the study and of allowing infected patients to go without medical treatment. Unexplained long-term side effects, interactions, possible resistances and an increased pressure on prostitutes to dispense with condoms – the ethical and political problems of PREP approaches are considerable. However, in view of the catastrophic number of new infections worldwide, they remain an approach which is worth further investigation. At the World AIDS Conference in Toronto, the results of a large PREP trial were first released (Petersen 2006). Approximately 1,200 women with a high HIV risk, in Ghana, Nigeria, and Cameroon, received either placebo or tenofovir daily. After one year, 6 versus 2 seroconversions were noted. Although this difference was not significant, the safety of PREP could at least be demonstrated. Currently, several placebo-controlled CDC studies are underway in the USA, Botswana, and Thailand.

Adherence

Adherence is the Achilles heel of antiretroviral therapy. Non-adherence is one the most important factors in treatment failure (review: Turner 2002). Insufficient plasma drug levels and partial suppression of viral load are the conditions under which resistance can develop. There is no question that HAART has to be taken regularly. All or nothing: with regard to resistance, it is still better not to take any drugs at all. Taking more than 90 % or less than 69 % of drugs were both associated with a lower risk for resistance (Sethi 2003). Compliance is defined as consent and acceptance of a treatment regimen by the patient. In the mid-90s a newer, more politically correct term was adopted – "adherence". This term describes both clinician and patient working together to achieve a treatment concept acceptable for both, and emphasizes, that not only the patient may be responsible for treatment failure. Adherence includes all factors that influence staying on a regimen, in terms of "acceptability". Whichever term is used, three facts remain:

1. If only 95 % of pills are taken, treatment success is put at risk.
2. Clinicians usually overestimate the compliance of their patients.
3. The more complex the therapy, the worse the compliance.

"Risk patients" for non-compliance include individuals with substance or alcohol abuse or those experiencing side effects. Many studies have, however, also identified patients with depression, living alone, or of a younger age, as being particularly at risk (Murri 2001, Frank 2002, Glass 2006). Positive factors are physician experience, confidence of the patient in the positive effects of HAART, and social support. Race, sex or stage of disease does not seem to be relevant. The individual's view of disease and health, acceptance of modern medicine and fear of side effects are further considerations. However, all of these factors vary greatly, and in the end, compliance is difficult to predict in individual cases (Lerner 1998). Experience and intuition of the healthcare professionals are required.

The importance of taking drugs regularly has been demonstrated in numerous studies. In one study of 99 patients, in which compliance was evaluated by way of an electronic monitoring system, the rate of treatment failure was only 22 % in patients with a level of compliance of at least 95 % (95 % of doses taken). Failure rates in patients with 80-94 % or < 80 % compliance were 61 % and 80 %, respectively (Paterson 2000). However, it must be taken into consideration that this much cited study is now relatively old. Newer drugs with longer half-lives, higher resistance barriers and better overall pharmacokinetics may be more forgiving of noncompliance.

In the aforementioned study, with regard to compliance, 41 % of patients were misjudged by their treating clinicians. Nurses seemed to have a better understanding of their patients, judging incorrectly in only 30 % of cases (Paterson 2000). In other studies, too, compliance tends to be overestimated (Miller 2002).

The importance of compliance is also demonstrated by the successes reported in patients with directly observed therapy (DOT). In Florida's correctional facilities 100 % of participants in a DOT study had a viral load below 400 copies/ml at 48 weeks, compared with 81 % in an unmonitored control group in the general population (Fischl 2001).

Poor adherence not only leads to virological failure. It also has immunological consequences. In an analysis of two prospective studies, patients with a compliance of 100 %, 80-99 % and 0-79 % experienced reductions in viral load of 2.77, 2.33 and 0.67 logs after one year. At the same time, the CD4 cell count rose by 179, 159 and 53 cells/µl, respectively (Mannheimer 2002). Furthermore, non-compliance also has clinical effects beyond the surrogate markers. In a Spanish study, patients who did not take more than 10 % of their drugs had a four-fold increase in mortality risk (Garcia 2002). This data has been confirmed in other studies (Maher 1999, Hogg 2000, Wood 2004). Hospital stays are also less frequent in patients with high compliance (Paterson 2000). In addition, it should be considered that noncompliant patients increase the risk of transmission of resistant viruses.

The basic mechanisms for development of resistance should be explained to patients. One must emphasize that, in contrast with other chronic illnesses, resistance mutations do not disappear once they have developed. Diabetes and hypertension make effective examples: whereas these diseases may "tolerate" forgetting the occasional tablet (blood glucose or blood pressure levels can easily be lowered again the next day), HIV is different. Even short-term lapses can have irreversible consequences. And every new occurrence of resistance makes therapy more complicated and more difficult. Patients have to be made aware of this unusual feature of HIV disease. These conversations should be repeated from time to time and become a standard component of routine care. Cooperation with special treatment discussion groups offered by various support organizations can be useful. The table below provides additional suggestions.

In addition, very different strategies have been investigated in order to improve compliance. They range from the employment of additional nurses to telephoning patients regularly. A large recent ACTG study showed that at least the regular telephone reminders do not appear to have any influence on compliance (Collier 2005).

In contrast, the cooperation with special therapy consultations, such as those offered by some AIDS-help groups has proven itself.

Twelve steps to improve adherence

1. Every patient should receive a written (legible!) treatment plan, which should be reviewed at the end of the visit. The plan should include a telephone number to call in case of problems or questions.
2. Patient and clinician should agree on the treatment plan. The patient's concerns or critical questions should be discussed.
3. The patient should have the impression that the treatment regimen was not randomly chosen, but tailored to his/her individual needs.
4. The explanation of a new or modified treatment plan takes time, and should not be rushed – all questions should be answered.
5. The reasons why adherence is so important should be explained. It makes sense to repeat such conversations – they should not only take place when initiating or modifying treatment, but should be part of routine care.
6. Possible side effects should be explained, as well as what can be done to alleviate them.
7. Support groups and other types of assistance should be utilized and offered.
8. It is important to tell the patient to come back if any problems are encountered with HAART – it is better to solve them together than have the patient try to deal with them alone at home.
9. The patient should know that the treatment regimen must be taken in its entirety ("Last month I left out the big tablets").
10. Prescriptions should be documented, in order to get a rough idea of adherence. Irregularities should be addressed openly.
11. During the early phases of therapy, the patient should be informed of treatment success as seen by reduction of viral load and rise in CD4 count.
12. Ensure clinical vigilance to detect the early signs of depression and treat appropriately.

If compliance remains low

Despite all efforts, some patients will not be able to improve their compliance. Physicians and other healthcare providers are advised not to take this personally or to feel offended should a patient not want to participate in the advances of medicine. Although it may be difficult to accept others' views on life, disease and treatment, tolerance and acceptance should remain fundamental to the interactions of all healthcare providers with their patients. Some providers, especially those who treat selective patient populations in university settings, sometimes forget the reality of routine medical practice. Upholding the principles of modern medicine usually doesn't help here, and putting patients under pressure achieves even less. It is important to clearly outline and explain one's own position.

The question of whether noncompliant patients should continue to be treated with antiretroviral therapy is not always easy to address. On the one hand, there are patients who benefit even from suboptimal therapy; on the other hand, drugs are ex-

pensive and should not be prescribed readily. If poor compliance is suspected in the initial consultation, restraint should be applied.

One also needs to be aware of criminal intentions – there have repeatedly been reports of patients who have done deals with pharmacists (black sheep occur everywhere!) for other medication (methadone, etc.) or money. Therefore, written prescriptions should be endorsed where possible. If in doubt about the compliance or honesty of the patient, plasma levels can be measured (preferably without prior warning).

The Duesberg sect

The patients that refuse antiviral treatment on principal are a special case. These patients are often treated by (shockingly misdirected) doctors, who call themselves "Duesbergians" (after the US virologist and AIDS dissident Peter Duesberg, who denied any association between AIDS and illness). For healthcare providers, it can be very difficult to watch patients go to their fate with open eyes, without doing anything. Informative consultations should be as detailed as possible and documented in writing. Below is an actual example:

An approximately 40-year-old patient with a long history of untreated HIV, 30 CD4 cells/µl and cerebral toxoplasmosis, which improved significantly after 4 weeks of acute treatment (the last MRI still showed scattered lesions) presented at the HIV outpatients department. Clinically, he was relatively well and fully oriented, and due for discharge that day. In a conversation, the patient categorically refused to start the urgently recommended antiretroviral therapy ("one can die from AZT, and the other drugs are not much better") as well as antibiotics. Therefore he could also not continue to take the toxoplasmosis maintenance therapy, which had caused him from the first day in hospital to suffer from diarrhea (NB, perhaps cryptosporidiosis), skin problems (seborrheic dermatitis, thrush), and an extreme loss of weight (MAC?). It was most important for him to have a break from everything.

In cases such as these, we make sure the patients sign the information sheets. Every patient is allowed to and should decide for himself (if fully oriented) – but he must know and be fully informed about what he is doing. It is important to give the patient control: if he changes his mind (and of course, if the toxoplasmosis relapses), he can return! Arguing with medical Duesbergians does not achieve anything in our experience. The view of the world that this sect has is closed. A discussion about the prayer-wheel-like repeated old arguments just uses up time and wastes energy.

Fortunately, these cases have become less common. The initial widespread skepticism about HAART has decreased significantly, due to its overwhelming success in the last few years. And: where Peter Duesberg is concerned (thankfully), it has also become quieter, at least as far as his HIV activities goes. The sect is in decline.

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6. Management of Side Effects

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Patients on HAART commonly suffer from side effects. As a result, treatment of HIV infection has become a complicated balancing act between the benefits of durable HIV suppression and the risks of drug toxicity. About 25 % of patients stop therapy within the first year on HAART because of side effects (d'Arminio Monforte 2000). About the same number of patients does not take the recommended dosages of their medication due to concerns regarding the side effects (Chesney 2000). Patients, who report significant side effects, are more often non-adherent to therapy (Ammassari 2001).

The patient should be counseled in detail about potential side effects, in order to be able to recognize them and to consult his physician in time. This can save lives, for example in the case of the abacavir hypersensitivity reaction, or prevent irreversible damage, such as polyneuropathy. Being prepared for the occurrence of possible problems and providing potential solutions improves both the acceptance of treatment and the adherence. However, patients should not be frightened by all this information – the extensive package inserts are often ominous enough. It may be difficult to distinguish between symptoms related to HIV infection and those caused by antiretroviral therapy. An accurate history, including any co-medication (not forgetting over-the-counter and "natural" products!) is paramount. It is important to consider the intensity, variation and reproducibility of complaints, as other possible causes should be excluded before symptoms are judged as being side effects of treatment.

It must be stressed that the majority of patients are able to tolerate HAART well, even over years. Nevertheless, the monitoring of treatment by an HIV clinician, is recommended in at least three-monthly intervals, even in asymptomatic patients, and more often at the beginning of a new HAART, when it should be weekly or fortnightly. Standard evaluations include a thorough history (allergies?, other side effects?), physical examination and measurement of vital signs and body weight. Routine investigations include a full blood count, liver, pancreas and renal function tests, electrolytes (plus phosphate in patients on tenofovir) as well as fasting cholesterol, triglycerides and glucose levels.

For lipodystrophy see chapter on "Lipodystrophy Syndrome".

Gastrointestinal side effects

Gastrointestinal problems are the most common side effects of almost all antiretroviral drugs - nucleoside analogs, NNRTIs and particularly protease inhibitors - and occur especially during the early stages of therapy. Typical signs and symptoms include abdominal discomfort, loss of appetite, diarrhea, nausea and vomiting. Heartburn, abdominal pain, meteorism and constipation may also occur. Nausea is a common symptom with zidovudine-containing regimens; diarrhea occurs frequently with zidovudine, didanosine and all PIs, particularly with lopinavir, fosameprena-

vir, nelfinavir and "baby dose" ritonavir. Treatment with zidovudine rarely leads to a severe form of gastritic pain, nausea and vomiting in the early phase of therapy, in which case it should be discontinued.

In addition to the often considerable impact on everyday life, gastrointestinal side effects can lead to dehydration, malnutrition with ensuing weight loss, and low plasma drug levels with the risk of development of resistant viral strains.

In most cases, symptoms occur at the beginning of therapy. Patients should be informed that these side effects usually resolve after four to six weeks of treatment. If gastrointestinal side effects occur for the first time after longer periods on HAART, other causes such as gastritis and infectious diarrhea are likely.

Nausea and vomiting

If administration on an empty stomach leads to nausea and vomiting, most drugs can also be taken together with meals. When a drug (e.g. didanosine, indinavir, rifampin) has to be administered on an empty stomach, small quantities of low-fat salty crackers may lessen the nausea. Ginger, peppermint or chamomile teas or sweets may also be helpful, as well as frequent small meals. Care should be taken with fatty foods and dairy products. Coffee, smoking, alcohol, aspirin and very spicy foods should be avoided if possible.

If symptomatic treatment is necessary, metoclopramide has been proven to be useful. Dimenhydrinate, cimetidine, ranitidine or ondansetron can also be taken. Antiemetic drugs should not be administered only when the patient is already feeling sick, but rather taken regularly, ideally 30 to 45 minutes before HAART. If taken on a regular basis, attention should be paid to side effects such as dyskinesia. After a few weeks, doses can generally be reduced slowly. If nausea persists for more than two months, a change of treatment should be considered – otherwise adherence problems will certainly occur.

Diarrhea

In patients with massive diarrhea, the priority is to treat dehydration and loss of electrolytes. Other causes such as gastrointestinal infections or lactose intolerance should be excluded. Difficult to digest foodstuffs (particularly those rich in fats or glucose) should be avoided and those that are easy to digest (e.g. potatoes, rice, noodles), eaten instead. It makes sense to remember homespun remedies (see table 1).

If significant dehydration and loss of electrolytes occur, coke and salty crackers, sports drinks, herbal teas or electrolyte solutions may be taken (reviews in: Highleyman 2000, Sherman 2000). Oral rehydration solution can be easily made from the juice of 5 oranges, 800 ml of boiled water or tea (cooled to room temperature), one teaspoon of iodized salt and two tablespoons of sugar.

Oat bran tablets have been proven to be useful and cheap for PI-associated diarrhea. They are taken together with antiretroviral therapy (daily dose 1500 mg). Pancrelipase, a synthetic pancreatic enzyme, has also been shown to be effective for PI-associated diarrhea.

PI-associated diarrhea is alleviated by calcium (Turner 2004), taken as calcium carbonate, at a dosage of 500 mg bid. However, as calcium binds many other substances, it should be taken 2 hours apart from HIV medication.

Oral supplements of glutamine (10 – 30 g/day) or alanyl–glutamine (up to 44 g/day) alleviate diarrhea and can also boost the levels of antiretroviral drugs in the blood (Bushen 2004, Heiser 2004). The probiotics, Saccharomyces boulardii and Lactobacillus acidophilus are used in infectious diarrhea and for the prevention of antibiotic-associated diarrhea. They can sometimes ameliorate medication-associated diarrhea. Case reports have implicated S. boulardii as an etiologic agent of possibly fatal invasive fungal infection. Particularly at risk were patients with an intravascular catheter or on antibiotic therapy (see review in: Enanche-Angoulvant 2005).

Alternatively, psyllium may be effective. It should not be taken together with loperamide or opium tincture, or at the same time as HIV medication.

The cornerstone of symptomatic treatment is loperamide which inhibits bowel movement (initially 2 – 4 mg, followed by 2 mg, up to a maximum of 16 mg daily). If loperamide is not effective, opium tincture is an alternative (initially 5 drops, maximum 15 to 20 drops), attention should be paid to the risk of intestinal obstruction, especially if overdosed. In some cases, a combination of different antidiarrheal drugs may be appropriate.

Table 1: “Approved” homespun remedies

Pectin
in apples (raw with skin), bananas (purée), carrots (purée, cooked, soup), St. John’s bread (oatmeal gruel or rice gruel with St. John’s flour). Pectin is a dietary fiber, which is not digested, it binds water and toxic substances and lessens the diarrhea.
Gruel
Soups made of oatmeal or rice gruel
Tanning agents
Black or green tea, dried blueberries (tea, powder), dark chocolate

Hepatotoxicity

Elevated liver function tests are common with HAART, and severe hepatotoxicity occurs in up to 6 % of patients (Becker 2004), but liver failure is rare (Nunez 2005). Occurrence of hepatotoxicity depends on the drug classes or agents used as well as on pre-existing liver dysfunction.

Nevirapine, ritonavir and tipranavir have been associated with severe hepatotoxicity. Several fatalities due to liver failure habe been linked to nevirapine (Bjornson 2006, De Maat 2003, Law 2003). Case reports also exist about liver failure due to indinavir, atazanavir, efavirenz, nelfinavir and different nucleoside analogs (Carr 2001, Clark 2002). Risk factors for the occurrence of severe hepatotoxicity are baseline elevation in serum aminotransferases, chronic hepatitis B or C coinfection as well as concomitant hepatotoxic medication, protease inhibitor therapy, thrombocytopenia and renal insufficiency (Servoss 2006, Sulkowski 2002).
Patients with pre-existing liver disease should receive the above mentioned drugs only under strict monitoring (Sulkowski 2004).

Hepatotoxic reactions occur at different time points for different drug classes: NNRTIs often cause a hypersensitivity reaction within the first 12 weeks, nucleoside analogs lead to hepatic steatosis, which is probably caused by mitochondrial toxicity and usually occurs after more than 6 months on treatment (Montessori 2003). PIs can lead to hepatotoxicity at any stage during the course of treatment – ,patients with chronic viral hepatitis are particularly at risk. One possible cause is an immune reconstitution syndrome on HAART, with increased cytolytic activity against the hepatitis virus-infected liver cells. Among the PIs, toxic hepatitis is seen most frequently in patients on boosted atazanavir, indinavir and tipranavir (Sulkowski 2004).

Nevirapine

Liver toxicity occurs more commonly on nevirapine than on other antiretroviral drugs. Clinically asymptomatic and symptomatic liver toxicity, including rapidly occurring fatal liver failure have been observed (Bjornsson 2006). Serious and fatal liver toxicity has been reported even during post-exposure prophylaxis, but not after single doses of nevirapine (Jackson 2003).

Data had shown a higher risk of symptomatic hepatotoxicity for females compared to males, and in females with CD4+ T-cell counts > 250/µl, as well as for males with CD4+ T-cell counts > 400/µl. The data was mainly derived from a retrospective analysis of the Boehringer Ingelheim data-bases, including almost exclusively antiretroviral-naïve patients. In a cohort of antiretroviral-naïve pregnant women in Mozambique severe hepatotoxicity from nevirapine-containing HAART was likewise more common at higher CD4 counts (Jamisse 2007).

The Indications and Usage section of the Viramune label therefore advises against starting nevirapine treatment in women with CD4+ T-cell counts greater than 250/µl unless benefits clearly outweigh risks (http://www.fda.gov/cder/drug/advisory/nevirapine.htm).

Different studies have now shown that in virologically suppressed patients switching to nevirapine as a part of a simplification regimen has no higher risk of hepatotoxicity or rash independent of gender or CD4 + T cell count (Mallolas 2006). Another open-label comparison of 742 patients with nevirapine or efavirenz based regimen found no increased hepatotoxicity in nevirapine treated subjects with regard to gender or CD4 + T cellcount (Manfredi 2006).

One risk factors was hepatitis C coinfection, if possible nevirapine should be avoided (Tossonian 2006, de Lazzari 2006). Another study showed that a body mass index (BMI) < 18.5 kg/m² in women is associated with a high risk of hepatotoxicity (Sanne 2005).

Liver toxicity occurs usually early during therapy (within 18 weeks of starting). If liver enzymes levels increase to > 3.5 times upper limit of normal (ULN) during treatment, nevirapine should be stopped immediately. If liver enzymes return to baseline values and if the patient has had no clinical signs or symptoms of hepatitis, rash, constitutional symptoms or other findings suggestive of organ dysfunction, it may, on a case-by-case basis, be possible to reintroduce nevirapine. However, frequent monitoring is mandatory in such cases. If liver function abnormalities recur, nevirapine should be permanently discontinued. If clinical hepatitis (anorexia, nau-

sea, jaundice, etc.) occurs, nevirapine must be stopped immediately and never re-administered.

Protease inhibitors

Atazanavir and indinavir inhibit the hepatic enzyme UDP-glucuronosyltransferase, increasing bilirubinlevels in up to 47 % of patients. Hyperbilirubinemia is not usually associated with signs or symptoms of hepatocellular injury, and clinically resembles Gilbert's syndrome. Hyperbilirubinemia is associated with higher atazanavir plasma levels (Smith 2006). Individualshomozygous for UGT1A1*28 are at particular risk of atazanavir or indinavir associated hyperbilirubinemia. Genotyping for UGT1A1*28 before initiation of therapy would identify individuals at risk, but might not be cost-effective (Rotger 2005, Rodriguez-Novoa 2007).

The levels of bilirubin return to normal following discontinuation of the drugs. If bilirubin is only mildly elevated (< 3 times ULN) and the serum liver enzyme levels are normal, treatment change is not mandatory. If the bilirubin is constantly markedly elevated, medication should be discontinued: nobody knows about the long-term consequences of hyperbilirubinemia (Sulkowsky 2004).

Tipranavir is associated with clinical hepatitis and hepatic decompensation including some fatalities. In a phase III study with 1458 patients grade 2 to 4 liver enzyme elevation was more frequent observed in patient treated with tipranavir compared with other PIs (both with ritonavir boosting) (17,5 % versus 9,9 % within 24 weeks, 24,4 % versus 12,8 % within 48 weeks) Patients with chronic hepatitis B or C co infection or baseline elevation in transaminases have an approximately 2.5 fold higher risk for developing further transaminase elevation or hepatic decompensation (Aptivus® Prescribing Information 2006).

As Tipranavir is mainly metabolized by the liver, tipranavir concentrations might be increased in patients with hepatic impairment. It is contraindicated in patients with hepatic insufficiency Child- Pugh Class B and C). Liver function test as well as close clinical monitoring are mandatory prior initiating and during therapy.

Besides serological and if necessary molecular testing for viral hepatitis, an abdominal ultrasound should be performed to recognize structural liver dysfunction, e.g. non-alcoholic steatohepatitis or liver cirrhosis early, before initiating HAART. Liver function should be monitored biweekly at the start of treatment with nevirapine and PIs and even more frequently in patients with pre-existing liver disease. Monthly tests are generally sufficient for all other drugs. If liver enzymes (ALT, AST) are moderately elevated (< 3.5 times ULN) in the absence of clinical symptoms, treatment can be continued under close monitoring. If liver enzymes are elevated to more than 3.5 times ULN, additional diagnostic tests should be performed, including an abdominal ultrasound. In cases of co-infection with hepatitis B or C, treatment of these conditions should be considered. With other pre-existing liver conditions, it may be useful to determine drug plasma levels. Discontinuation of treatment may not be necessary (exception: nevirapine).

If liver enzymes are elevated in a later phase of therapy (after more than 6 months), a thorough investigation including serology for viral hepatitis, CMV, and EBV, as well as an abdominal ultrasound, should be performed. Lactic acidosis, hypersensitivity reactions to abacavir and other hepatotoxic drugs should also be considered.

Furthermore, analysis of blood gases including pH, base excess and bicarbonate concentration, lactate levels and a thorough drug history can help.

Liver biopsy reveals macro- and microvesicular steatosis and mitochondrial alterations in NRTI-induced steatosis and is therefore helpful to identify a nucleoside-induced hepatopathy and to distinguish it from other causes of liver injury.

In patients with HCV co-infection, hepatitis C should, if possible, be treated before the initiation of HAART, to reduce the frequency of severe hepatotoxicity (see Chapter "Hepatitis C"). In HBV co-infection, the HAART regimen should include lamivudine and/or tenofovir. Patients with pre-existing liver dysfunction should undergo drug plasma level monitoring, especially during treatment with PIs. Doses can be adjusted according to the plasma levels so that a premature discontinuation of therapy can be avoided. However, no relationship has been found between hepatic injury and plasma levels of nevirapine.

Finally, drug interactions and hepatotoxicity related to other drugs (e.g. ACE inhibitors or antidepressants), taken concomitantly, should not be overlooked.

Renal problems

Tenofovir

Tenofovir has been approved since 2001 and is, like the two nephrotoxic drugs, adefovir and cidofovir, a nucleotide analog. Animal studies showed a dose-related nephrotoxicity. Severe renal toxicity occurs rarely, but a significant proportion of patients develop kidney dysfunction (Crane 2007, Sax 2007). In one study graded elevation of serum creatinine occurred in 2,2 % of the patients (Nelson 2007)). Acute renal failure and proximal tubulopathy with Fanconi's syndrome and nephrogenic diabetes insipidus and rarely hypophosphatemic osteomalacia have been reported Rollot 2003,Saumoy 2004). Proximal tubular damage manifests as proximal tubular acidosis, normoglycemic glycosuria, hypophosphatemia, hypouricemia, hypokalemia, generalized aminoaciduria, and proteinuria. Renal toxicity occurs after some months, rarely at the beginning of therapy (Hansen 2004, Izzedine 2004, Rifkin 2004). Risk factors include a relatively high tenofovir exposure, pre-existing renal impairment, low body weight, increased age, co-administration of nephrotoxic drugs, amprenanvir and didanosine. Furthermore, extensive pre-treatment with nucleoside reverse transcriptase inhibitors seems to be another risk factor (Saumoy 2004). However, even in patients without any predisposing factors, nephrotoxicity may occur (Barrios 2004).

Case reports suggested that the use of lopinavir/ritonavir, atazanavir and ritonavir with tenofovir is associated with a higher risk of kidney dysfunction through the interaction of PIs with the renal transport of organic anions, leading to proximal tubular intracellular accumulation of tenofovir (Izzedine 2004, Rollot 2003, Zimmermann 2006). However, three studies did not find an increase in tenofovir-asscociated kidney dysfunction among patients receiving lopinavir/ritonavir, atazanavir, or ritonavir (Gallant 2005, Antoniou 2005, Crane 2007)

In case of renal dysfunction, especially in patients with low body weight, tenofovir should be avoided if possible, or the dosing interval should be adjusted. The manufacturer recommends administering tenofovir every 48 hours in patients with a cre-

atinine clearance between 30 and 49 ml/min and twice a week between 10 and 29 ml/min.In these cases therapeutic drug monitoring is recommended.

Normal creatinine levels may be misleading especially in subjects with low body weight, which is why creatinine clearance should be measured before initiating tenofovir treatment. Urine-beta2 microglobuline might be a more sensitive marker of renal tubular injury caused by tenofovir (Gatanaga 2006). Renal function tests including creatinine, urea, creatinine clearance, proteinuria, glycosuria, blood and urine phosphate should be monitored every other week.

Tenofovir is not recommended for use in patients with pre-existing renal insufficiency. It should also be avoided with concomitant or recent use of nephrotoxic agents such as aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir or interleukin-2. Usually the abnormalities resolve after discontinuation of the drug (Izzedine 2004, Rifkin 2004, Roling 2006).

An increase in creatine kinase (CK, CK-MB) is common with tenofovir (Shere-Wolfe 2002). Analysis of CK-MB isoenzyme activity and mass concentration revealed evidence for Macro CK 2 (Schmid 2006). Therefore, the elevated CK might not be an indicator of ischemic heart disease but Macro CK-2 appearance on tenofovir treatment. The CK elevation resolves after discontinuation of tenofovir.

Indinavir

Renal problems occur particularly on indinavir treatment, and are caused by indinavir crystals, which may be found in the urine of up to 20 % of patients. Approximately 10 % of patients develop nephrolithiasis, which is not visible on X-ray, accompanied by renal colic. Nephrolithiasis is primarily caused by high indinavir levels in relation to a low BMI, drug interactions and individual fluctuations of the drug plasma level. In one study, the intake of indinavir/ritonavir 800/100 mg with a light meal reduced the indinavir plasma concentration, probably reflecting a food-induced delay in the absorption of indinavir (Aarnoutse 2003). In case of suspected high indinavir levels, therapeutic drug monitoring should be performed and the dose adjusted (Collin 2007). Interruption of therapy, following a single incidence of colic, is not usually necessary. More than 20% of patients have persistent asymptomatic leukocyturia associated with a gradual loss of renal function without urological symptoms (Dielemann 2003). However, renal failure is rare (see also chapter HIV and Renal Function).

Atazanavir

Similar to Indinavir where 19% of the drug is excreted unchanged in the urine, 7% of Atazanavir is found in the urine of healthy persons. In contrast to indinavir, nephrolithiasis seems to be a very rare adverse event with atazanavir. Hitherto, three case reports have been published (Chang 2006, Pacanowski 2006, Anderson 2007), and the US Food and Drug Administration's Adverse Event Reporting System identified 30 cases of symptomatic nephrolithiasis (Chan-Tack 2007).

Neurological side effects

Peripheral polyneuropathy

Peripheral polyneuropathy is mainly caused by the NRTIs, zalcitabine, didanosine and stavudine. It usually presents with a distal symmetrical distribution and sensorimotor paralysis. Patients complain of paresthesia and pain in their hands and feet, and often, with zalcitabine, about perioral dysesthesia. The symptoms often begin gradually after several months of therapy. HIV infection itself can lead to peripheral polyneuropathy, but the drug-induced form becomes apparent much earlier and may develop within a shorter period of time. Patients must be informed that they should consult their treating physician as soon as possible if the typical complaints develop. Additional risk factors for polyneuropathy, such as vitamin B12 deficiency, alcohol abuse, diabetes mellitus, malnutrition, or treatment with other neurotoxic drugs, e.g. INH, should be addressed in the appropriate manner. Symptoms frequently improve within the first two months following discontinuation of the drugs responsible, but may initially increase in intensity and are not always fully reversible. Because treatment is difficult, and there is no specific therapy, it is extremely important that peripheral polyneuropathy is recognized early by the doctor, resulting in an early change of treatment. The causative agent has to be abandoned.

An easy test, in practice, is to test vibration with a tuning fork. A 64-Hz tuning fork (Rydel-Seiffer) is applied to the appropriate bony surface (e.g., distal hallux, medial malleolus or lateral malleolus) bilaterally. The patient is asked to report the perception of both the start of the vibration sensation and the cessation of vibration on dampening. As the intensity of the vibration starts to diminish the two triangles move closer together again. The intensity at which the patient no longer detects the vibration is read as the number adjacent to the intersection. It can thus be quantified and compared to the results of other tests. Through this simple method first signs of polyneuropathy can be recognized easily and early.

Apart from symptomatic treatment with metamizole, acetaminophen (paracetamol), carbamazepine, amitriptyline, gabapentine and opioids, methods such as acupuncture or transcutaneous nerve stimulation have been tried with variable success. Vitamin B supplementation can help to improve peripheral polyneuropathy faster. Tight shoes or long periods of standing or walking should be avoided; cold showers may relieve pain before going to bed.

CNS disorders

In up to 40 % of patients, treatment with efavirenz leads to CNS side effects such as dizziness, insomnia, nightmares; even mood fluctuations, depression, depersonalization, paranoid delusions, confusion and suicidal ideation may occur . Efavirenz changes the time spent in several key sleep stages, therefore patients report about persistence of dream recollection and morning sluggishness (Moyle 2006).

These side effects are observed mainly during the first days and weeks of treatment. Discontinuation of therapy becomes necessary in only 3 % of patients. There is an association between high plasma levels of efavirenz and the occurrence of CNS symptoms (Marzolini 2001).

On the one hand, high efavirenz plasma levels can be caused by medication interactions, so a thorough drug history should be taken; on the other hand the different perception of drug tolerance of the patients can play an important role. Patients should be informed about the nature of these symptoms, and that they are usually expected to resolve after a short period of time. Driving cars or bicycles or operating machinery can be impaired in the first weeks. If dizziness or drowsiness is experienced, these activities should be avoided. Treatment with efavirenz should not be started before exams or other important events.

If the CNS side effects persist for more than two to four weeks, it is reasonable to prescribe 200 mg pills, so that the dose can be divided into a 400 mg night dose and a 200 mg morning dose. We experienced a reduction in unpleasant CNS side effects in 50 % of our patients. The daily dose should not be reduced from 600 mg to 400 mg because of the higher risk of therapy failure and development of drug resistance.

Measurement of drug levels makes sense from the second week of therapy to verify overdosage, but the only consequence is the splitting of the 600 mg dosage (by no means should the dose be reduced to 400 mg). Taking 400 mg/200 mg can reduce the Cmax levels and therefore the toxic potential becomes milder.

Lorazepam can diminish the CNS side effects, and haloperidol can be given for panic attacks and nightmares, but both drugs should be restricted to severe cases, because of their side effects and addictive potency (lorazepam).

Efavirenz is metabolized by cytochrome P4502B6 (CYP2B6). An American study showed that an allelic variant CYP2B6, which is more common in African-Americans than in Caucasians, was associated with significantly greater efavirenz plasma exposure during HIV therapy (Haas 2004). CNS side effects are rarely seen with other NNRTIs. If they persist even after splitting the dosage for more than six weeks, efavirenz should be replaced, for example by nevirapine.

Lamivudine/abacavir

Depression, insomnia and even psychosis rarely occur or get worse on lamivudine or abacavir therapy. If the patient complains of CNS-related side effects, lamivudine or abacavir should be considered as a possible cause (Foster 2004).

Haematological changes

HIV infection itself may cause pancytopenia. A very low CD4+ T-cell count may therefore be rarely due to a severe leukopenia. In this case, the percentage of the CD4+ T-cells and the CD4/CD8 ratio are nearly normal.

Some of the antiretroviral drugs (especially zidovudine) are myelosuppressive, especially with respect to the red cells, and therefore lead to anemia (de Jesus 2004). Most commonly affected are patients with advanced HIV infection and pre-existing myelosuppression, on chemotherapy or co-medication with other myelotoxic drugs such as cotrimoxazole, pyrimethamine, amphotericin B, ribavirin, and interferon, or with other antiretroviral drugs.

5 to 10 % of patients taking zidovudine develop anemia – usually during the first 3 months of therapy, but sometimes even after years on treatment (Carr 2001). Zidovudine should be discontinued in severe cases, and a blood transfusion may be

necessary. MCV is always elevated, even in patients on zidovudine without anemia, and is therefore a good proof of adherence. It sometimes makes sense to change from Combivir™ to the single drugs Retrovir™ and Epivir™ in anemic patients, because of the lower zidovudine dose in Retrovir™ (250 mg) compared to Combivir™ (300 mg). In patients with advanced HIV infection and multiple viral resistance, and therefore no options to change to less myelotoxic drugs, erythropoietin is an option, but should be avoided as a long-term option if possible, due to the associated high costs (Henry 2004).

Due to drug-induced neutropenia, it is possible that despite viral suppression the CD4+ T-cell count remains low after an initial rise. In these cases treatment should be changed to less myelotoxic antiretroviral drugs such as stavudine, lamivudine, most of the PI and all NNRTIs. Zidovudine should be avoided. Leukopenia may also occur on indinavir, abacavir or tenofovir.

In Patients on tenofovir and didanosine as the nuke backbone a gradual decrease in the CD4+ T-cell count was observed (see chapter Antiretroviral Therapy).

Increased bleeding episodes

HIV patients with hemophilia A or B may have increased episodes of spontaneous bleeding into joints and soft tissues after some weeks of treatment with protease inhibitors. Rarely, intracranial or gastrointestinal bleeding has occurred. The etiology remains unclear (Review: Wilde 2000).

Over the course of all clinical trials with tipranavir/r the manufacturer received 14 reports of intracranial hemorrhage (ICH), including 8 fatalities, in 13 out of 6,840 HIV-1 infected individuals. So far, there have been no more spontaneous reports of intracranial hemorrhage on marketed tipranavir.

The median time to onset of an ICH event was 525 days on Tipranavir/r. Many of the patients had other risk factors for intracranial hemorrhage such as CNS lesions, head trauma, recent neurosurgery, coagulaopathy, hypertension or alcohol abuse, or were receiving anticoagulant or antiplatelet agents.

In an in-vitro experiment, tipranavir was observed to inhibit human platelet aggregation. No pattern of abnormal hematologic or coagulation parameters was observed. Therefore, routine measurement of coagulation parameters is not currently indicated. Tipranavir/r should be avoided if possible in patients with the above mentioned risk factors. This applies also for patients on antiplatelet agents or anticoagulants. Patients should be informed about the possible risk of intracranial hemorrhage (Important Safety Information, Boehringer Ingelheim 2006).

Allergic reactions

Allergic reactions are frequent during HIV therapy. They occur with all NNRTIs, as well as with the nucleoside analog, abacavir (see below) and the PIs, amprenavir, atazanavir, tipranavir and darunavir. Because amprenavir, tipranavir and darunavir are sulfonamide, they should be given with caution to patients with sulfonamide allergies. When there are limited alternative treatment options, desensitization may permit continued use of amprenavir in patients with a history of amprenavir-

induced maculopapular eruptions (Kohli-Pamnani 2005). Atazanavir-associated macular or maculopapular rash is reported in about 6 % of patients and is usually mild, so that treatment withdrawal is not necessary (Ouagari 2006).

NNRTIs

Nevirapine and delavirdine may cause a slight rash in 15 to 20 % of patients, 5 to 10 % of which discontinue treatment. The rash is seen less frequently on efavirenz therapy, where only 2 % of the patients discontinue the drug (Carr 2001).

The NNRTI allergy is a reversible, systemic reaction and typically presents as an erythematous, maculopapular, pruritic and confluent rash, distributed mainly over the trunk and arms. Fever may precede the rash. Further symptoms include myalgia (sometimes severe), fatigue and mucosal ulceration. The allergy usually begins in the second or third week of treatment. Women are more often and more severely affected (Bersoff-Matcha 2001). If symptoms occur later than 8 weeks after initiation of therapy, other drugs should be suspected. Severe reactions such as the Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome) or anicteric hepatitis are rare (Rotunda 2003).

Treatment should be discontinued immediately in cases with mucous membrane involvement, blisters, exfoliation, hepatic dysfunction (transaminases > 5 times the upper limit of normal) or fever > 39°C.

If patients present with a suspected nevirapine-associated rash, additional hepatotoxicity and liver failure should be considered and liver function tests should be performed. Patients with rash-associated AST or ALT elevations should be permanently discontinued from nevirapine.

Approximately 50 % of NNRTI allergies resolve despite continuation of therapy. Antihistamines may be helpful. Prophylactic treatment with glucocorticosteroids or antihistamines has been shown to be of no benefit for the prevention of nevirapine allergy; in fact, rashes were even more common in some studies (Knobel 2001, Montaner 2003, The Grupo Estudio 2004). Following a severe allergic reaction, the drug responsible for the reaction should never be given again.

Abacavir hypersensitivity

Abacavir causes a hypersensitivity reaction (HSR), which may be life threatening if not recognized in time. It occurs in approximately 4-5 % of patients (reviews: Hewitt 2002, Clay 2002). A higher rate is noted in patients on a once-daily regime, in art-naïve patients, in patients with a nevirapine allergy, and in acute HIV infection . The HSR occurs after a median of 8 days, more than 90% within the first 6 weeks.

Abacavir hypersensitivity is strongly associated with the human leukocyte antigen (HLA-B*-5701 allele, probably mediated through HLA-B*5701-restricted CD8 cells (Phillips 2005). Exclusion of HLA-B*5701 individuals from abacavir treatment could therefore largely prevent HSR (Rauch 2006, Zucman 2007, Mallal 2007). Pre-prescription routine HLA typing or flow cytometry for HLA-B57 (Martin 2006) may be reasonable and cost-effective in the future. A more simple and therefore cheaper alternative approach might be a screening of HIV reverse tran-

scriptase for a signature B*5701-associated cytotoxic T lymphocyte escape mutation at RT codon 245 as part of routine drug- resistance testing (Chui 2007).

The rash associated with the abacavir hypersensitivity reaction is often discrete, in contrast to the skin reactions caused by nevirapine and efavirenz; in 30 % of patients it may not occur at all. 80 % of patients have fever. In addition to general malaise (which gets worse from day to day!), other frequent symptoms include gastrointestinal side effects such as nausea, vomiting, diarrhea and abdominal pain. Respiratory symptoms, such as dyspnea, cough and sore throat, are rare. Changes in the blood count, elevation of liver transaminases, alkaline phosphatase, creatinine and LDH may accompany the HSR. There is usually no eosinophilia. One case of Stevens-Johnson syndrome has been described (Bossi 2002).

The synchronous start of therapy with abacavir and NNRTIs is not recommended because of the difficulties of differentiating between allergic reactions to NNRTIs and HSR. If abacavir is part of the initial therapy and flu-like symptoms occur, it is difficult to distinguish between immune reconstitution inflammatory syndrome (IRIS) and HSR; hence HIV therapy should be carried out by experienced doctors. The HSR is diagnosed clinically but often difficult to distinguish from an intercurrent infection. Criteria in favor of HSR include the development of symptoms within the first six weeks of treatment, deterioration with each dose taken and the presence of gastrointestinal side effects. If abacavir is discontinued in time, the HSR is completely reversible within a few days. HSR may be fatal if not diagnosed. Following discontinuation of abacavir, further supportive treatment includes intravenous hydration and possibly steroids.

If the suspicion of HSR is only vague, and abacavir not stopped, the patient should be seen or spoken to (by telephone) daily, to be able to react immediately in case of clinical deterioration. Once the diagnosis of HSR has been established, rechallenge with abacavir can be fatal and is strictly contraindicated. If there was only a vague suspicion of HSR, rechallenge under in-patient conditions is possible. Whenever treatment has been interrupted, it should be noted that the HSR can occur for the first time after restarting treatment, even without a prior HSR or after switching from the twice-daily to the once-daily formulation (Gervasoni 2007).

Treatment with abacavir requires detailed counseling (and documentation!) on the possible occurrence and symptoms of the HSR. Patients should know whom to contact in cases of suspected HSR, preferably also at night and at weekends. It is important, however, not to frighten patients to the extent that they themselves discontinue treatment too early.

Lactic acidosis

In comparison to asymptomatic hyperlactacidemia, which occurs in approximately 15-35 % of NRTI-treated patients (Carr 2001, Hocqueloux 2003), lactic acidosis is a rare but life-threatening complication. NRTIs are thought to cause mitochondrial toxicity via inhibition of the mitochondrial DNA polymerase (see also chapter on Mitochondrial Toxicity).

It occurs most frequently on treatment with stavudine and didanosine, less often in patients on zidovudine, abacavir and lamivudine. Risk factors are obesity, female sex, pregnancy and therapy with ribavirin or hydroxyurea, a diminished creatinine

clearance and a low CD4+ T-cell nadir (Bonnet 2003, Butt 2003, Wohl 2006). In case treatment with ribavirin is necessary, didanosine has to be replaced.The clinical symptoms, including fatigue, nausea and vomiting, abdominal pain, weight loss and dyspnea, are non-specific and may develop acutely or more gradually. Blood results show elevated lactate levels with or without metabolic acidosis (blood should be taken without using a tourniquet in a cooled fluoride oxalate tube, with transport on ice and the lactate measured within 4 hours). CPK, LDH, lipase, amylase, liver enzymes and the anion gap may be increased; serum bicarbonate may be decreased. Hepatic steatosis can be seen on ultrasound or CT.

Cases of severe lactic acidosis can occur without prior symptomatic hyperlactacidemia. Lactate levels should therefore not be monitored routinely, as increases are not predictive and may lead to unnecessary changes in treatment (Brinkman 2000, Tan 2006, Vrouenraets 2002). In contrast, lactate levels should be tested immediately in symptomatic patients complaining of fatigue, sudden weight loss, abdominal disturbances, nausea, vomiting or sudden dyspnea, in pregnant women on NRTI treatment and in patients, who receive NRTIs again after having suffered a lactic acidosis (Carr 2003).

For lactate levels between 3 and 5 mmol/l, "watchful waiting" with regular monitoring is recommended (see Brinkman 2001). If the resistance profile allows, NRTI treatment may be modified, e.g. switch from stavudine/didanosine to abacavir, zidovudine or tenofovir. At levels above 5 mmol/l, NRTI treatment should be stopped immediately and supportive treatment initiated; such as correction of the acidosis. For the treatment of lactic acidosis see chapter on Mitochondrial Toxicity. Mortality of patients with lactate levels above 10 mmol/l is approximately 80 % (Falco 2002).

Avascular necrosis

The incidence of asymptomatic avascular necrosis is approximately 0.4 % of HIV patients, significantly more frequent than in the general population (Lawson-Ayayin 2005). The postulated association with PIs could not be confirmed (Miller 2002, Loiseau-Peres 2002). Risk factors for avascular necrosis are alcohol abuse, hyperlipidemia, steroid treatment, hypercoagulability, hemoglobinopathy, trauma, nicotine abuse and chronic pancreatitis. Virological (viral load) or immunological parameters are not associated with a risk of developing avascular necrosis (Miller 2002, Mondy 2003, Lawson-Ayayin 2005).

The most common site of the necrosis arethe femoral head and, less frequently, the head of the humerus. Initially, patients complain of pain when bearing weight on the affected joint, with symptoms worsening over days and weeks. The initial stages may be asymptomatic, but are followed by severe bone pain and reduced mobility. Necrosis of the femoral head produces pain in the hip or groin, which may radiate to the knee.

All patients on HAART, especially those with additional risk factors (steroids!) should be monitored closely if hip pain occurs for the first time. Even in subjects with moderate bone or joint pain, an MRI should be performed early on, as this is more sensitive than conventional radiography. Early diagnosis and treatment can spare patients pain, loss of mobility and surgical intervention.

Once the diagnosis is confirmed, patients should be referred to an orthopedic surgeon as soon as possible. Different treatment strategies are available for reducing bone and joint damage as well as pain, depending on the stage of disease, localization and grade of severity. In the early stages, reduced weight bearing with crutches is often sufficient. Surgical core decompression is an option: several holes are drilled in the femoral neck or head, causing new blood vessels to develop and thereby reducing the pressure within the bone. In the more advanced stages, the chances of success decrease with the size of the necrosis. The alternative – osteotomy – has the disadvantage of reducing the mobility of patients over long periods of time. In severe cases, a total endoprosthesis (TEP) is usually necessary.

Further risk factors need to be identified and eliminated. If possible, steroids should be discontinued. Sufficient data are missing as to whether treatment modification on non–PI therapy is successful (Mondy 2003). Physiotherapy is recommended. Nonsteroidal anti-inflammatory drugs (e.g. ibuprofen) are the treatment of choice for analgesia.

Osteopenia/osteoporosis

HIV-infected individuals have a lower bone density than uninfected individuals (Loiseau-Peres 2002). Bone density is determined by the measurement of X-ray absorption (e.g. DEXA scan). Results are given as the number of standard deviations (the T-score) from the mean value in young, healthy individuals. Values between -1 and -2.5 standard deviations (SD) are referred to as osteopenia, values above -2.5 SD as osteoporosis.

In addition to HIV infection, other factors such as malnutrition, diminished fat tissues, steroid treatment, hypogonadism, immobilization and treatment with PIs and NRTIs, seem to play a role in the pathogenesis of this disorder. Osteopenia and osteoporosis are often asymptomatic. Osteoporosis occurs mainly in the vertebrae, lower arms and hips.

The following tests should be performed on all patients with AIDS: a lumbar spine X-ray in the standard anteroposterior and lateral views, bone density measurement (DEXA scan) of the lumbar spine and hip; and laboratory blood tests, including calcium, phosphate and alkaline phosphatase. Osteopenia should be treated with 1000 I.E. vitamin D daily and a calcium-rich diet or calcium tablets with a dose of 1200 mg/day. Patients should be advised to exercise and give up alcohol and nicotine. In cases with osteoporosis, bisphosphonates (e.g. alendronat 70 mg once a week) should be added. The tablets should be taken on an empty stomach 30 min before breakfast, and an upright position should be maintained for at least 30 min. No calcium should be taken on this day. Antiretroviral therapy should not be taken together with calcium. Because testosterone suppresses osteoclasts, hypogonadism should be treated. Alcohol and smoking should be avoided; regular exercise is an essential part of the therapy.

Specific side effects

Enfuvirtide (T-20)

The typical side effect of enfuvirtide is an injection site reaction (ISR) with erythema, induration, nodules, pruritus, ecchymosis, pain and discomfort. Almost every patient is affected, most of them, however, only mildly. ISR, therefore, rarely limits treatment, and only 3 to 7 % of patients discontinue therapy (Lazzarin 2003). The practitioner and the patient have to get used to the injection technique and the management of ISR. Good injection technique (including aseptic conditions) in conjunction with rotating injection sites (see Table 1), may be most effective in minimizing the incidence and severity, as well as the incidence of associated events, including infections. The appropriate management of ISR can lessen the reaction (see Table 1, Clotet 2004, Buhk 2004).

Desensitization therapy is available for the skin rash that occurs rarely with enfuvirtide (Shahar 2005). Another side effect, observed after 48 weeks in the TORO study, was a higher rate of bacterial pneumonia (gram+/ gram-) in patients taking enfuvirtide. The cause is unclear. Thus, patients undergoing enfuvirtide therapy should be monitored for pneumonia (Clotet 2004, Tashima 2003).

Patients taking enfuvirtide and traveling to foreign countries should be prepared for questions about the injection material. Taking along a medical certificate stating that the patient is on subcutaneous injection therapy can help to avoid unpleasant situations.

Table 1: Suggestions for prevention and management of injection site reactions (ISR) and other injection-related adverse events (Clotet 2004)

Good injection technique

- Ensure solution is at room temperature
- Avoid muscle by bevelling needle at 45–90 degrees, depending on body habitus
- Inject slowly
- Maintain sterile technique (wash hands, use gloves, clean injection area and vial caps with alcohol swabs, never touch needle)
- Feel for hard, subcutaneous bumps, avoid injecting into sites of previous ISR
- Avoid indurated or erythematous areas
- Avoid injections on the belt line
- Rotate sites (abdomen, thighs, arms) and never inject two consecutive doses into the same place
- Gentle manual massage after every injection

Interventions for ISR

1. Injection pain
- Topical anesthetic (e.g. lidocaine gel)
- Oral analgesics pre-injection (e.g. ibuprofen or metamizole)
- Numb area with ice or a cool pack before injecting

2. Management of pruritus
- Oral antihistamines
- Emollient creams or lotions (non-alcohol based and fragrance-free)

Emtricitabine

About 2% of patients on emtricitabine have skin discolouration, which is typically reported as hyperpigmentation and usually affecting either the palms of the hands or the soles of the feet. It is more frequent in patients of African origin (Nelson 2004) .

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7. Lipodystrophy Syndrome

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Background

The HIV lipodystrophy syndrome, which includes metabolic complications and altered fat distribution, is of major importance in HIV therapy. The metabolic abnormalities may harbor a significant risk of developing cardiovascular disease, with as yet unknown consequences. In addition, several studies report a reduced quality of life in patients with body habitus changes leading to reduced treatment adherence. Despite the impact of lipodystrophy syndrome on HIV management, little is known about the pathogenesis, its prevention, diagnosis and treatment. Current data indicate a rather multifactorial pathogenesis where HIV infection, its therapy, and patient-related factors are major contributors. The lack of a clear and easy definition reflects the clinical heterogeneity, limits a clear diagnosis and impairs the comparison of results among clinical studies. Therapeutic and prevention strategies have so far been of only limited clinical success. Thus, general recommendations include dietary changes and life style modifications, altering antiretroviral drug therapy (replacement of protease inhibitors with NNRTI or replacement of stavudine and zidovudine with e.g. abacavir or tenofovir), and finally, the use of metabolically active drugs. Here we summarize the pathogenesis, diagnosis and treatment options of the HIV lipodystrophy syndrome.

Clinical manifestation

Lipodystrophies were originally described as acquired or inherited disorders characterized by regional or generalized loss of subcutaneous fat. The non-HIV-associated forms, such as congenital or familial partial lipodystrophy, have a very low prevalence. Generally, these forms are associated with complex metabolic abnormalities and are difficult to treat. The term “lipodystrophy syndrome” in association with HIV, was introduced to describe a complex medical condition including the apparent abnormal fat redistribution and metabolic disturbances seen in HIV-patients receiving protease inhibitor therapy (Carr 1998). But, even years after its first description, there is still no consensus on a case definition for lipodystrophy syndrome in HIV patients. Thus, the diagnosis of lipodystrophy in clinical practice often relies on a more individual interpretation than on an evaluated classification. Finally, changes in the fat distribution have to be considered as being rather dynamic processes. In most cases, lipoatrophy is clinically diagnosed when significant fat loss has already occurred.

HIV-associated lipodystrophy includes both clinical and metabolic alterations (Behrens 2000). The most prominent clinical sign is a loss of subcutaneous fat (lipoatrophy) in the face (periorbital, temporal), limbs, and buttocks. Prospective studies have demonstrated an initial increase in limb fat during the first months of therapy, followed by a progressive decline over the ensuing years (Mallon 2003). Peripheral

fat loss can be accompanied by an accumulation of visceral fat, which can cause mild gastrointestinal symptoms. Truncal fat increases initially after therapy and then remains stable (Mallon 2003). Visceral obesity, as a singular feature of abnormal fat redistribution, appears to occur in only a minority of patients. The study of Fat Redistribution and Metabolic Change in HIV Infection (FRAM), a large cross-sectional analysis of HIV-positive and control men, reported that peripheral lipoatrophy was more frequent in HIV-positive men than in controls (38.3% vs. 4.6%, p=0.001), whereas central lipohypertrophy was less frequent (40.2% vs.55.9%, p=0.001). Among HIV-positive men, the presence of central lipohypertrophy was not positively associated with peripheral lipoatrophy (odds ratio = 0.71, 95%CI: 0.47 to 1.06, p= 0.10). HIV-positive men (age 33-45 years) both with and without lipoatrophy had less subcutaneous adipose tissue (SAT) than controls, with legs and lower trunk more affected than upper trunk. Fat accumulation may also be found locally as dorsocervical fat pads ("buffalo hump") or dissiminated within the muscle and the liver. Female HIV patients sometimes complain about painful breast enlargement, which has been attributed to the lipodystrophy syndrome. There is now accumulating evidence that the major clinical components – lipoatrophy, central adiposity and the combination of both – result from different pathogenetic developmental processes.

The prevalence of lipodystrophy syndrome has been estimated to be between 30 and 50 %, based on cross-sectional studies. A prospective study over an 18-month period after initiation of therapy revealed a prevalence of 17 %. Lipodystrophy, and in particular lipoatrophy, has been observed most frequently in patients receiving a combination regimen of nucleoside analogues and protease inhibitors, although almost all antiretroviral drug combinations can be associated with fat redistribution. The risk of the syndrome increases with the duration of treatment, the age of the patient and the level of immunodeficiency. Lipodystrophy has been observed during the therapy of both the acute and chronic states of HIV infection and even following post-exposure prophylaxis. Children can be affected, like adults, with clinical fat redistribution shortly after initiation or change of antiretroviral therapy. The evolution of the individual clinical components of the lipodystrophy syndrome is variable. Subcutaneous fat loss has been observed during exclusive therapy with NRTIs. The nucleoside analogues linked most strongly to lipoatrophy are zidovudine and stavudine, the latter particularly when used in combination with didanosine. Tenofovir combined with lamivudine and efavirenz is associated with less loss of limb fat than stavudine in a similar combination in therapy-naïve HIV patients.

Frequently, complex metabolic alterations are associated with the described body shape alterations. These include peripheral and hepatic insulin resistance, impaired glucose tolerance, type 2 diabetes, hypertriglyceridemia, hypercholesterolemia, increased free fatty acids (FFA), and decreased high density lipoprotein (HDL). Often these metabolic abnormalities appear or deteriorate before the manifestation of fat redistribution. The prevalence of insulin resistance and glucose intolerance has been reported in the literature at 20 to 50% depending on the study design and measurement methods. Frank diabetes is less frequent with a prevalence of between 1 and 6 %. Lipodystrophic patients present with the highest rates of metabolic disturbances.

Hyperlipidemias are a frequently observed side effect of antiretroviral therapy, especially in combinations that include protease inhibitors. Given that many HIV patients present with already decreased HDL levels, these are not further reduced by antiretroviral drugs. Hypertriglceridemias, especially in patients with evidence of body-fat abnormalities, are the leading lipid abnormality either alone or in combination with hypercholesterinemia. Several weeks after initiation or change of HIV therapy, lipid levels usually reach a plateau and remain stable. All protease inhibitors can potentially lead to hyperlipidemia, although to different extents. For example, atazanavir (Reyataz™) appears to be less frequently associated with dyslipidemia and insulin resistance. In contrast, ritonavir (Norvir™) often leads to hypertriglyceridemia correlating to the drug levels.

The therapy-induced dyslipidemias are characterized by increased triglyceride-rich very low density lipoproteins (VLDL) and to a lesser extend by raising low density lipoproteins (LDL). Detailed characterization revealed an increase of apoplipoprotein B, CIII and E. Raised levels of lipoprotein(a) have been described in protease inhibitor recipients. Mild hypercholesterolemia can occur during therapy with efavirenz (Sustiva™) but is not typical under therapy with nevirapine (Viramune™). Stavudine-based, antiretroviral therapy is associated with early and statistically significant increases in total triglycerides and cholesterol. It is important to note that HIV infection itself is associated with disturbed lipid metabolism. During disease progression, the total cholesterol, LDL, and HDL levels decline and the total triglyceride level rises. It has been postulated that the raised LDL-cholesterol levels after initiation of HIV-therapy reflect rather a reconstitution of LDL-cholesterol concentration as before HIV-infection than an independent increase in LDL-cholesterol by antiretroviral regimens.

HAART, lipodystrophy syndrome and cardiovascular risk

The fat redistribution and disturbances in glucose and fat metabolism resemble a clinical situation that is known as the “metabolic syndrome” in HIV-negative patients. This condition includes symptoms such as central adipositas, insulin resistance and hyperinsulinemia, hyperlipidemia (high LDL, Lp(a) hypertriglyceridemia and low HDL) and hypercoagulopathy. Given the well-established cardiovascular risk resulting from this metabolic syndrome, there is growing concern about a potential therapy-related increased risk of myocardial infarction in HIV patients. These fears are further sustained by reports of arterial hypertension on HAART, a high rate of smoking among HIV patients and increased levels of tissue plasminogen activator (tPA) and plasminogen activator inhibitor-1 (PAI-1) in patients with lipodystrophy. Although many of the, mainly retrospective, studies dealing with this issue are inconclusive, data from a large international study (D:A:D study) provide evidence for an increased relative risk of myocardial infarction during the first 7 years of HAART (Friis-Møller 2003). The incidence of myocardial infarction increased from 1.39/1,000 patient years in those not exposed to HAART, to 2.53/1,000 patient years in those exposed for < 1 year, to 6.07/1,000 patient years in those exposed for ≥ 6 years (RR compared to no exposure: 4.38 [95 % CI 2.39 to 8.04], $p = 0.0001$). After adjustment for other potential risk factors, there was a 1.17-fold [1.11 to 1.24] increased risk of myocardial infarction per additional year

of combined ART exposure. It is, however, of note that older age, male gender, smoking, diabetes mellitus, and pre-existing coronary artery disease were still associated with a higher risk of sustaining cardiovascular events than HAART in this study. Although the CHD risk profile in D:A:D patients worsened over time, the risk of myocardial infarction decreased over time after controlling for these changes. More recently, further analyses of the D:A:D cohort proposed an independent contribution of protease inhibitor therapy to the development of coronary heart disease. After adjustment for exposure to the other drug class and established cardiovascular risk factors (excluding lipid levels), the relative rate of myocardial infarction per year of protease-inhibitor exposure was 1.16 (95% confidence interval [CI], 1.10 to 1.23), whereas the relative rate per year of exposure to non-nucleoside reverse-transcriptase inhibitors was 1.05 (95% CI, 0.98 to 1.13). Adjustment for serum lipid levels further reduced the effect of exposure to each drug class to 1.10 (95% CI, 1.04 to 1.18) and 1.00 (95% CI, 0.93 to 1.09), respectively (Friis-Møller 2003). Data of the SMART study revealed that episodic antiretroviral therapy guided by the CD4 cell count significantly increased the risk of opportunistic disease or death from any cause, as compared with continuous antiretroviral therapy. Surprisingly, the hazard ratio for the drug conservation group vs. the viral suppression group was 1.6 (95% CI, 1.0 to 2.5; P=0.05) for fatal or non-fatal cardiovascular disease. These data may provide evidence for the role of the immune system and/or viral replication in the occurence of cardiovascular events in HIV-patients (El Sadr 2007). Several other studies used ultrasonography to measure the thickness of the carotid intima media or endothelial function to predict the cardiovascular risk. Some of these investigations found abnormal test results (e.g. reduced flow-mediated dilation) that correlated either with the use of protease inhibitors or the presence of dyslipidemia (Currier 2003). While there is some indication of an increased rate of coronary artery disease during HAART, the benefit of suppressed viral replication and improved immune function resulting in reduced morbidity and mortality, clearly argues for the use of antiretroviral drugs according to current international guidelines. It seems obvious however, that pre-existing cardiovascular risk factors in individual patients need to be considered more carefully before starting or switching HAART.

Recommendations such as the National Cholesterol Education Program (NECP) have been proposed for non-HIV-infected patients with similar risk constellations. These guidelines are being proposed by some authors for HIV patients as well (Dube 2003, Schambelan 2002, Grinspoon 2005). According to these recommendations, the overall cardiovascular risk in HIV-infected patients can be determined from specific risk factors by using the Framingham equation. Prediction of coronary heart disease using this equation, however, may have some limitations. A 10-year CHD risk estimation at any time point is determined by the individual's past and expected future lipid levels (best assessed as area under the curve). Hyperlipidemia in many treated HIV patients, however, does not follow the 10-year time course seen in the "normal population" due to frequent therapy changes that may lower total cholesterol, increase HDL, and improve atherogenic risk. Thus, the validity of this calculation for the long-term cardiovascular risk assessment in young patients with changing lipid levels and medication regimens requires further studies.

Clearly, more clinical studies are necessary to assess whether these recommendations are also applicable in the presence of HIV and to determine the clinical value

of lipid lowering drug therapy in these patients. Most importantly, the information about drug interactions of lipid lowering and antiretroviral drugs is still incomplete. The accumulation of pre-existing and drug-related risk factors will get more clinical attention, because, by improving the HIV-associated morbidity and mortality, HAART consequently increases an additional relevant cardiovascular risk factor: the age of patients who are effectively treated with antiretroviral drugs.

Pathogenesis

For a better understanding of the pathogenesis of the complex metabolic abnormalities, it is useful to separate individual aspects of the lipodystrophy syndrome: adipocytes/fat redistribution, lipid metabolism, and carbohydrate metabolism. Studies published during recent years provide evidence for two fundamental assumptions: firstly, lipoatrophy and lipoaccumulation result from divergent or only partially overlapping pathogenetic reasons. Secondly, NRTIs, NNRTIs, PIs, and even drugs within each class contribute to the lipodystrophy syndrome and its individual features by different, probably overlapping and certainly synergistic mechanisms.

NRTI and lipodystrophy

The patterns of fat redistribution in patients who are exclusively receiving NRTIs are unlike those observed in patients during PI therapy. Peripheral fat loss is the major symptom observed in NRTI therapy (particularly using stavudine and didanosine combinations), although a few clinical studies have described a minimal intra-abdominal fat increase in these patients, which is clearly less than under PIs. Given that, commonly, only a mild increase in triglycerides has been observed, exclusive NRTI therapy seems to be of minor impact on lipid metabolism. Postprandially elevated FFA in patients with lipodystrophy, together with in vitro experiments, have led to the hypothesis that NRTIs could impair fatty acid binding proteins (FABP) which are responsible for cellular fat uptake and intracellular fat transport. In contrast, addition of stavudine (Zerit™) to a dual PI regimen does not result in a further increase in the total cholesterol or triglyceride levels.

It is well established that long-term NRTI therapy can cause mitochondrial toxicity. The clinical manifestation of this side effect presents in symptoms such as hepatic steatosis, severe hyperlactatemia, and polyneuropathy. As an explanation for these symptoms, the “pol-γ hypothesis” has been proposed, which was later extended to reveal the lipoatrophy observed under NRTIs (Brinkmann 1999). To maintain an adequate bioenergetic level for accurate cell function, all metabolically active cells depend on a persistent polymerase γ-mediated mitochondrial (mt) DNA synthesis. Mitochondria require a constant supply of nucleosides for this process. The mitochondrial DNA polymerase γ retains both DNA- as well as RNA-dependent DNA polymerase activity. The latter is perhaps responsible for the HIV reverse transcriptase activity and therefore its susceptibility for interactions with NRTIs. Experimental data revealed that, for NRTI uptake into mitochondria, the subsequent phosphorylation and then incorporation into the DNA, certain pharmacodynamic requirements need to be fulfilled. These requirements, which include thymidine kinase activity and deoxynucleotide transport specificity of the mitochondrial

membrane, are apparently different for zidovudine (Retrovir™) and stavudine (Zerit™), which partially explains the prevailing association between lipoatrophy and stavudine therapy. The postulated mechanisms of NRTI-induced mitochondrial dysfunction consist of competitive inhibition, incorporation into the mtDNA resulting in mtDNA depletion, impairment of mitochondrial enzymes, uncoupling of oxidative phosphorylation and induction of apoptosis. Depletion of mtDNA and structural changes in the mitochondria, resulting in increased rates of apoptosis in subcutaneous adipocytes, have been confirmed by some studies. Despite the experimental link between mitochondrial toxicity and fat tissue as one potential target organ, the degree to which mitochondrial damage contributes to fat distribution abnormalities and its specificity remains unknown. In contrast, mitochondrial damage is widely believed to be responsible for other NRTI-related side effects, such as myopathy, hyperlactatemia, microvesicular steatosis, and steatohepatitis with lactic acidosis (Nolan & Mallal 2004).

Protease inhibitors and lipodystrophy

PIs account for the majority of metabolic abnormalities associated with lipodystrophy syndrome. Numerous studies report increases in the levels of total triglycerides and triglyceride-rich lipoproteins (VLDL) accompanied by raised LDL levels after initiation of PI therapy (Walli 1998). Conversely, these parameters improved substantially in most studies after discontinuation of the PI or on switching to abacavir (Ziagen™) or nevirapine (Viramune™). The hyperlipidemic changes are frequently associated with hyperinsulinemia and/or insulin resistance.

It has been proposed, based on in vitro experiments, that PIs such as saquinavir (Invirase™), indinavir (Crixivan™), and ritonavir (Norvir™) are able to inhibit proteasomal degradation of apolipoprotein B leading to intracellular stockpiling of this lipoprotein and excessive release in response to FFA (Liang 2001). Using stable isotopes in vivo, other authors demonstrate a dramatic increase in FFA turnover together with increased lipolysis and decreased clearance of triglyceride-rich VLDL and chylomicrons (Shekar 2002). These conditions point towards an impaired postprandial insulin-mediated lipid metabolism, since insulin, on the one hand, normally inhibits lipolysis and, on the other hand, increases uptake of FFA, triglyceride synthesis, and fat oxidation in favor of glucose oxidation.

So far, it remains unclear whether impaired insulin action eventually leads to dyslipidemia, or whether hyperlipidemia is responsible for reduced insulin function and insulin resistance in the periphery. Presumably, both mechanisms are important given that some PIs (e.g. indinavir) have been shown to induce insulin resistance without changes occurring in lipid metabolism after short-term administration (Noor 2001, Noor 2002), whereas other PIs (e.g. ritonavir) have been demonstrated to cause mainly hypertriglyceridemia due to increased hepatic synthesis without major changes occurring in glucose metabolism. However, comparative clinical studies on the association of different PIs with insulin resistance are still lacking.

It is reasonable to speculate that lipid abnormalities and, in particular increased FFA levels, contribute substantially to the peripheral and central insulin resistance of skeletal muscles and the liver, presumably due to the increased storage of lipids in these organs (Gan 2002). Given this hypothesis, the visceral adiposity could re-

flect the adaptation of the body in response to raised FFA concentrations and an attempt to minimize the lipotoxic damage to other organs.

Several in vitro experiments have indicated that almost all PIs can potentially lead to insulin resistance in adipocytes. Short-term administration of indinavir caused an acute and reversible state of peripheral insulin resistance in healthy volunteers, which was determined in an euglycemic-hyperinsulinemic clamp. These effects are most likely caused by the inhibition of glucose transport mediated by GLUT-4, the predominant transporter involved in insulin-stimulated cellular glucose uptake in humans (Murata 2002). A common structural component found in most PIs has been proposed to cause GLUT-4 inhibition. In some patients with lipodystrophy, additional impairment of glucose phosphorylation may contribute to insulin resistance (Behrens 2002). This is presumably due to an impaired insulin-mediated suppression of lipolysis and subsequently increased FFA levels (Behrens 2002, van der Valk 2001) and accumulation of intramyocellular lipids. Peripheral insulin resistance may also account for an increase in the resting energy expenditure in HIV lipodystrophy and a blunted insulin-mediated thermogenesis.

Indinavir may also induce insulin resistance by inhibiting the translocation, processing or phosphorylation of the sterol regulatory element-binding protein 1c (SREBP-1c) (Caron 2001, Bastard 2002). Either directly or via the peroxisome proliferator activated receptor γ (PPARγ), SREBP-1 regulates FFA uptake and synthesis, adipocyte differentiation and maturation, and glucose uptake by adipocytes. Similarly, the function of these factors has been proposed to be disturbed in inherited forms of lipodystrophy. Finally, hypoadiponectinemia, as found in patients with abnormal fat distribution, may contribute to insulin resistance (Addy 2003).

Diagnosis

Both the lack of a formal definition and uncertainty about the pathogenesis and possible long-term consequences, leads to a continuing discussion about appropriate guidelines for the assessment and management of HIV lipodystrophy syndrome and its metabolic abnormalities. Outside clinical studies, the diagnosis relies principally on the occurrence of apparent clinical signs and the patient reporting them. A standardized data collection form may assist in diagnosis (Grinspoon 2005). This appears sufficient for the routine clinical assessment, especially when the body habitus changes develop rather rapidly and severely. For clinical investigations however, especially in epidemiological and interventional studies, more reliable measurements are required. But so far, no technique has demonstrated sufficient sensitivity, specificity or predictive value to definitively diagnose the HIV lipodystrophy syndrome by comparison with results obtained from a “normal” population. A recent multicenter study to develop an objective and broadly applicable case definition proposes a model including age, sex, duration of HIV infection, HIV disease stage, waist-to-hip ratio, anion gap, serum HDL cholesterol, trunk to peripheral fat ratio, percentage leg fat, and intra-abdominal to extra-abdominal fat ratio. Using these parameters, the diagnosis of lipodystrophy had a 79 % sensitivity and 80 % specificity (Carr 2003). Although this model is largely for research and contains detailed body composition data, alternative models and scoring systems, incorpo-

rating only clinical and metabolic data, also gave reasonable results (for more information, see http://www.med.unsw.edu.au/nchecr).

Despite individual limitations, several techniques are suitable for measuring regional fat distribution. These include dual energy x-ray absorptiometry (DEXA), computer tomography (CT), magnetic resonance imaging (MRI) and sonography. Anthropometric measurements are safe, portable, cheap and much easier to perform than imaging techniques. Waist circumference alone, as well as sagittal diameter, are more sensitive and specific measures than waist-to-hip ratio. Repeated measurements of skin fold thickness can be useful for individual long-term monitoring but need to be performed by an experienced person.

The main imaging techniques (MRI, CT, DEXA) differentiate tissues on the basis of density. Single-slice measurements of the abdomen and extremities (subcutaneous adipose tissue = SAT, visceral adipose tissue = VAT) and more complex three-dimensional reconstructions have been used to calculate regional or total body fat. Limitations of these methods include most notably their expense, availability and radiation exposure (CT). Consequently, CT and MRI should only be considered in routine clinical practice for selected patients (e.g. extended dorso-cervical fat pads, differential diagnosis of non-benign processes and infections).

DEXA is appropriate for examining appendicular fat, which is comprised almost entirely of SAT, and has been successfully employed in epidemiological studies. However, SAT and VAT cannot be distinguished by DEXA, which therefore limits the evaluation of changes in truncal fat. Application of sonography to measure specific adipose compartments, including those in the face, requires experienced investigators and has been minimally applied in HIV infection so far. Bioelectrical impedance analysis estimates the whole body composition and cannot be recommended for measurement of abnormal fat distribution.

Patients should routinely be questioned and examined for cardiovascular risk factors, such as smoking, hypertension, adiposity, type 2 diabetes, and family history. For an accurate assessment of blood lipid levels, it is recommended to obtain blood after a fasting of at least 8 hours. Total cholesterol and triglycerides together with LDL and HDL cholesterol should be obtained prior to the initiation of, or switch to, a new potent antiretroviral therapy and repeated 3 to 6 months later. Fasting glucose should be assessed with at least a similar frequency. The oral glucose tolerance test (OGTT) is a reliable and accurate instrument for evaluating insulin resistance and glucose intolerance. An OGTT may be indicated in patients with suspected insulin resistance such as those with adipositas (BMI > 27 kg/m^2), a history of gestational diabetes and a fasting glucose level of 110 to 126 mg/dl (impaired fasting glucose). The diagnosis of diabetes is based on fasting glucose levels > 126 mg/dl, glucose levels of > 200 mg/dl independent of fasting status, or a 2-hour OGTT glucose level above 200 mg/dl. Additional factors that could lead to or assist in the development of hyperlipidemia and/or insulin resistance always need to be considered (e.g. alcohol consumption, thyroid dysfunction, liver and kidney disease, hypogonadism, concurrent medication such as steroids, β-receptor blockers, thiazides, etc.).

Therapy and Prevention

So far, most attempts to improve or even reverse the abnormal fat distribution by modification of the antiretroviral treatment have shown only modest clinical success. In particular, peripheral fat loss appears to be resistant to most therapeutic interventions. The metabolic components of the syndrome may be easier to improve (Table 3) and more detailed information can be obtained form the Guidelines on the Prevention and Management of Metabolic Diseases in HIV by the European AIDS Clinical Society (www.eacs.eu)

Given the inadequate treatment options to resolve lipoatrophy, much attention has been given to prevent the development of abnormal fat distribution in HIV-patients. Unfortunately, many of these studies so far have not sufficient follow-up periods to fully assess the impact of the respecitve antiretroviral drug combinations on body composition. ACTG 5142 is a multi-centre open-label randomized 96-week study (Haubrich 2007). The study compared the development of lipoatrophy, defined as a 20% loss of peripheral fat from baseline, at week 98 in therapy-naïve patients receiving either two nucleoside analogues + lopinaivr/r, two nucleoside analogues + efavirenz, or lopinavir/r + efavirenz only. The results again identified stavudine and zidovudine as major culprits leading to peripheral fat wasting but surprisingly, in a univariate analysis all patients on lopinavir/r-containing regimens had significantly less lipoatrophy (17%) in comparison to efavirenz-containing regimens (32%) independent of the nucleoside analogues that were combined with these drugs. Patients receiving lopinavir/r + efavirenz had lowest rates of lipoatrophy (9%) at week 96. Whether efavirenz had an independent effect on the development of lipoatrophy or whether lopinavir/r exerts some protective effects, remains unclear. Longer follow-up with more detailed statistical analysis of this trial is required before definite conclusions can be drawn.

Lifestyle changes

Dietary interventions are commonly accepted as the first therapeutic option for hyperlipidemia, especially hypertriglyceridemia. Use of NCEP guidelines may reduce total cholesterol and triglycerides by 11 or 21 %, respectively. Whenever possible, dietary restriction of the total fat intake to 25-35 % of the total caloric intake should be a part of the treatment in conjunction with lipid-lowering drugs. Consultation with professional and experienced dieticians should be considered for HIV-infected patients and their partners. Patients with excessive hypertriglyceridemia (>1000 mg/dl) may benefit from a very low fat diet and alcohol abstinence to reduce the risk of pancreatitis, especially if there is a positive family history or concurrent medications that may harbor a risk of developing pancreatitis. Regular exercise may have beneficial effects, not only on triglycerides and insulin resistance, but probably also on fat redistribution (reduction in truncal fat and intramyocellular fat) and should be considered in all HIV-infected patients (Driscoll 2004). All patients should be advised and supported to cease smoking in order to reduce the cardiovascular risk. Cessation of smoking is more likely to reduce cardiovascular risk than any choice or change of antiretroviral therapy or use of any lipid-lowering drug.

Table 3. Therapeutic options for HIV-associated lipodystrophy and related metabolic complications

Lifestyle changes (reduce saturated fat and cholesterol intake, increase physical activity, cease smoking)
Change antiretroviral therapy [replacement of PI, replacement of stavudine (Zerit™) or zidovudine (Retrovir™)]
Statins [e.g. Atorvastatin (Sortis™), Pravastatin (Pravasin™), Fluvastatin (Lescol™)]
Ezetimibe (Ezetrol™)
Fibrates [e.g. Gemfibrozil (Gevilon™) or Bezafibrat (Cedur™)]
Metformin (e.g. Glucophage™)
Thiazolidinediones [rosiglitazone (Avandia™), pioglitazone (Actos™)]
Recombinant human growth hormones (e.g. Serostim™)
Surgical intervention

Specific interventions

Given the extensive indications that PIs are the culprits substantially contributing to the metabolic side effects, numerous attempts have tried to substitute the PI component of a regimen with nevirapine, efavirenz, or abacavir. Similarly, given the close association of stavudine-based therapy with lipoatrophy, replacement of this thymidine nucleoside analogue by, for example, abacavir or tenofovir has been evaluated in several studies. Indeed, these "switch studies" have demonstrated substantial improvement, although not normalization, of serum lipids (total and LDL cholesterol, triglycerides) and/or insulin resistance in many patients. In patients with hyperlipidemia, substitution of PIs with alternative PIs that have less metabolic side effects (e.g. atazanavir) has also been proven to be a successful strategy (Martinez 2005, Moebius 2005). Protease inhibitor cessation has not been shown to improve lipoatrophy. However, stopping administration of the thymidine nucleoside analogue stavudine or zidovudine usually leads to a slow recovery (over months and years) measured by DEXA and moderate clinical increase in limb fat (Moyle 2005). Under restricted inclusion criteria and study conditions, most patients maintained complete viral suppression after changes to the HAART regimen, but not all of these studies included control groups with unchanged antiretroviral therapy. The MITOX study showed that, in addition to limb fat gains, switching to abacavir had no significant effect on HIV-1 RNA, fasting lipids or glucose after 24 weeks (51; 56). Modest but significant increases in limb fat were observed in those switching to abacavir over 2 years (mean increases of 0.39 kg and 1.26 kg at weeks 24 and 104, respectively); the benefits on limb fat mass were largely restricted to individuals switching away from stavudine. Other randomized studies confirmed these findings and have suggested that switching therapy may also prevent limb fat loss. Recently, a pilot study evaluating the effect of uridine (NucleomaxX™) on lipoatrophy in HIV patients continuing their HAART regimen described a significant increase in subcutaneous fat after only three months (Sutinen 2005). Further studies with uridine, a sugar cane extract, will be necessary to fully assess the effectiveness and safety of this compound for patients with the lipodystrophy syndrome.

Other advantageous changes of metabolic parameters have been observed after replacement of the PI by nevirapine or abacavir. This option is, however, not always suitable, and the clinical benefit of effective viral suppression and improved immune function needs to be considered in view of the drug history, current viral load, and resistance mutations. When options are limited, antiretroviral drugs that may lead to elevation of lipid levels should not be withheld for fear of further exacerbating lipid disorders.

Table 4. Preliminary treatment recommendations and LDL cholesterol goals for HAART-associated hyperlipidemias

Risk Category	**Recommendations** "aimed for" LDL	diet if LDL	Lipid-lowering drugs if LDL
CHD or risk equivalent	< 100 mg/dl	≥ 100 mg/dl	≥ 130 mg/dl
≥ 2 RF and 10-years risk ≤ 20%			
10-year risk 10-20%	< 130 mg/dl	≥ 130 mg/dl	≥ 130 mg/dl
10-year risk <10%	< 130 mg/dl	≥ 130 mg/dl	≥ 160 mg/dl
0-1 risk factors	< 160 mg/dl	≥ 160 mg/dl	≥ 190 mg/dl

Coronary heart disease (CHD) includes history of myocardial infarction, unstable angina, stable angina, coronary artery procedures, or evidence of clinically significant myocardial ischemia. CHD risk equivalents include clinical manifestations of non-coronary forms of atherosclerotic disease, diabetes, and >2 risk factors with 10-year risk for hard CHD >20 %. Risk factors (RF) include: age (male ≥ 45 years, female ≥ 55 years or premature menopause without hormone replacement), positive family history for premature CHD (in first-degree relatives < 55 years and first-degree female relatives < 65 years), cigarette smoking, hypertension (blood pressure ≥ 140/90 mmHg or taking antihypertension drugs), HDL < 40 mg/dl (1.0 mmol/l). If HDL cholesterol is over > 60 mg/dl (1.6 mmol/l), subtract one risk factor from the total (adapted from Dubé 2000 and Schambelan 2002).

Lipid lowering agents should be considered for the treatment of severe hypertriglyceridemia, elevated LDL or a combination of both. The clinical benefit, however, of lipid lowering or insulin-sensitizing therapy in HIV patients with lipodystrophy remains to be demonstrated. In light of the potentially increased cardiovascular risk to recipients of antiretroviral therapy, an American AIDS clinical trial group (ACTG) published recommendations based on the National Cholesterol Education Program (NCEP) for primary and secondary prevention of coronary artery disease in seronegative patients (Table 4). In addition, more detailed recommendations by the European AIDS Clinical Society (www.eacs.eu) have been published recently. However, these recommendations should be considered as being rather preliminary, given the so far limited numbers, sizes and durations of the clinical studies they are based on. It appears reasonable to measure fasting lipid levels annually before and 3-6 months after antiretroviral therapy is initiated or changed. Whenever possible, the antiretroviral therapy least likely to worsen lipid levels should be selected for patients with dyslipidemia. Decision on lipid lowering therapy can be based on estimating the 10-year risk for myocardial infarction according to the Framingham equation (http://hin.nhlbi.nih.gov/atpiii/calculator.asp or http://cphiv.dk/tools.aspx).

HMG-CoA reductase inhibitors have been successfully used in combination with dietary changes in HIV patients with increased total and LDL cholesterol. These drugs may decrease total and LDL cholesterol by about 25 % (Grinspoon 2005) and even more effective decrease in lipids have been described when combined with ezetimibe. Many of the statins (as well as itraconazole, erythromycin, diltiazem, etc.) share common metabolization pathways with PIs via the cytochrome P450 3A4 system, thereby potentially leading to additional side effects due to increased plasma levels of statins which can then cause liver and muscle toxicity. Based on limited pharmacokinetic and clinical studies, atorvastatin (Sortis™), fluvastatin (Lescol™), and pravastatin (Pravasin™), carefully administered at increasing doses, are the preferred agents for a carefully monitored therapy in HIV-infected patients on HAART. Lovastatin (Mevinacor™) and simvastatin (Zocor™) should be avoided due to their potential interaction with PIs.

Fibric acid analogues such as gemfibrozil or fenofibrate are particularly effective in reducing the triglyceride levels by up to 50 % (Rao 2004, Badoui 2004, Miller 2002, Calza 2003) and should be considered in patients with severe hypertriglyceridemia (>1000 mg/dl). Omega 3 acid ester may be considered as alternative agents. Fibric acid analogues retain a supportive effect on lipoprotein lipase activity and can thereby lower LDL levels. Despite their potentially synergistic effect, co-administration of fibric acid analogues and statins in patients on HAART should only be used carefully in selected individuals, since both can cause rhabdomyolysis. Niacinic acid has been shown to only minimally improve the hyperlipidemia induced by HAART. It does, however, increase peripheral insulin resistance (Gerber 2004). Extended-release niacin (Niaspan™) has been shown to have beneficial effects mainly on triglycerides and was well tolerated at a dose of 2,000 mg daily in a study with 33 individuals. Finally, it should be stressed that the long-term effects of lipid-lowering agents and their impact on cardiovascular outcomes, especially in HIV patients with moderate or severe hypertriglyceridemia, are unknown.

Metformin has been evaluated for the treatment of lipodystrophy syndrome. Some studies have revealed a positive effect on the parameters of insulin resistance and the potential reduction of intra-abdominal (but also subcutaneous) fat, although not clinically obvious. Together with exercise training, metformin has been described to reverse the muscular adiposity in HIV-infected patients (Driscoll 2004). Metformin, like all biguanides, can theoretically precipitate lactic acidosis but this adverse interaction has not been described. Use of metformin should be avoided in patients with creatinine levels above 1.5 mg/dl, increased aminotransferase levels, or hyperlactatemia. Thiazolidinediones, such as rosiglitazone (Avandia™) or pioglitazone (Actos™), exhibit the potency to improve insulin sensitivity via stimulation of the PPARγ and other mechanisms. Rosiglitazone has been successfully used to treat abnormal fat distribution in genetic lipodystrophies. Three published studies on HIV patients, however, revealed no or only a minimal improvement in the abnormal fat distribution. But, insulin sensitivity was increased at the expense of increased total cholesterol and triglycerides (Carr 2004, Hadigan 2004, Sutinen 2003, Cavalcanti 2005). Thus, at least rosiglitazone cannot be recommended for general treatment of lipoatrophy in HIV patients at this time (Grinspoon 2005). It also reduces the bioavailability of nevirapine, but not of efavirenz and lopinavir (Oette 2005). Recently, a randomized double-blind placebo-controlled trial (ANRS 113) revealed a significant increase in subcutaneous fat 48 weeks after treatment with pioglita-

zone 30 mg once daily without demonstrating negative effects on lipid parameters (Slama 2006).

Recombinant growth hormone (e.g. Serostim™) at doses of 4-6 mg/d sc over a time course of 8-12 weeks has been demonstrated in some small studies to be a successful intervention for reducing visceral fat accumulation, but it also reduces subcutaneous fat (Kotler 2004). Unfortunately, these improvements have been shown to consistently reverse after the discontinuation of growth hormone therapyThe possible side effects associated with growth hormone therapy include arthralgia, peripheral edema, insulin resistance and hyperglycemia. The FDA declined to approve Serostim for the treatement of the lipoadystrophy syndrome in July 2007.

Surgical intervention (liposuction) for the treatment of local fat hypertrophy has been successfully performed, but appears to be associated with an increased risk of secondary infection, and recurrence of the fat accumulation is possible. For the treatment of facial lipoatrophy, repeated subcutaneous injection of substances such as poly-L-lactic acid (Sculptra™, New-Fill™), a resorbable molecule that promotes collagen formation, has been effectively used in HIV patients (Valantin 2003, Lafaurie 2003¸ Guaraldi 2004, Mest 2004, Casavantes 2004). In 2004, Sculptra™ was approved by the FDA as an injectable filler to correct facial fat loss in people with human immunodeficiency virus. We recommend consultation with experienced specialists for surgical treatments and injection therapy. Further evaluation in long-term follow-up studies is necessary to fully assess the value of these methods.

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8. Mitochondrial Toxicity of Nucleoside Analogs

Ulrich A. Walker and Grace A. McComsey

Introduction

Two years after the introduction of protease inhibitors into the armamentarium of antiviral therapy, reports of HIV-infected individuals experiencing clinically relevant changes in body metabolism began to surface. These "metabolic" symptoms were initially summarized under the term "lipodystrophy" (Carr 1998). Today, ten years after the introduction of highly active antiretroviral therapy (HAART), this lipodystrophy syndrome is increasingly understood as the result of overlapping, but distinct effects of the different drug components within the HAART antiretroviral cocktail. The main pathogenetic mechanism through which nucleoside analogs are thought to contribute to the metabolic changes and organ toxicities is mitochondrial toxicity (Brinkman 1999).

Pathogenesis of mitochondrial toxicity

NRTIs are prodrugs (Kakuda 2000) because they require activation in the cell through phosphorylation before they are able to inhibit their target, e.g. HIV reverse transcriptase. In addition to impairing the HIV replication machinery, the NRTI-triphosphates also inhibit a human polymerase called "polymerase-gamma", which is responsible for the replication of mitochondrial DNA (mtDNA). Thus, the inhibition of polymerase-gamma by NRTIs leads to a decline (depletion) in mtDNA, a small circular molecule normally present in multiple copies in each mitochondrion and in hundreds of copies in most human cells (Lewis 2003). The only biological task of mtDNA is to encode for enzyme subunits of the respiratory chain, which is located in the inner mitochondrial membrane. Therefore, by causing mtDNA-depletion, NRTIs also lead to a defect in respiratory chain function.

An intact respiratory chain is the prerequisite for numerous metabolic pathways. The main task of the respiratory chain is to oxidatively synthesize ATP. In addition, the respiratory chain consumes NADH and FADH as end products of fatty acid oxidation. This fact explains the micro- or macrovesicular accumulation of intracellular triglycerides, which often accompanies mitochondrial toxicity. Last but not least, a normal respiratory function is also essential for the synthesis of DNA, because the de novo synthesis of pyrimidine nucleosides depends on an enzyme located in the inner mitochondrial membrane. This enzyme is called dihydroorotate dehydrogenase (DHODH) (Löffler 1997). The clinical implications of this fact are detailed below.

The onset of mitochondrial toxicity follows certain principles (Walker 2002a):

1. Mitochondrial toxicity is concentration dependent with high NRTI-concentrations causing a more pronounced mtDNA-depletion. The clinical dosing

of some nucleoside analogs is close to the limit of tolerance with respect to mitochondrial toxicity.

2. The onset of mitochondrial toxicity requires time. Changes in mitochondrial metabolism are observed only if the amount of mtDNA-depletion exceeds a certain threshold, an effect observed solely with prolonged NRTI-exposure. As a consequence of this effect, the onset of mitochondrial toxicity is typically not observed clinically in the first few months of HAART. Furthermore, long-term NRTI exposure may also lead to mitochondrial effects despite relatively low NRTI concentrations.

3. There are significant differences in the relative potencies of nucleoside and nucleotide analogs in their ability to interact with polymerase-gamma. The hierarchy of polymerase-gamma inhibition for the active NRTI metabolites has been determined as follows: ddC (HIVID™) > ddI (Videx™) > d4T (Zerit™) > 3TC (Epivir™) ≥ ABC (Ziagen™) ≥ TDF (Viread™) ≥ FTC (Emtriva™).

4. AZT may be peculiar because its active triphosphate is only a weak inhibitor of polymerase-gamma. However, another mechanism can explain how AZT could cause mtDNA-depletion independent from polymerase-gamma inhibition. AZT is an inhibitor of mitochondrial thymidine kinase type 2 (TK2), and, as such, interferes with the synthesis of natural pyrimidine nucleotides, thus potentially impairing the formation of mtDNA (McKee 2004, Saada 2001). AZT may also be metabolized to d4T, at least within some cells in our body (Becher 2003, Bonora 2004).

5. Mitochondrial toxicity is tissue specific. Tissue specificity is explained by the fact that the uptake of the NRTIs into cells and their mitochondria, as well as activation by phosphorylation may be different among individual cell types.

6. There may be additive or synergistic mitochondrial toxicities if two or more NRTIs are used in combination.

7. Mitochondrial transcription may also be impaired without mtDNA-alterations (Mallon 2005, Galluzzi 2005). The mechanism and the clinical significance of this observation are however not yet understood.

Clinical manifestations

MtDNA-depletion may manifest clinically in one or several main target tissues (Fig. 1).

In the *liver* mitochondrial toxicity is associated with increased lipid deposits, resulting in micro or macrovesicular steatosis. Steatosis may be accompanied by elevated liver transaminases. Such steatohepatitis may be observed with even one NRTI such as DDI and progress to liver failure and lactic acidosis, a potentially fatal, but fortunately rare complication (Lambert 1990). Hepatotoxicity is now predominantly observed under treatment with dideoxynucleosides, i.e. with ddI, d4T, and ddC, but also with AZT. The onset of hepatic mtDNA-depletion is dependent on the time of NRTI exposure (Walker 2004a). On electron microscopy, morphologically abnormal mitochondria are observed.

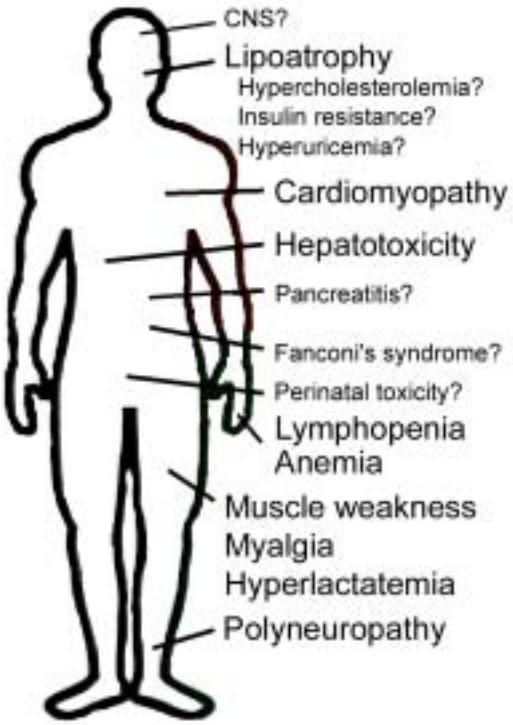

Figure 1: Organ manifestations of mitochondrial toxicity. The question marks signify manifestations, which are still under debate.

A typical complication of mitochondrial toxicity is an *elevation in serum lactate*. Such hyperlactatemia was more frequently described with prolonged d4T treatment (Saint-Marc 1999, Carr 2000), especially when combined with ddI. The toxicity of ddI is also increased through the interactions with ribavirin and hydroxyurea. The significance of asymptomatic hyperlactatemia is unclear. When elevated lactate levels are associated with symptoms, these are often non-specific (nausea, right upper quadrant abdominal tenderness, myalgias). In the majority of cases, the serum bicarbonate levels and the anion gap (Na^+ - [$HCO3^-$ + Cl^-]) are normal, although liver transaminases are mildly elevated in the majority of cases. Therefore, the diagnosis relies on the logistically more cumbersome direct determination of serum lactate. In order to avoid artifacts, venous blood must be drawn without the use of a tourniquet from resting patients. The blood needs to be collected in fluoride tubes and transported to the laboratory on ice for immediate analysis. Non-mitochondrial causes must also be considered in the differential diagnosis of lactic acidosis (Table 1) and underlying organ toxicities should be looked for.

Table 1. Causes of hyperlactatemia/ lactic acidosis

Type A lactic acidosis	Type B lactic acidosis
(*Tissue hypoxia)*	*(Other mechanisms)*
Shock	Thiamine deficiency
Carbon monoxide poisoning	Alkalosis (pH>7.6)
Heart failure	Epilepsy
	Adrenalin (iatrogenic, endogenous)
	Liver failure
	Neoplasm (lymphoma, solid tumors)
	Intoxication (nitroprusside, methanol, methylene glycol, salicylates)
	Fructose
	Rare enzyme deficiencies
	mtDNA mutations
	mtDNA depletion

A *mitochondrial myopathy* in antiretrovirally treated HIV patients was first described with high dose AZT therapy (Arnaudo 1991). Skeletal muscle weakness may manifest under dynamic or static exercise. The serum CK is often normal or only minimally elevated. Muscle histology helps to distinguish this form of NRTI toxicity from HIV myopathy, which may also occur simultaneously. On histochemical examination, the muscle fibers of the former are frequently negative for cytochrome c-oxidase and carry ultrastructurally abnormal mitochondria, whereas those of the latter are typically infiltrated by CD8+ T-lymphocytes. Exercise testing may detect a low lactate threshold and a reduced lactate clearance, but in clinical practice these changes are difficult to distinguish from lack of aerobic exercise (detraining).

Prolonged treatment with D-drugs may also frequently lead to a predominantly symmetrical, sensory and distal *polyneuropathy* of the lower extremities (Simpson 1995, Moyle 1998). An elevated serum lactate level may help to distinguish this axonal neuropathy from its HIV-associated phenocopy, although in most cases the lactate level is normal. The differential diagnosis may also take into account the fact that the mitochondrial polyneuropathy mostly occurs weeks or months after initiation of D-drugs. In contrast, the HIV-associated polyneuropathy generally does not worsen and may indeed improve with prolonged antiretroviral treatment.

In its more narrow sense, the term “lipodystrophy” denotes a change in the distribution of body fat under prolonged HAART exposure. Some subjects affected with lipodystrophy may experience abnormal fat accumulation in certain body areas (most commonly abdomen or dorsocervical region), whereas others may develop fat wasting (Bichat’s fat pad in the cheeks, temporal fat, or subcutaneous fat of the extremities). Both fat accumulation and fat loss may at times occur simultaneously in the same individuals. Fat wasting (also called *lipoatrophy*) is partially reversible and generally observed not earlier than one year after the initiation of HAART. In the affected subcutaneous tissue, ultrastructural abnormalities of mitochondria and reduced mtDNA levels have been identified, in particular in subjects treated with d4T (Walker 2002b). In vitro and in vivo analyses of fat cells have also demonstrated diminished intracellular lipids, reduced expression of adipogenic transcription factors (PPAR-gamma and SREBP-1), and increased apoptotic indices. NRTI

treatment may also impair some endocrine functions of adipocytes. For example, they may impair the secretion of adiponectin and through this mechanism may promote insulin resistance. d4T has been identified as a particular risk factor, but other NRTIs such as AZT may also contribute. When d4T is replaced by another NRTI, mtDNA-levels and apoptotic indices improve along with an objectively measurable, albeit small increase of subcutaneous adipose tissue (McComsey 2004). In contrast, switching away from PIs did not ameliorate lipoatrophy and adipocyte apoptosis. Taken together, the available data point towards a predominant effect of NRTI-related mitochondrial toxicity in the pathogenesis of lipoatrophy.

Some studies have suggested an effect of NRTIs on the mtDNA levels in blood (Coté 2003, Miro 2003). The functional consequence of such mitochondrial toxicity on *lymphocytes* is still unknown. In this context, it is important to note that a delayed loss of CD4+ and CD8+ T-lymphocytes was observed, when ddI plasma levels were increased by comedication with TDF, or by low body weight (Negredo 2004). Exposure of mitotically stimulated T-lymphocytes to slightly supratherapeutic concentrations of ddI also demonstrated a substantial mtDNA-depletion with a subsequent late onset decline of lymphocyte proliferation and increased apoptosis (Setzer 2005). These data suggest that the mitochondrial toxicity of NRTIs on lymphocytes is responsible for the late onset decline of lymphocytes observed with ddI and has immunosuppressive properties.

Asymptomatic elevations in *serum lipase* are not uncommon under HAART, but of no value in predicting the onset of pancreatitis (Maxson 1992). The overall frequency of pancreatitis has been calculated as 0.8 cases/ 100 years of NRTI-containing HAART. Clinical pancreatitis is associated with the use of ddI in particular. ddI reexposure may trigger a relapse and should be avoided. A mitochondrial mechanism to explain the onset of pancreatitis has been hypothesized but remains unproven.

Prolonged treatment with didexoynucleosides is also associated with *hyperuricemia* (Walker 2006a). The mechanism may be two-fold. Mitochondrial dysfunction may increase the formation of lactate, which competes with urate for tubular secretion in the kidney. Respiratory chain failure also causes ATP depletion, which is known to increase urate production in the purine nucleotide cycle.

The existence of mitochondrial damage to the *kidney* is controversial. Supratherapeutic doses of TDF (Viread™) induced a Fanconi syndrome with tubular phosphate loss and consecutive osteomalacia in animals (Tenofovir review team 2001). TDF is a nucleotide analogue and taken up into the renal tubules by means of a special anion transporter. Excessive intratubular drug concentrations may impair mtDNA replication, despite the fact that TDF is only a weak inhibitor of polymerase-gamma. Decreased mtDNA levels have recently been found in renal biopsies from patients exposed to TDF plus ddI, a NRTI combination that for several reasons is no longer recommended (Côté 2006). It should be noted that neither the trials leading to the approval of TDF, nor the subsequent field data were able to prove the mitochondrial nephrotoxicity of TDF. Most trials only measured creatinine clearance and serum phosphate (Izzedine 2005) although a compromise in renal function is not expected in Fanconi's syndrome and increased renal phosphate loss may be masked by preserved by homeostatic phosphate mobilization from bone. More sensitive methods have recently revealed a diminished renal

phosphate reabsorption and an elevated alkaline phosphatase in patients treated with TDF (Kinai 2005). Cases of phosphate diabetes were also reported under treatment with other NRTIs.

ZDV is also used to reduce the risk of HIV vertical transmission and in this setting was associated with low mtDNA levels in the placenta and in the peripheral cord blood of *neonates* (Shiramizu 2003, Divi 2005). ZDV also causes a transient anemia in the newborn, as well as neutropenia, thrombopenia and lymphopenia, which may persist for months (Venhoff 2006). A French cohort found an increased frequency of mitochondrial myopathies in infants perinatally exposed to NRTIs (Blanche 1999). Hyperlactatemia is not infrequently observed in the perinatal setting and may persist for several months after delivery (Noguera 2003). Long-term data are lacking and better surveillance systems should be implemented (Venhoff 2006).

Monitoring and diagnosis

There is currently no method to reliably predict the mitochondrial risk of an individual. The quantification of mtDNA-levels in the peripheral blood is not useful. Quantifying mtDNA within affected tissues is likely to be more sensitive; but invasive and not prospectively evaluated with regard to clinical endpoints.

Once symptoms are established, histological examination of a tissue biopsy may contribute to the correct diagnosis. The following findings in tissue biopsies point towards a mitochondrial etiology: ultrastructural abnormalities of mitochondria, diminished histochemical activities of cytochrome c-oxidase, the detection of intracellular and more specifically microvesicular steatosis, and the so-called ragged-red fibers.

Treatment and prophylaxis of mitochondrial toxicity

Drug interactions

Drug interactions may precipitate mitochondrial symptoms and must be taken into account. The mitochondrial toxicity of ddI for example is augmented through drug interactions with ribavirin, hydroxyurea and allopurinol (Ray 2004). When ddI is combined with TDF, the ddI dose must be reduced to 250 mg QD. The thymidine analog brivudine is a herpes virostatic that may sensitize for NRTI-related mitochondrial toxicity because one of its metabolites is an inhibitor of DHODH (see below). Brivudine should therefore not be combined with antiretroviral pyrimidine analogues.

An impairment of mitochondrial metabolism may also result from ibuprofen, valproic acid and acetyl salicylic acid as these substances impair the mitochondrial utilization of fatty acids. Acetyl salicylic acid may damage mitochondria and such damage to liver organelles may result in Reye's syndrome. Valproic acid may trigger a life threatening lactic acidosis. Amiodarone and tamoxifen also inhibit the mitochondrial synthesis of ATP. Acetaminophen and other drugs impair the anti-

oxidative defense (glutathione) of mitochondria, allowing for their free radical mediated damage. Aminoglycoside antibiotics and chloramphenicol not only inhibit the protein synthesis of bacteria, but under certain circumstances also impair the peptide transcription of mitochondria as bacteria-like endosymbionts. Adefovir and cidofovir are also inhibitors of polymerase-gamma. Alcohol is also a mitochondrial toxin.

The most important clinical intervention is the discontinuation of the NRTI(s) responsible for mitochondrial toxicity. Randomized studies have demonstrated that switching d4T to a less toxic alternative leads to a slight and slowly progressive improvement in lipoatrophy (McComsey 2004, Martin 2004, Moyle 2006). Switching away from PIs to NNRTIs however was not associated with an improvement of lipoatrophy. These findings stress the crucial role of mitochondrial toxicity in the pathogenesis of fat wasting.

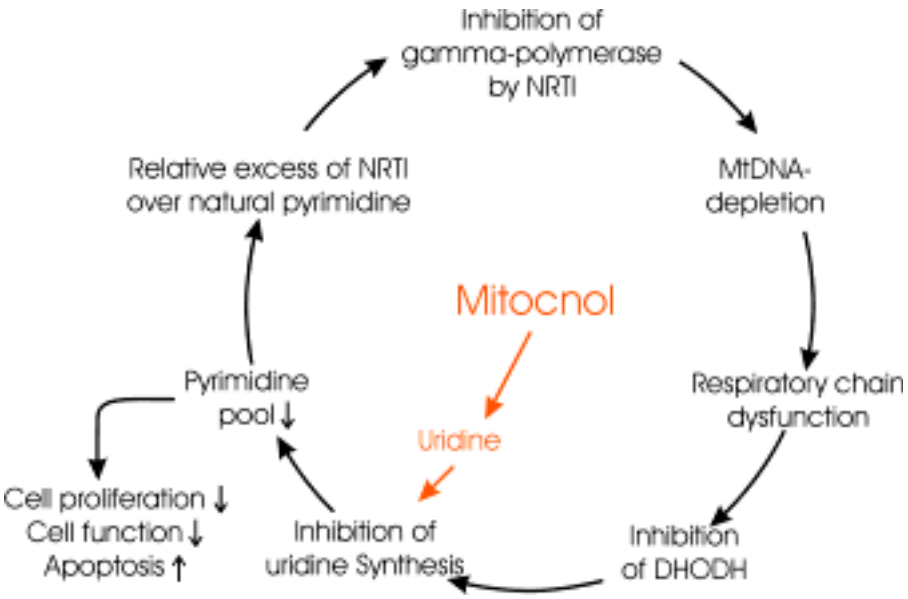

Figure 2: Mechanism of Mitocnol (NucleomaxX™) in the prevention and treatment of mitochondrial toxicity.

Uridine

The so far only therapy of mitochondrial toxicity under unchanged NRTI-treatment consists of the supplementation of uridine or its precursors. As outlined above, any respiratory chain impairment also results in the inhibition of DHODH, an essential enzyme for the synthesis of uridine and its derived pyrimidines (Fig 2). This decrease in intracellular pyrimidine pools leads to a relative excess of the exogenous pyrimidine nucleoside analogs, with which they compete at polymerase-gamma. A vicious circle is closed and contributes to mtDNA-depletion. By supplementing uridine this vicious circle can be interrupted, resulting in increased mtDNA-levels.

Indeed, uridine abolished in hepatocytes all the effects of mtDNA-depletion and normalized lactate production, cell proliferation, the rate of cell death and intracellular steatosis. (Walker 2003). In contrast, vitamin cocktails were not beneficial in this model. Uridine also normalizes the lipoatrophic phenotype in adipocytes exposed to d4T (Walker 2006b).

Uridine is well tolerated by humans, even at high oral and intravenous doses (van Groeningen 1986, Kelsen 1997). A food supplement called Mitocnol was shown to have a more than 8-fold uridine bioavailability over conventional uridine (Venhoff 2005). Mitocnol was studied in a randomized placebo-controlled double-blind trial in lipoatrophic subjects under continued therapy with d4T or AZT where it has objectively improved subcutaneous fat (Sutinen 2007). In comparison with switch strategies (e.g. the replacement of stavudine and zidovudine by antivirals with a reduced potential of mitochondrial toxicity), the effect of Mitocnol on subcutaneous fat gain was more rapid and quantitatively more pronounced (Fig 3).

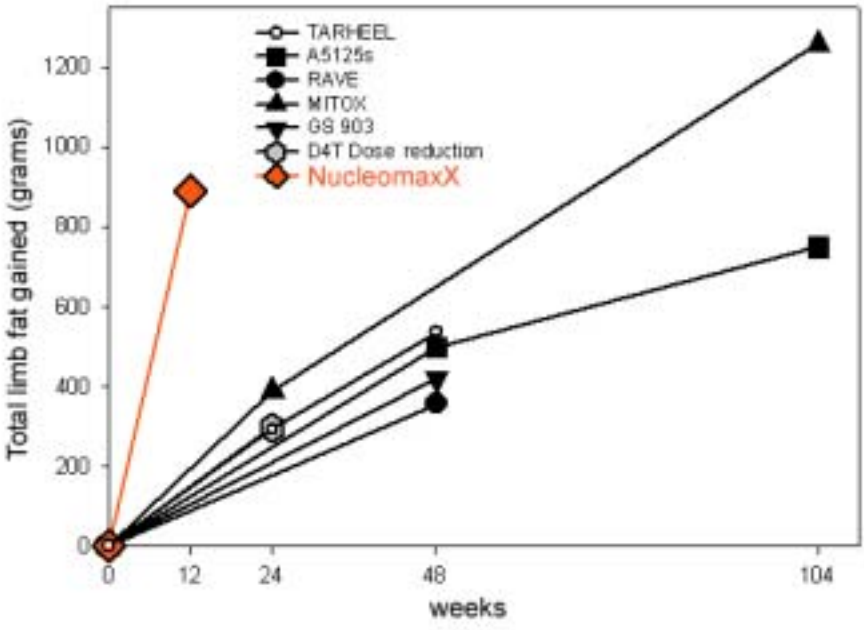

Figure 3: Subcutaneous fat gain with Mitocnol under d4T and AZT treatment (in comparison with strategies sparing thymidine-analogue NRTI).

A second trial has also suggested Mitocnol to be efficacious with regard to patient and physician assessed lipoatrophy scores (McComsey 2007).

In vitro, animal and clinical data indicate, that Mitocnol also antagonizes mitochondrial steatohepatitis. (Walker 2004b, Banasch 2006, Lebrecht 2007). Animal data indicate that uridine supplementation also counteracts AZT-induced hematotoxicity and myopathy (Sommadossi 1988).

Mitocnol is well tolerated and adverse events have not been observed so far. In one study, a clinically insignificant HDL-decline was suggested, while another trial

showed no change in HDL cholesterol (McComsey 2007). There are no known negative interactions of uridine with the efficacy of the antiretroviral treatment (Sommadossi 1988, Koch 2003, McComsey 2007, Sutinen 2007). In Europe and North America, Mitocnol is available as a dietary supplement called NucleomaxX® and can be acquired in pharmacies and the internet (www.nucleomaxX.com).

In symptomatic hyperlactatemia and in lactic acidosis, all NRTIs should be immediately discontinued (Brinkman 2000). The supplementation of vitamin cocktails has been recommended, but there are no data that demonstrate the efficacy of this intervention with respect to mtDNA-depletion (Walker 1995, Venhoff 2002). After discontinuation of NRTIs, normalization of lactate may require several weeks. More mitochondrial friendly NRTIs may then be reintroduced, but patients should be monitored closely. The proposed supportive treatment of hyperlactatemia and lactic acidosis is summarized in Table 2.

Table 2. Supportive treatment of lactate elevation in HIV-infected patients (non-pregnant adults)

Lactate 2-5 mmol/L + symptoms	**Lactate > 5 mmol/L or lactic acidosis**
Discontinue mitochondrial toxins	Discontinue NRTIs and all mitochondrial toxins
Consider vitamins and	Intensive care
NucleomaxX (36g TID on 3 consecutive days/ month)	Maintain hemoglobin > 100 g/L
	Avoid vasoconstrictive agents
	Oxygen
	Correct hypoglycemia
	Bicarbonate controversial – 50-100 mmol if pH<7.1
	Coenzyme Q_{10} (100 mg TID)
	Vitamin C (1 g TID)
	Thiamine (Vit. B_1, 100 mg TID)
	Riboflavin (Vit. B_2, 100 mg QD)
	Pyridoxine (Vit. B_6, 60 mg QD)
	L-acetyl carnitine (1 g TID)
	NucleomaxX (36 g TID until lactate <5 mmol/L)

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9. HIV Resistance Testing

Eva Wolf

The development of resistant viral strains is one of the main reasons for failure of antiretroviral therapy. If there is resistance to several drug classes, the number of alternative treatment regimens is limited and the virological success of subsequent therapies, or so-called salvage regimens, may be short-lived.

The rapid development of resistant variants is due to the high turnover of HIV – approximately 10 million new viral particles are produced every day (Perelson 1996) – and the exceptionally high error rate of HIV reverse transcriptase. This leads to a high mutation rate and constant production of new viral strains, even in the absence of treatment. In the presence of antiretroviral drugs, resistant strains are selected for as the dominant species (Drake 1993).

Besides the basic principles concerning resistance testing and interpretation, this chapter focuses on the sequencing of the reverse transcriptase, the protease, the intergrase and the env gene and as well as on the respective resistance patterns that emerge with treatment. Most data are derived from patients with subtype B viruses (representing only 12 % of the worldwide HIV-infected population). However, by now, non-subtype B viruses have also been investigated for the development of resistance. Resistance pathways and patterns may differ in the various subtypes (Snoeck 2006).

Assays for resistance testing

There are two established assays for measuring resistance or sensitivity of HIV to specific antiretroviral drugs – the genotypic and the phenotypic resistance tests (Wilson 2003). Both assays are commercially available. Examples of commercially available genotypic resistance tests are: HIV-1 TrueGene™, *Bayer Healthcare Diagnostics/Siemens Medical Solutions Diagnostics;* or ViroSeq™, *Celera Diagnostics/Abbott Laboratories*; both assays are approved by the FDA. Other genotypic resistance assays such as virco™TYPE HIV-1, *Virco,* GenoSure (Plus), *LabCorp,* or GeneSeq, *Monogram Biosciences (formerly Virologic)* are established in the laboratories of the respective manufacturers and are used in clinical trials. Phenotypic resistance tests include: Antivirogram™, *Virco*; PhenoSense™, *Monogram Biosciences (formerly ViroLogic);* and Phenoscript™, *Viralliance*.

Disadvantages of phenotypic testing include the lengthy procedure and high expense of the assay. The cost of genotyping ranges from 350 to 500 Euro per sample, depending on the assay and laboratory used. It is approximately twice as much for phenotyping.

The drawback with both methods is that a minimum amount of virus is necessary in order to perform the test. A viral load below 500-1,000 copies/ml often does not allow any detection of resistance.

Phenotyping

Phenotypic resistance tests involve direct quantification of drug sensitivity. Viral replication is measured in cell cultures under the selective pressure of increasing concentrations of antiretroviral drugs and is compared to viral replication of wild-type virus.

Drug concentrations are expressed as IC_{50} values (50 % inhibitory concentration). The IC_{50} is the concentration of drug required to inhibit viral replication by 50 %. The sensitivity of the virus is expressed as the IC_{50} divided by the IC_{50} of a wild-type reference virus (fold-change value) and compared to the so-called cut-off value. The cut-off value indicates by which factor the IC_{50} of an HIV isolate can be increased in comparison to that of the wild type, whilst still being classified as sensitive. Determination of the cut-off is crucial for the interpretation of the results!

Cut-off definitions

Three different cut-offs are currently used. The *technical cut-off* is a measure of the methodological variability of the assay. The *biological cut-off* involves the inter-individual variability of wild-type virus isolates from ART-naïve HIV patients..

The *clinical cut-off* indicates up to which levels of IC_{50} virological success can still be expected. Both vircoType™ and PhenoSense™ reports have included lower and upper clinical cut-offs. The lower clinical cut-off is the fold-change in IC_{50} which indicates a slightly reduced virological response. A fold-change above the upper clinical cut-off indicates resistance, and a fold-change between the two cut-offs indicates partial resistance.

Genotyping

Genotypic assays are based on the analysis of mutations associated with resistance. These are determined primarily by the direct sequencing of the amplified HIV genome, but also by specific hybridization techniques with wild-type or mutant oligonucleotides. Of intereset is the sequencing of the *pol* region which encodes the viral enzymes protease, reverse transcriptase and integrase, and the *env* region encoding the HIV envelope glycoprotein which is composed of gp41 and gp120 subunits. Genotype tests only detect viral mutants comprising at least 20 to 30 % of the total population and provide an indirect measurement of drug resistance. Mutations that are associated with reduced sensitivity have been well described for most HIV drugs, but the high number of different resistance patterns, which may also contain compensatory mutations, makes the determination of the degree of resistance to particular drugs difficult.

The interpretation of genotypic resistance patterns is based on the correlation between genotype, phenotype and virological response. Data is available from *in vitro* studies, clinical observations and duplicate testing, in which genotypically localized mutations were investigated for phenotypic resistance.

Ruled-based interpretation systems

For the phenotypic interpretation of genotypic mutation patterns, rule-based interpretation systems are commonly available. Based on the literature and clinical out-

comes, expert panels (e.g. the French ANRS AC11 Resistance group or the HIV-GRADE group) have developed algorithms which are adapted and re-evaluated annually or bi-annually.

Data-based interpretation systems and virtual phenotype

In contrast to the knowledge-based interpretation rules, data-based interpretation systems like geno2pheno or vircoType™ use mathematical models to predict the phenotype and/or virological response from a genotype. This approach is called "virtual" phenotype: a genotypic mutation pattern is interpreted with the aid of a large database of samples of paired genotypic and phenotypic data.

Geno2pheno implements machine learning approaches such as decision trees and support vector machines (Beerenwinkel 2003). The system learns from paired geno- and phenotypic information, identifies principles and thus predicts phenotypic drug resistance for a given genotypic profile.

For the vircoType™ interpretation, genotypes matching the patient's virus are identified through a database search. The IC_{50} results of each of the matching viruses are averaged, thus producing the probable phenotype of the patient's virus. In the updated version of vircoType™, all mutations and mutation pairs of the patient's virus that contribute to specific drug resistance according to the new multiple linear regression modeling are identified. They are then included in the respective linear regression model using the drug-specific resistance weight factors of the observed mutations and mutation pairs. The outcome variable of the regression model is the predicted fold-change comparing the IC_{50} of the patient's virus to the IC_{50} of the wild-type reference virus.

The vircoType™ interpretation is based on a multiple, linear regression model, which is applied to a large database containing >45,000 matched geno- and phenotypes: The fold-change in IC_{50} is modeled by a function involving all possible mutations and pairs of mutations. Interactions between single mutations are considered by including the pairs of mutations. Linear regression analysis evaluates drug-specific resistance weight factors for all mutations and pairs of mutations. Synergistic effects of mutations are depicted with a positive weight factor, antagonistic or re-sensitizing effects with a negative weight factor.

Some of the most important databases for resistance profiles and interpretational systems are available free of charge on the following websites:

- Stanford-Database: http://hiv.net/link.php?id=24
- Los Alamos-Database: http://hiv.net/link.php?id=25
- geno2pheno: http://hiv.net/link.php?id=26
- HIV Genotypic Drug Resistance Interpretation – ANRS AC11: http://hiv.net/link.php?id=138
- HIV-GRADE: http://www.hiv-grade.de/cms/grade/homepage.html

Some commercial suppliers of resistance tests also provide interpretation guidelines for their systems (e.g. vircoType™ HIV-1, *Virco* or GuideLines© (TruGene™), *Bayer HealthCare Diagnostics*).

Ruled-based resistance interpretation systems

- HIV-GRADE: http://www.hiv-grade.de/cms/grade/homepage.html
- Stanford-Database: http://hiv.net/link.php?id=24
- HIV Genotypic Drug Resistance Interpretation – ANRS AC11: http://hiv.net/link.php?id=138
- Los Alamos-Database: http://hiv.net/link.php?id=25

Data-driven resistance interpretation systems

- geno2pheno: http://hiv.net/link.php?id=26

Background

Within the nucleotide sequences of the HIV genome, a group of three nucleotides, called a codon, defines a particular amino acid in the protein sequence. Resistance mutations are described using a number, which shows the position of the relevant codon, and two letters: the letter preceding the number corresponds to the amino acid specified by the codon at this position in the wild-type virus; the letter after the number describes the amino acid that is produced from the mutated codon. M184V indicates a mutation in codon 184 of the reverse transcriptase gene leading to a valine for methionine substitution in the reverse transcriptase enzyme.

Mechanisms of resistance

Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs) are pro-drugs that only become effective after being converted to triphosphates. Nucleotide analogs require only two instead of three phosphorylation steps. Phosphorylated NRTIs compete with naturally occurring dNTPs (deoxynucleotide triphosphates). The incorporation of a phosphorylated NRTI into the proviral DNA blocks further elongation of the proviral DNA and leads to interruption of the chain.

There are two main biochemical mechanisms that lead to NRTI resistance (De Mendoza 2002). *Sterical inhibition* is caused by mutations enabling the reverse transcriptase to recognize structural differences between NRTIs and dNTPs. Incorporation of NRTIs is then prevented in favor of dNTPs (e.g. in the presence of the mutations M184V, Q151M, L74V, or K65R; Naeger 2001, Clavel 2004).

Phosphorylysis via ATP (adenosine triphosphate) or pyrophosphate leads to the excision of the NRTIs already incorporated in the growing DNA chain. This is the case with the following mutations: M41L, D67N, K70R, L210W, T215Y and K219Q (Meyer 2000). Phosphorylysis leads to cross-resistance between NRTIs, the degree of which may differ between substances (AZT, d4T > ABC > ddI > 3TC). Contrary to the excision mutations, K65R leads to a decreased excision of all NRTIs when compared to the wild-type, resulting in a greater stability once incorporated. For K65R, the combined effect of its opposing mechanisms - on the one hand decreased incorporation and on the other, decreased excision - results in a de-

creased susceptibility to most NRTIs but an increased susceptibility to AZT (White 2005).

Non-nucleoside RT inhibitors (NNRTIs) also inhibit the viral enzyme reverse transcriptase (RT). NNRTIs are small molecules that bind to the hydrophobic pocket close to the catalytic domain of the RT. Mutations at the NNRTI binding site reduce the affinity of the NNRTI to the RT and thus lead to loss of antiviral activity of NNRTI and treatment failure.

Protease inhibitors (PIs) hinder the cleavage of viral precursor gag-pol-polyprotein by the enzyme protease, thereby producing immature, non-infectious viral particles. PI resistance usually develops slowly, as several mutations must first accumulate. This is also referred to as the genetic barrier. For PIs, a distinction is made between *major* (or *primary)* and *minor* (or *secondary) mutations*.

Major mutations are responsible for phenotypic resistance. They are selected for early on in the process of resistance to one drug, and are located within the active site of the target enzyme, the HIV protease. They reduce the ability of the protease inhibitor to bind to the enzyme. Major or primary mutations may also lead to a reduced activity of the protease.

Minor mutations (often referred to as secondary mutations*)* are located outside the active site and usually occur after major mutations. Minor mutations can be particularly found at polymorphic sites of non-B subtypes. Minor mutations can compensate for the reduction in viral fitness caused by major mutations (Nijhuis 1999, Johnson 2006).

Table 1. Major and minor protease mutations

Major mutations
D30N, V32I, M46I/L/V, I47V/A, G48V/M, I50V/L, I54VM/L/T/A/S, L76V, V82A/T/F/T/L/S/M/C, I84V/A/C, N88D/S/T/G, L90M
Minor mutations
L10IVFRY, V11I, L23I, L24IF, L33F/I, E35G, K43T, F53L/Y, Q58E, A71V/T/I, G73C/A/T/S, T74P, N83D, L89V

(HIV Drug Resistance Database, Sequence Analyses Program, version 4.2.5, 2006-12-04; http://hivdb.stanford.edu/pages/asi/releaseNotes/updates.html)

Entry inhibitors differ from NRTIs, NNRTIs and PIs, which block the replication of HIV in the infected cell. Instead, entry inhibitors prevent HIV from entering its target cells. The first step in cell entry occurs when the HIV envelope glycoprotein, gp120, binds to the CD4 receptor of the target cell, leading to conformational changes in gp120 and thus enabling binding of .the V3 loop of gp120 to the chemokine co-receptors, CCR5 or CXCR4.

Interactions between the two heptad repeat regions HR1 and HR2 within the transmembrane glycoprotein subunit gp41 induce a conformational change in gp41, leading to insertion of the gp41 fusion peptide into the target cell membrane, thereby enabling entry of the viral core into the target cell.

CCR5 co-receptor antagonists function by binding specifically to the CCR5 molecule which then is unable to bind to the viral gp120 subunit. Thus, the conforma-

tional changes leading to insertion of the gp41 fusion peptide are prevented and viral entry is stopped.

Fusion inhibitors prevent fusion of viral and cell membranes. T-20 (enfuvirtide), a synthetic peptide consisting of 36 amino acids, mimics the C-terminal HR2 domain of gp41 and competitively binds to HR1. Thus, interactions between HR1 and HR2 are blocked and the conformational change of gp41 that is necessary for fusion of virions to host cells is inhibited. A single amino acid substitution in gp41 can reduce the efficacy of T-20.

Transmission of resistant HIV strains

The prevalence of mutations already present in treatment-naïve patients differs among demographic regions. High prevalences of more than 20 % were observed in big US cities with large populations of homosexual men and a long period of access to antiretroviral treatment. Comparably high rates of resistance transmission were observed in Madrid in the late nineties (Grant 2003, Wensing 2003, De Mendoza 2003+2005a, Truong 2006).

In the German seroconverter study performed by the Robert Koch Institute transmission of (partially) resistant virus was observed in 14 % of seroconverters between 1996 and 2005 (Kuecherer 2006). In chronically infected patients the proportion with primary resistance was 11 % between 2001 and 2004 (RESINA study, Oette 2006).

In the European CATCH study - which later transferred into the European SPREAD study (Strategy to Control Spread of HIV Drug Resistance) - the prevalence of primary resistance was 10.4 % in 2.208 newly diagnosed HIV patients between 1996 and 2002 (Wensing 2005). Whereas the proportion of NRTI mutations decreased over time, the frequency of NNRTI resistance mutations increased. The frequency of PI resistance remained relatively stable. Primary resistance was mainly observed in subtype B infections (which represent 70% of all new diagnoses). However, an increase over time was also observed in non-B subtypes.

Follow-up data from the years 2002 and 2003 are derived from the SPREAD study: 9.1 % of the 1,050 newly diagnosed HIV patients were infected with a virus carrying resistance mutations (Wensing 2006). In less than 1 % of patients resistance against two drug classes was observed.

Transmission rates of resistant virus are possibly underestimated in the different regions. Minority viral populations below 20-30 % are not detected by standard sequencing techniques. Forty-nine virus isolates of acute seroconverters were tested for the presence of L90M, K103N and M184V by quantitative real-time polymerase chain reaction using specific oligonucleotides for the three key resistance mutations. In 10 out of 49 patients these mutants were detected. In 5 of these 10 patients the detected population represented a minor viral quasi-species and was not detected by direct sequencing (Metzner 2005).

Table 2. Prevalence of resistance prior to initiation of antiretroviral therapy (selection)

Author	Region	Period	HIV Study Population	N	Primary Resistance
Wensing 2006	Europe (19 countries)	2002-03	Newly diagnosed	1050	9.1 %
Cane 2005	Great Britain	1996-2003	Chronically infected	2357	14.2 %
Oette 2006	Germany (Nordrhein-Westfalia)	2001-2004	Chronically infected	269	11.2 %
Kuecherer 2006	Germany	1996-2005	Seroconverters	827	14.1 %
De Mendoza 2005	Spain	1997-2004	Seroconverters	198	12.1 %
Little 2002	USA (10 North American cities)	1995-2000	Seroconverters	377	22.7 %
Truong 2006	San Francisco	2004	Newly diagnosed	129	13.2 %
Jayaraman 2006	Canada	1999-2003	Newly diagnosed	768	10.2 %

Transmitted primary resistance can persist for a long time (Pao 2004). In a Spanish seroconverters study, 10 patients with primary resistance mutations like T215Y, T215N/S/C, M41L, L74V, I54V, V82S/A, or L90M were followed over a median time of 41 months. In only three of 10 cases (partial) reversion (of T215Y) was observed: T215Y revertants (T215S) were detected in two patients, and wild-type virus was detected in one patient after 7 years (De Mendoza 2005b). In an observation of our own patients, transmitted resistance mutations persisted for more than four years (Table 3).

Transmitted resistance mutations can limit further treatment options and reduce treatment response rates (Harzic 2002, Little 2002, Riva 2002, Hanna 2001). However, on careful consideration of any pre-existing resistance, primary treatment success is often possible (Oette 2006).

In early 2005, a patient from New York caused a sensation. He was infected with a multi-drug resistant virus harboring 7 relevant NRTI mutations, 2 NNRTI mutations and 12 PI mutations. After 4 to 20 months (the exact time of infection is unknown), the patient's CD4 count had decreased to 80 cells/µl. The replication capacity of this resistant virus was comparable to that of wild-type virus. Only two available antivirals, T-20 and efavirenz were still active. Even though the transmission of multi-drug resistant virus and rapid clinical progression are rare events, this case report demonstrates the possible clinical consequences of primary drug resistance (Markowitz 2005).

Table 3. Persistance of resistance mutations in a patient infected with multi-drug resistant virus (last negative HIV test in 1997, newly diagnosed 06/2000).

	Index person	**Patient**			
	02/2000	03/2001	01/2002	01/2003	07/2004
NRTI					
M41L	M41L	M41L	M41L		
D67N	D67N	D67N	D67N	D67N	D67N
K70R	K70R				
V75M	V75M	V75M	V75M		
M184V		M184V			
L210W	L210W				
T215F	T215F	T215F			
K219Q	K219Q	K219Q	K219Q	K219Q	K219Q
NNRTI					
G190A	G190A	G190A	G190A	G190A	G190A
PI					
M46I	M46I	M46I	M46I	M46I	M46I
L63P	L63P				
A71V	A71V	A71V	A71V	A71V	A71V
G73S	G73S				
I84V	I84V	I84V	I84V	I84V	
L90M	L90M	L90M	L90M	L90M	L90M

Clinical studies

The clinical relevance of resistance testing before changing therapy has been demonstrated in several prospective, controlled studies such as Viradapt, CPCRA 046 or Havana (Durant 1999, Baxter 1999, Tural 2001). This is also true for phenotypic resistance testing (VIRA 3001; Cohen 2000). Patients whose physicians had access to information about any existing mutations before the therapy was changed usually had more significant decreases in the viral load than patients in whom treatment was changed without knowledge of the resistance profile.

Since these studies, new NRTIs, as well as new NNRTIs and PIs with different resistances profiles have been developed. The options after treatment failures improved and thereby the importance of resistance testing increased. The clinical relevance of resistance testing after the approval of new drug classes like integrase inhibitors or CCR5 antagonists remains to be proven.

Interpretation of genotypic resistance profiles

NRTIs

For several NRTIs, such as lamivudine, and for NNRTIs, a high degree of resistance can develop following only a single mutation (Havlir 1996, Schuurman

1995). For this reason, such drugs should only be used in highly effective regimens. However, the lamivudine-specific mutation, M184V, also reduces viral replication capacity (often referred to as “reduced viral fitness”) by 40–60 % (Sharma 1999, Miller 2003). After 52 weeks on lamivudine monotherapy, the viral load remained 0.5 logs below the initial levels, despite early development of the M184V mutation (Eron 1995). When compared to treatment interruptions, continuous monotherapy with 3TC delays virological and immunological deterioration (Castagna 2006).

FTC (emtricitabine) has the same resistance pattern as 3TC. Treatment failure is associated with the M184V mutation (van der Horst 2003).

Thymidine analog mutations, mostly referred to as "TAMs", include the mutations M41L, D67N, K70R, L210W, T215Y and K219Q, which were initially observed on zidovudine therapy (Larder 1989). However, these mutations can also be selected for by stavudine (Loveday 1999). Three or more TAMs are associated with a relevant reduction in the sensitivity to stavudine (Calvez 2002, Lafeuillade 2003). The term "NAMs" (nucleoside analog mutations) is also used instead of TAMs, as these mutations are associated with cross-resistance to all other nucleoside analogs, with the exception of 3TC and FTC.

Viral mutants, isolated from patients in whom treatment on AZT, 3TC or abacavir has failed, usually have a measurable phenotypic resistance. Two TAMs result in a 5.5-fold, three TAMs in a 29-fold and four TAMs or more in a > 100-fold reduced sensitivity to zidovudine. The use of abacavir in cases where there is a more than 7-fold reduction in sensitivity no longer promises success. This usually requires at least 3 TAMs in addition to the M184V mutation (Harrigan 2000).

A score, which has been developed in the context of the Narval study (ANRS 088), seems to have a good predictive value concerning virological response to abacavir. Virological response is poor if 5 mutations out of M41L, D67N, L74V, M184V, L210W, and T215Y/F are present (Brun-Vézinet 2003).

The virological response to ddI depends on the number of specific TAMs. In the Jaguar study, using treatment-experienced patients, T215Y/F, M41L and L210W – to a lesser extent also D67N und K219Q – were associated with a reduced efficacy (Marcelin 2005). The virological response was not dependent on the presence of the mutations M184V and K70R.

Clinical data indicates that tenofovir is effective even in the presence of NAMs such as D67, K70R, T215Y/F or K219Q/E. However, if three or more NAMs including either M41L or L210W, a reduced virological response can be expected (Antinou 2003).

The lamivudine-associated mutation, M184V, as well as the L74V mutation, observed on didanosine treatment, and the NNRTI-specific mutations, L100I and Y181C, may have an antagonistic effect on the development of resistance (Vandamme 1999).

M184V induces re-sensitization to AZT, resulting in a 50-60 % reduction of IC_{50}. Re-sensitization to stavudine results in a 30 % reduction of IC_{50}. However, re-sensitization is of clinical relevance only if there are no more than three other AZT- or d4T-associated mutations present (Shafer 1995, Underwood 2005). Phenotyping of 9,000 samples showed a more than 10-fold decreased susceptibility to AZT in 79 % of samples if the mutations M41L, L210W and T215Y were detected. If the

M184V mutation was also present, only 52 % had a more than 10-fold decreased susceptibility to AZT (Larder 1999a). The M184V mutation also increases the sensitivity to tenofovir (Miller 2001, Miller 2004a). In contrast, the presence of M184V plus multiple NAMs or mutations at positions 65, 74 or 115 increased the resistance to ddI and abacavir (Harrigan 2000, Shafer 2003).

So-called multi-drug resistance (MDR) to all nucleoside analogs – except lamivudine – is established if one of the following combinations occurs: T69SSX, i.e. the T69S mutation plus an insertion of 2 amino acids (SS, SG or SA) between positions 69 and 70, plus an AZT-associated mutation or Q151M, plus a further MDR mutation, e.g. V75I, F77L or F116Y (Masquelier 2001).

The MDR mutation, Q151M, alone leads to intermediate resistance to AZT, d4T, ddI and abacavir. It is relatively uncommon with a prevalence of less than 5 %. In contrast Q151M does not lead to a marked loss of activity towards tenofovir. Combination with the mutations at positions 75, 77, and 116 leads to high-grade resistance to AZT, ddI, d4T and abacavir and intermediate resistance to TDF (Shafer 2003).

The T69S insertion induces an approximately 20-fold increase in the resistance to tenofovir (Miller 2001, Miller 2004a).

The insertion T69SSX together with the mutation M184V, as well as the mutation Q151M together with M184V, leads to a 70 % reduction in the viral replication capacity (Miller 2003).

The L74V mutation emerges under ddI or abacavir and leads to a 2- to 5-fold increase in the resistance to ddI (Winters 1997). The loss of efficacy by a factor of around 2-3 for abacavir is not considered clinically relevant and requires further mutations (Tisdale 1997, Brun-Vézinet 2003).

L74V/I with or without M184V leads to a reduction in IC_{50} of about 70 %; phenotypic susceptibility increases by a factor of 3 (Underwood 2005).

The K65R mutation can emerge while on tenofovir, abacavir or ddI and leads to an intermediate resistance to tenofovir, abacavir, ddI, 3TC, FTC, and possibly d4T (Shafer 2003, Garcia-Lerma 2003). There is no cross-resistance with AZT (Miller 2004b). In antiretroviral combinations containing AZT, the incidence of the K65R mutation is lower. K65R emerges very rarely together with TAMs on the same genome. K65R and TAMs represent two antagonistic resistance pathways. Genotypes harboring K65R and L74V are also very unlikely (Wirden 2005). Since abacavir was mostly used as part of the combination AZT+3TC+abacavir or in the presence of multiple TAMs, K65R was rare prior to the use of tenofovir. Similar to large clinical trials using tenofovir within divergent (PI- or NNRTI-containing) treatment regimens, the incidence of K65R stabilized at ≤ 5 %. However, virological failure of triple NRTI combinations such as Tenofovir+3TC+ABC or Tenofovir+3TC+ddI was often associated with the development of K65R (Farthing 2003, Gallant 2003, Landman 2003, Jemsek 2004). The main reason for the high failure rate seems to be the low genetic barrier of these regimens: the emergence of K65R induces a loss of sensitivity to all three drugs.

K65R increases the sensitivity to AZT and induces a resensitization to zidovudine in the presence of (few) TAMs. K65R alone increases sensitivity to AZT by a factor of 2, together with M184V/I by a factor of 2.5 (White 2005, Underwood 2005).

Vice versa, TAMs reduce the K65R-associated resistance to TDF, abacavir and ddI (Parikh 2004).

As with M184V, the mutation K65R leads to a reduction in the viral replication capacity. This is not the case with TAMs or L74V/I. The median replication capacities for viruses with M184V/I (n=792), K65R (n=72) or L74V/I (n=15) alone were 68 % ($P < 0.0001$), 72 % ($p < 0.0001$) and 88 % ($p=0.16$), respectively. With the exception of M184V, NAMs did not change the replication capacities of viruses containing K65R or L74V/I (McColl 2005). If both mutations, K65R and M184V, were present, a replication of only 29 % was observed (Miller 2003).

The V75T mutation, which is associated with an approximately 5-fold increase in the resistance to d4T, ddI and ddC, is only rarely observed (Lacey 1994).

In large patient cohorts, quantitative measurements of sensitivity have shown that up to 29 % of NRTI-experienced patients have a hypersusceptibility to NNRTIs (i.e. a reduction in the inhibitory concentration by a factor of 0.3 - 0.6). A reduction in the AZT or 3TC sensitivity correlated with an increased NNRTI susceptibility. Shulman et al. pheno- and genotyped 444 virus isolates from NRTI-experienced patients. Mainly the reverse transcriptase mutations T215Y, H208Y and V118I were predictive for efavirenz hypersusceptibility. A database analysis of pair wise geno- and phenotypes showed NNRTI hypersusceptibility for TAMs and for non-thymidine analog-associated NAMs. Hypersusceptibility for efavirenz was detected for 1-2 TAMs, multiple TAMs plus M184V and for non-thymidine analog-associated NAMs such as K65R, T69X, M184V and in particular for K65R+M184V (Whitcomb 2000, Shulman 2004, Coakley 2005a). However, these results have not influenced treatment strategies so far.

NNRTIs

For NNRTIs two resistance pathways are described: K103N, V106M, and Y188L as well as L100I, V106A, Y181C/I, G190S/A and M230L.

A single mutation can confer a high degree of resistance to one or more NNRTIs. In the presence of K103N or Y188L further use of first generation NNRTIs is not recommended (Antinori 2002).

The relatively frequent K103N mutation leads to a 20- to 30-fold increase in resistance to all available NNRTIs (Petropolus 2000). Further use of the approved first generation NNRTIs in the presence of this mutation is therefore not recommended.

V106A leads to a 30-fold increase in nevirapine resistance and intermediate efavirenz resistance. In contrast to subtype B viruses, the mutation V106M is more frequent in subtype C viruses. V106M is associated with high-level resistance not only to nevirapine but also to efavirenz (Grossman 2004).

A98G (which occurs more frequently in subtype C viruses), K101E and V108 lead to low-grade resistance to all available NNRTIs. Intermediate resistance to efavirenz and delavirdine and low-grade resistance to nevirapine result from the L101I mutation. Y181C/I causes a 30-fold increase in nevirapine resistance, and response to efavirenz is only temporary. G190A is associated with a high degree of nevirapine resistance and an intermediate resistance to efavirenz and delavirdine. G190S and Y188C/L/H are mutations that result in a high degree of nevirapine and efavirenz resistance (Shafer 2002b, De Mendoza 2002).

PIs

The spectrum of PI mutations is very large. Although there is a moderate to high degree of cross-resistance between PIs, the primary mutations are relatively specific for the individual drugs. If treatment is changed early on to another PI combination, i.e. before the accumulation of several mutations, the subsequent regimen may still be successful.

First generation PIs

Most data on primary mutations selected for first in the presence of a PI, are derived from studies using unboosted PIs. In studies evaluating first-line triple therapy with boosted lopinavir, fosamprenavir or saquinavir, no patient with virological failure developed detectable major PI mutations, and the incidence of minor mutations was low (Gulick 2004, DeJesus 2004, Anaworanich 2005). Development of primary PI resistance in patients failing boosted PI therapy – even PI monotherapy- is rare (Conradie 2004, Friend 2004, Lanier 2003, Coakley 2005b).

Saquinavir: G48V mainly emerges under unboosted saquinavir and leads to a 10-fold decrease in the susceptibility to saquinavir – in combination with L90M it results in a high degree (over 100-fold) of decreased susceptibility to saquinavir (Jakobson 1995). Yet generally, any 4 mutations out of L10I/R/V, G48V, I54V/L, A71V/T, V77A, V82A, I84V and L90M, are required to reduce the efficacy of RTV-boosted saquinavir (Valer 2002). Marcelin et al. (2005) re-evaluated the genotypic interpretation of saquinavir resistance in a retrospective analysis of 138 PI-experienced patients. In this retrospective study the mutations 10F/I/M/R/V, 15A/V, 20I/M/R/T, 24I, 62V, 73ST, 82A/F/S/T, 84V, and 90M were identified as those most strongly associated with virological response. The presence of 3 to 4 mutations was associated with a reduced response to boosted saquinavir in the 138 PI-experienced patients, (Marcelin 2005).

Nelfinavir (in several countries no longer): The typical nelfinavir-specific resistance profile, with the D30N primary mutation and further secondary mutations, results in only a low degree of cross-resistance to other PIs (Larder 1999a). Virological failure on nelfinavir can also be associated with the emergence of L90M (Craig 1999). In subtype B viruses, treatment with nelfinavir generally leads to the emergence of D30N or M46I plus N88S. In subtype C, G and AE viruses, however, the mutations L90M and I84V occur more frequently.

One reason for these different resistance pathways is the prevalence of natural polymorphisms: whereas the polymorphism M36I is present in only 30 % of subtype B viruses, M36I is present in 70 – 100 % of non-B subtypes. For subtypes C or G primary resistance pathways are 82I/V + 63P + 36I/V or 82I + 63P + 36I + 20I, for subtype F resistance pathways are 88S or 82A + 54V (Gonzales 2004, Grossman 2004b, Sugiura 2002, Snoeck 2006).

A comparison between the replicative capacities of a virus with a single protease mutation (D30N or L90M) and that of the wild-type virus, demonstrated a significant loss of viral fitness in the presence of the D30N mutation selected by nelfinavir. In contrast, the L90M mutation only leads to a moderate reduction in the replicative capacity, which can be compensated for by the frequently occurring L63P polymorphism. Conversely, the L63P mutation hardly influences the reduced replicative capacity of D30N mutants (Martines 1999).

Unboosted **indinavir** and/or **ritonavir** mainly selected for the major mutation V82A(T/F/S), which in combination with other mutations led to cross-resistance to other PIs (Shafer 2002c). Mutants that frequently developed under indinavir, harboring M46I, L63P, V82T, I84V or L10R, M46I, L63P, V82T, I84V, were just as fit as the wild-type virus.

Fos-/Amprenavir: In the course of failing treatment with unboosted amprenavir or fosamprenavir, the following mutations have been selected: I54L/M, I50V or V32I plus I47V – often together with the mutation M46I. In a small study, the corresponding virus isolates showed full susceptibility to saquinavir and lopinavir (Chapman 2004, Ross 2003).

Researchers working on a small study with 49 PI-experienced patients who were switched to boosted amprenavir, developed an algorithm that also included resistance mutations at positions 35, 41, 63 and 82 (Marcelin 2003, Table 4).

The Zephir study evaluated virological response to boosted fosamprenavir in 121 patients. In the presence of less than three mutations out of L10I/F/R/V, L33F, M36I, M46I/L, I54L/M/T/V, I62V, L63P, A71I/L/V/T, G73A/C/F/T, V82A/F/S/T, I84V and L90M, viral load reduction at week 12 was 2.4 log in comparision to only 0.09 log if 4 or more mutations were present. Viral load was < 400 copies/ml in ≥ 80 % of patients with ≤ 3 mutations, 35 – 45 % of patients with 4-7 mutations and 10 % of patients with ≥ 8 mutations, respectively (Pellegrin 2005).

In a smaller cohort of 63 patients, the mutations L10F/I/V, L33F, M46I/L, I47V, I54L/M/V/A/T/S, A71V, G73S/A/C/T, V82A/F/C/G, and L90M were associated with reduced virological response to boosted fosamprenavir. The most relevant mutations were I54L/M/V/A/T/S, V82A/F/C/G, and L90M: In case of two mutations reduced response was likely, in case of three mutations resistance was observed. N88S/D was associated with improved response (Masquelier 2006).

The response to **lopinavir** in PI-experienced patients correlates with the number of any of the following mutations: L10F/I/R/V, K20M/R, L24I, M46I/L, F53L, I54L/T/V, L63P, A71I/L/T/V, V82A/F/T, I84V, and L90M Five mutations or less result in an increase in the IC_{50} by a median factor of 2.7, with 6-7 mutations this factor is 13.5, and with at least 8 mutations it is 44 (Kempf 2000, Kempf 2001).

In studies where boosted lopinavir is part of a first-line regimen, no primary PI-mutations have been observed to date. Very few case reports of primary lopinavir resistance have been published. In one patient, virological failure was associated with the occurrence of V82A followed by the mutations V32I, M46M/I and I47A. Phenotyping resulted in high-grade lopinavir resistance. Susceptibility to other PIs, especially saquinavir, was not affected (Friend 2004, Parkin 2004). In a second case, with some pre-existing polymorphisms (M36I, L63P and I93L), the mutations 54V and V82A, followed by L33F, were selected (Conradie 2004).

A different algorithm to predict lopinavir resistance also includes mutations at novel amino acid positions. Viruses with any 7 mutations out of L10F/I, K20I/M, M46I/L, G48V, I50V, I54A/M/S/T/V, L63T, V82A/F/S, G16E, V32I, L33F, E34Q, K43T, I47V, G48M/V, Q58E, G73T, T74S, and L89I/M display approximately a 10-fold increase in IC_{50}. Mutations at positions 50, 54 and 82 particularly affect the phenotypic resistance (Parkin 2003, Jimenez 2005).

In-vivo selection of lopinavir resistance was described in 54 PI-experienced patients failing treatment with boosted lopinavir. Mutations at positions 82, 54 and 46 frequently emerged. Mutations such as L33F, I50V or V32I together with I47V/I were selected less frequently. New mutations at positions 84, 90 and 71 were not observed (Mo 2005).

I47A, which has rarely been observed since lopinavir has become available, reduces the binding affinity to lopinavir and results in an 86- to > 110-fold loss in sensitivity. In contrast, I47A leads to saquinavir hypersusceptibility due to an enhanced binding affinity to saquinavir (Kagan 2005).

A German team reported that even with 5-10 PI-mutations, which normally confer broad PI cross-resistance, resensitization is possible. The mutation L76V, which is primarily selected for by lopinavir and rarely by amprenavir, is associated with resistance to lopinavir,,(fos-)amprenavir and darunavir, but can lead to resensitization to atazanavir, saquinavir and tipranavir (Müller 2004, De Meyer 2006b).

The resistance profile of **atazanavir**, an aza-peptidomimetic PI, partly differs to that of other PIs. In patients, in whom first-line treatment with atazanavir failed, the mutation I50L – often combined with A71V, K45R, and/or G73S – was primarily observed. On the one hand, I50L leads to a loss of sensitivity to atazanavir; on the other hand, I50L leads to an increased susceptibility to other currently approved PIs. Mutants harboring I50L plus A71V showed a 2- to 9-fold increase in the binding affinity to the HIV protease. Even in the presence of other major and minor PI mutations, I50L can increase susceptibility to other PIs (Colonno 2002, Colonno 2004a, Weinheimer 2005, Yanchunas 2005). In PI-experienced patients, the I50L mutation was selected for in only one third of patients failing atazanavir (Colonno 2004b).

In PI-experienced patients, at least partial cross-resistance to atazanavir is probable (Snell 2003). The accumulation of PI mutations such as L10I/V/F, K20R/M/I, L24I, L33I/F/V, M36I/L/V, M46I/L, M48V, I54V/L, L63P, A71V/T/I, G73C/S/T/A, V82A/F/S/T, L90M, and, in particular, I84V, leads to a loss of sensitivity to atazanavir. In the expanded access program using unboosted atazanavir, the number of the respective PI mutations correlated with the change in viral load. For unboosted atazanavir, the threshold for resistance is generally met if 3 or 4 PI mutations are present; for boosted atazanavir, resistance is likely with 6 or more mutations (Colonno 2004b, Gianotti 2005).

The Reyaphar resistance score which was developed by a French group, consists of the following mutations: L10I/F/R/V, K20I/M/R, L241, M461/L, 154L/M/T/V, Q58E, L63P, A71I/L/V/T, G73A/C/F/T, V771, V82A/F/S/T, 184V and L90M. With < 5 Reyaphar mutations, the mean viral load reduction at week 12 was -1.4 log, with ≥ 5 mutations it was -0.5 log, respectively (Pellegrin 2006).

A further resistance score for atazanavir includes the mutations 10F/I/V, 16E, 33I/F/V, 46I/L, 60E, 84V, 85V and 90M. In a study of 63 patients, activity of boosted atazanavir was reduced markedly in the presence of three or more mutations (Vora 2006).

Second generation PIs

- **Tipranavir**, the first non-peptidic protease inhibitor, shows good efficacy against viruses with multiple PI mutations. Even in case of reduced susceptibility to darunavir, about half of 586 virus samples remained susceptible to tipranavir (De Meyer 2006a).

A reduced sensitivity can be anticipated if three or more PRAMs (protease inhibitor-resistance associated mutations) – also referred to as UPAMs (universal PI-associated mutations) – are present. PRAMs include the following mutations: L33I/V/F, V82A/F/L/T, I84V and L90M. On the other hand, a sufficient short term reduction in the viral load of 1.2 logs was seen after two weeks on treatment with boosted tipranavir plus an optimized backbone in patients with at least three PRAMs, compared to only 0.2-0.4 logs with boosted amprenavir, saquinavir or lopinavir plus an optimized backbone (Cooper 2003, Johnson 2006, Mayers 2004).

In a pooled analysis of 291 patients in three phase II trials, the mutations, V82T, V82F and V82L, but not L90M or V82A, were associated with tipranavir-resistance. The mutations, D30N, I50V and N88D, were associated with an increased susceptibility for tipranavir (Kohlbrenner 2004).

In pooled data analyses of phase II and III studies, a tipranavir mutation score was developed including 21 mutations at 16 positions (I10V, I13V, K20M/R/V, L33F, E35G, M36I, N43T, I47V, I54A/M/V, Q58E, H69K, T74P, V82L/T, N83D and I84V). Regression analyses showed that per increase of one in the mutation score, virological response was decreased by 0.16 log. The presence of 4 to 7 mutations led to a moderately reduced tipranavir response. The accumulation of 8 or more mutations was predictive for tipranavir failure (Baxter 2006).

In vitro, L33F and I84V were the first mutations that were selected for by tipranavir, but the respective loss in sensitivity was only two-fold. At the end of the selection experiments, virus isolates with 10 mutations (L10F, I13V, V32I, L33F, M36I, K45I, I54V, A71V, V82L, I84V) and sensitivity reduced by 87-fold, were observed (Doyon 2005). Similar resistance mutations were also found in clinical isolates of tipranavir-treated patients (L10F, I13V, K20M/R/V, L33F, E35G, M36I, K43T, M46L, I47V, I54A/M/V, Q58E, H69K, T74P, V82L/T, N83D, I84V) (Croom 2005).

Darunavir, a non-peptidic protease inhibitor, shows good activity, both *in vitro* and *in vivo*, against a broad spectrum of PI-resistant viruses. *In vitro*, resistance emerged more slowly against TMC 114 than against nelfinavir, amprenavir or lopinavir. Resistance against TMC 114 occurred with the mutations R41T and K70E, which were also associated with a reduction in replication capacity. One selected virus with a 10-fold reduction in susceptibility to TMC 114 showed a < 10-fold reduction to the current PIs (atazanavir not assessed), with the exception of saquinavir (De Meyer 2002, De Meyer 2003, De Meyer 2005).

Pooled data analyses of the clinical studies Power 1, 2 and 3 showed that the presence of specific baseline mutations was associated with reduced virological response (i.e. V11I, V32I, L33F, I47V, I50V, I54L/M, G73S, L76V, I84V, and L89V). The mutations V32I, L33F, I47V, I54L or L89V developed in ≥ 10 % of subjects into virological failures (De Béthune 2006). A preceding failure on lopinavir was not predictive for virological outcome on TMC 114 (Koh 2003, Peters

2004). Out of 447 PI-experienced patients with a median number of 8 PI mutations and a median of 3 major PI mutations, 30 to 47 % of patients in the different TMC114 study arms had a viral load of < 50 copies/ml compared to only 10 % in the control PI arm (Katlama 2005).

Eleven baseline mutations at 10 positions were associated with reduced response to darunavir in PI-experienced patients: V11I, V32I, L33F, I47V, I50V/L, I54L/M, G73S, L76V, I84V und L89V. With at least three or four mutations response to darunavir was poor. However, the single mutations of this darunavir resistance score seemed to have differnt effects on darunavir susceptibility with a relative order of I50V, followed by I54M, L76V and I84V, and then by V32I, L33F and I47V. V11I, I54L, G73S and L89V had the smallest impact. This preliminary weighting of mutations must still be validated.

New mutations emerging on failing darunavir were V32I, L33F, I47V, I54L and L89V. The corresponding median fold change in IC_{50} for darunavir was 8.14. Tipranavir did not show an increase in IC_{50}, the respective median fold change was 0.82. About 50 % of virus isolates were still sensitive to tipranavir. Vice versa, in more than 50 % of isolates with reduced tipranavir susceptibility, sensitivity to darunavir was observed (De Meyer 2006a, De Meyer 2006b, Johnson 2006, Prezista US Product Information 2006).

Fusion inhibitors

This section focuses on **enfuvirtide (T-20)** resistance. The gp41 genome has positions of high variability and highly conserved regions. There seems to be no differences between B and non-B subtypes. Polymorphic sites are observed in all regions of gp41. The heptad repeat 2 (HR2) region has the highest variability. Primary T-20 resistance is a rare phenomenon (Wiese 2005).

Loss of efficacy is generally accompanied by the appearance of mutations at the T-20 binding site, which is the heptad repeat 1 (HR1) region of gp41. In particular, mutations at positions 36 to 45 emerge, most frequently with substitutions at positions 36, 38, 40, 42, 43 and 45 (e.g. G36D/E/S, 38A/M/E, Q40H/K/P/R/T, N42T/D/S, N43D/K, or L45M/L).

The IC_{50}fold change, which ranges from ≤ 10 to several hundred, depends on the position of the mutation and the substitution of the amino acid. The decrease in susceptibility is higher for double mutations than for a single mutation. For double mutations such as G36S+L44M, N42T+N43K, N42T+N43S or Q40H+L45M, a fold-change of > 250 has been observed. Additional mutations in HR2 and envelope regions also contribute to T-20 resistance (Sista 2004, Mink 2005). In clinical isolates with G36D as a single mutation, a 4- to 450-fold decrease in susceptibility was found. In the isolate showing a 450-fold decrease in susceptibility, a heterozygote change at position 126 in HR2 was observed (N/K).

In a small study, 6 out of 17 patients with virological failure additionally developed the mutation S138A in the HR2 region of gp41 – mostly combined with a mutation at position 43 in the HR1 region and a range of HR2 sequence changes at polymorphic sites (Xu 2004).

The replication capacity (RC) in the presence of HR1 mutations is markedly reduced when compared to wild-type virus with a relative order of RC wild type > N42T > V38A > N42T, N43K ≈ N42T, N43S > V38A, N42D ≈ V38A, N42T (Lu 2004). Viral fitness und T-20 susceptibility are inversely correlated (r=0.99, $p < 0.001$) (Lu 2004).

New drugs

The following chapter describes the resistance profiles of several newly developed antiretroviral drugs.

- **Etravirine (TMC125)**, a second generation NNRTI, is effective against viruses with NNRTI mutations such as L100I, K103N, Y188L and/or G190A/S.

  In a study on 25 virus isolates with one or two NNRTI-associated mutations, etravirine was still active in 18 isolates with only a small change in IC_{50} (less than 4-fold). A more than 10-fold increase in IC_{50} was observed in only 3 virus isolates. The corresponding resistance profile noted in one case was the combination L100I+K103N, and in the two other cases the single mutations Y181I and F227C. However, the prevalence of these mutations is small; 3 % for L100I+K103N and ≤ 0.5 % for Y181I and F227C (Andries 2004). Etravirine has a higher genetic barrier than other NNRTIs due to its flexible binding to the reverse transcriptase. High-grade resistance is observed only with multiple mutations. After several *in-vitro* passages the dominant virus population showed the RT mutation V179F (a new variant at this position) and Y181C. Further mutations that were selected for *in vitro* were L100I, E138K, Y188H, G190E, M230L, M230L and V179I (Brillant 2004, Vingerhoets 2005).

  In a placebo-controlled study with etravirine, virological outcome was – adjusted for other NNRTI mutations and the use of T-20 – comparable with or without K103N. The mutation Y181C was related to reduced virological response (Vingerhoets 2006).

  In patients with documented NNRTI resistance and at least three primary PI mutations, virological response to etravirine plus optimized backbone decreased with the number of NNRTI mutations. In patients without NNRTI mutations at baseline, the mean viral load reduction at week 48 was 1.67 log in the 800 mg study arm. With one, two or three mutations viral load reductions were 1.38, 0.90 and 0.54 logs (Cohen 2006).

  In the Duet trials, 13 TMC125 resistance associated mutations (RAMs) were identified: V90I, A98G, L100I, K101E/P, V106I, V179D/F, Y181C/I/V, G190A/S. In the presence of 0-2 TMC125 RAMs virological response was not compromised, but with three or more RAMs, virological response was markedly reduced (Mills 2007, Katlama 2007).

- **TMC278 (Rilpivirin)**, another second generation NNRTI, also has a unique profile of activity against NNRTI-resistant viruses and displays a high genetic barrier comparable to that of TMC125 (Goebel 2005, De Béthune 2005).

- **CCR5 antagonists:** On failing therapy with **maraviroc** or **vicriviroc** amino acid changes in the V3 loop of the HIV-1 envelope glycoprotein gp120 were observed, but the pattern of amino acid changes was different between patients. Plateaus in maximal percentage inhibition were identified as a phenotypic

marker of maraviroc resistance. In contrast, shifts in IC_{50} were not identified as a common phenotypic marker of maraviroc resistance. These findings are consistent with the use by maraviroc resistant HIV variants of both free CCR5 molecules and those occupied by maraviroc. In some cases a shift from CCR5- to CXCR4-tropic virus was observed. However, also in the controls arm several co-receptor shifts occurred. Genotypic and phenotypic evaluations of maraviroc failures still deserve further examination (Landovitz 2006, Greaves 2006, Mori 2007).

- **Integrase inhibitors**: Genotypic analysis of patients with failing first-line therapy with **raltegravir**, tenofovir and lamivudine indicated two cases with the signature mutation N155H, in one of two along with additional integrase resistance mutations. Some patients failed while harbouring only a 3TC mutation (Markowitz 2007). In treatment experienced patients raltegravir failure was generally associated with one of two genetic pathways: N155H or Q148K/R/H. Secondary mutations commonly observed with N155H included V151I, T97A, G163R, L74M and E92Q. Viruses that evolved resistance via the Q148H/R/K pathway tended to select E138K and G140S/A. Another pathway involved in raltegravir resistance is Y143R/C together with L74A/I, E92Q, T97A, I203M, and S230R (Cooper 2007, Steigbigel 2007, Hazuda 2007).

  The emergence of subsequent mutations in addition to the signature mutations N155H or Q148K/R/H leads to an increase in resistance. Both pathways also confer resistance to elvitegravir. The most frequent mutations that emerged under **elvitegravir** were E92Q, E138K, Q148R/H/K, and N155H. There is high grade cross resistance between raltegravir and elvitegravir in the presence of Q148H/R+G140S (Mc Coll 2007, DeJesus 2007)

Summary

In countries with access to antiretroviral treatment primary resistance mutations are observed in ≥10°% of treatment naïve patients. With the aid of HIV resistance tests prior to initiation of antiretroviral treatment, virological response rates can be improved. Virological rebound occurs primarily due to the emergence of resistant HIV variants. In case of virological failure, subsequent treatment decisions should always be guided by resistance testing.

Pharmaco-economic studies have shown that these tests are cost-effective both in treatment-experienced and in ART-naïve patients (Sax 2005, Corzillius 2004, Weinstein 2001).For several years, national and international HIV treatment guidelines have recommended the use of resistance testing. With some delay, the costs for resistance testing prior to ART initiation and in case of virological failure are covered by public health insurances in several countries.

Currently, both genotypic and phenotypic tests show good intra- and inter-assay reliability. However, the interpretation of genotypic resistance profiles has become very complex and requires constant updating of the guidelines. New antiretrovirals such as CCR5 antagonists or integrase inhibitors must be implemented in resistance evaluation. The determination of the thresholds associated with clinically relevant phenotypic drug resistance is crucial for the effective use of (virtual) phenotypic testing.

Even if treatment failure requires the consideration of other causal factors, such as compliance of the patient, metabolism of drugs and drug levels, resistance testing is of great importance in optimizing antiretroviral therapy.

Finally, it needs to be emphasized that – even with the benefit of well-interpreted resistance tests – only experienced HIV practitioners should start, stop or change antiretroviral therapy always taking into consideration the clinical situation and the psychosocial context of the patient.

Resistance tables

Table 1: Mutations on the reverse transcriptase gene leading to NRTI resistance (adapted from the rules of the Drug Resistance Mutations Group of the International AIDS Society-USA (Johnson 2006) and the ANRS – AC 11 Groupe Resistance (2006), and respective literature)

RTI	Resistance mutations
Zidovudine	T215 Y/F (esp. with other TAMs)
	≥ 3 of the following mutations: M41L, D67N, K70R, L210W, K219Q/E
	Q151M (esp. with A62V/F77L/F116Y)
	T69SSX (insertion)*
Stavudine	V75M/S/A/T
	T215Y/F (usually in combination with other TAMs)
	≥ 3 TAMs*
	Q151M (esp. with A62V/F77L/F116Y)
	T69SSX (insertion)*
Abacavir	≥ (4-) 5 of the following mutations M41L, D67N, L74V, M184V, L210W T215Y/F
	K65R+L74V+115F+ M184V
	Q151M (esp. with A62V/F77L/F116Y)
	T69SSX (insertion)*
	K65R (resistance possible)
Lamivudine	M184V/I
	T69SSX (insertion)*
	K65R (resistance possible)
Emtricitabine	M184V/I
	T69SSX (insertion)*
	K65R (resistance possible)
Didanosine	L74V, esp. with T69D/N or TAMs
	Q151M (esp. with A62V/F77L/F116Y)
	T69SSX (insertion)*
	K65R (partial resistance, esp. with T69D/N)
	T215Y/F and ≥ 2 of the following mutations: M41L, D67N, K70R, L210W, K219Q/E
Tenofovir DF	T69SSX (insertion)*
	≥ 3 TAMs with M41L or L210W (in some cases only partial resistance)
	(≥ 3 -) 6 of the following mutations: M41L, E44D, D67N, T69D/N/S, L74V, L210W, T215Y/F
	K65R (partial resistance)

TAMs = thymidine analog mutations

* T69SSX in combination with T215Y/F and other TAMs leads to a high degree of resistance to all NRTIs and tenofovir

Table 2: Mutations on the reverse transcriptase gene leading to NNRTI resistance resistance (adapted from the rules of the Drug Resistance Mutations Group of the International AIDS Society-USA (Johnson 2006) and the ANRS – AC 11 Groupe Resistance (2006), and respective literature)

Mutations associated with a high degree of resistance in **bold font**.

NNRTIs	Resistance mutations
Efavirenz	L100I
	K101E
	K103N(H/S/T)
	V106M
	V108I (with other NNRTI mutations)
	Y181C(I)
	Y188L(C)
	G190S/A (C/E/Q/T/V)
	P225H (with other NNRTI mutations)
	M230L
Nevirapine	A98G
	L100I
	K101E
	K103N (H/S/T)
	V106A/M
	V108I
	Y181C/I
	Y188C/L/H
	G190A/S (C/E/Q/T/V)
	M230L
TMC125 (Etravirine)	≥3 of the following mutations: V90I, A98G, L100I, K101E/P, V106I, V179D/F, Y181C/I/V, G190A/S.
	L100I+K103N
	F227C

Table 3: (adapted from the rules of the Drug Resistance Mutations Group of the International AIDS Society-USA (Johnson 2006) and the ANRS – AC 11 Groupe Resistance (2006), and respective literature)

Pis	Relevant resistance mutations and patterns	Further mutations associated with resistance
Indinavir	M46I/L V82A/F/S/T I84A/V when boosted with ritonavir, several mutations are required for a relevant loss of sensitivity	L10I/V/F, K20R/M/I, L24I, V32I, M36I, I54V/L/M/T, A71V/T, G73S/A, V77I and L90M ≥ 2 PRAMs*
Saquinavir/ Ritonavir (1000/100 mg BID)	≥ 4 of the following mutations: L10I/ R/V, G48V, I54V/L, A71V/T, V77I, V82A, I84V and L90M or ≥ 3-4 of: L10F/I/M/R/V, I15A/V, K20I/M/R/T, L24I, I62V, G73ST, 82A/F/S/T, I84V and L90M	≥ 2 PRAMs*
Nelfinavir	D30N I84A/V N88S/D L90M	V82A/F/S/T and at least 2 of the following mutations: L10I, M36I, M46I/L, I54V/L/M/T, A71V/T, V77I ≥ 2 PRAMs*
Fosamprenavir	I50V (esp. with M46I/L) V32I plus I47V I54L/M I84V	
Fosamprenavir/ Ritonavir (700/100 mg BID) or Amprenavir/ Ritonavir (600/100 mg BID)	≥ 6 of the following mutations: L10F/I/V, K20M/R, E35D, R41K, I54V/L/M, L63P, V82A/F/T/S, I84V V32I plus I47V or ≥ 3 mutations of: L10I/F/R/V, L33F, M36I, M46I/L, I54L/M/T/V, I62V, L63P, A71I/L/V/T, G73A/C/F/T, V82A/F/S/T, I84V and L90M	G73S
Lopinavir/ Ritonavir	≥ 8 of the following mutations: L10F/I/R/V, K20M/R, L24I, V32I, L33F, M46I/L, I47V/A, I50V, F53L, I54L/T/V, L63P, A71I/L/V/T, G73S, V82A/F/T, I84V, L90M L76V together with further P mutations I47V	5-7 of the following mutations: L10F/I/R/V, K20M/R, L24I, V32I, L33F, M46I/L, I47V/A, I50V, F53L, I54L/T/V, L63P, A71I/L/V/T, G73S, V82A/F/T, I84V, L90M ≥ 2 PRAMs*

Table 3: (adapted from the rules of the Drug Resistance Mutations Group of the International AIDS Society-USA (Johnson 2006) and the ANRS – AC 11 Groupe Resistance (2006), and respective literature)

Atazanavir and Atazavir/Ritonavir (300/100 mg QD)	I50L – frequently in combination with A71V – ≥ 3-4 of the following mutations for unboosted atazanavir and ≥ 6 of the following mutations for boosted atazanavir: L10I/V/F, K20R/M/I, L24I, L33I/F/V, M36I/L/V, M46I/L, M48V, I54V/L, L63P, A71V/T/I, G73C/S/T/A, V82A/F/S/T, I84V and L90M or ≥5 mutations of: L10I/F/R/V, K20I/M/R, L24I, M461/L, I54L/M/T/V, Q58E, L63P, A71I/L/V/T, G73A/C/F/T, V771, V82A/F/S/T, 184V and L90M	N88S ≥ 2 PRAMs*
Tiprana-vir/Ritonavir	≥ 3 PRAMs* ≥ 8 of the following mutations: I10V, I13V, K20M/R/V, L33F, E35G, M36I, N43T, I47V, I54A/M/V, Q58E, H69K, T74P, V82L/T, N83D, and I84V	L10I/V, K20M/L/T, M46I, I54V, V82A/F/L/T 4-7 of the following mutations: I10V, I13V, K20M/R/V, L33F, E35G, M36I, N43T, I47V, I54A/M/V, Q58E, H69K, T73P, V82L/T, N83D und I84V
Daruna-vir/Ritonavir	≥ 4 of the following mutations: V11I, V32I, L33F, I47V, I50V, I54L/M, G73S, L76V, I84V, L89V	3 of the following mutations: V11I, V32I, L33F, I47V, I50V, I54L/M, G73S, L76V, I84V, L89V

*PRAMs (protease inhibitor resistance associated mutations) include the following mutations: L33I/F/V, V82A/F/S/T, I84V and L90M. They lead to high PI cross-resistance.

Table 4: Mutations on the env (gp41) gene leading to T-20 resistance resistance
(adapted from the rules of the Drug Resistance Mutations Group of the International AIDS Society-USA (Johnson 2006) and the ANRS – AC 11 Groupe Resistance (2006), and respective literature)

Fusion inhibitors	Resistance mutations
T-20	G36A/D/E/S/V
	38A/M/E/K/V
	Q40H/K/P/R/T
	N42T/D/S
	N43D/K/H/S
	N42T+N43S
	N42T+N43K
	G36S+L44M
	L44M
	L45M/L/Q

The reduction in susceptibility is generally higher for double mutations than for single mutations.

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10. Pregnancy and HIV

Therapy for mothers and prevention for neonates

Mechthild Vocks-Hauck

Perinatal (vertical) HIV infection has become rare in since the introduction of antiretroviral transmission prophylaxis and elective cesarean section. While the vertical HIV transmission rate ranged amounted to about 15 % in Europe at the beginning of the nineties, it now amounts to only a few percent (Connor 1994, European Collaborative Study 2005). Postpartum HIV infections are avoidable provided that HIV-infected mothers do not breastfeed. At the same time as transmission prophylaxis was introduced, the treatment of HIV infection changed too. Nowadays, pregnancy is no longer a general contraindication for antiretroviral therapy (Agangi 2005, CDC 2006 a)).

The following chapter summarizes the recommendations of different guidelines for HIV therapy in pregnancy.

Reference is made to the European (Coll 2002, British HIV Association 2005), German (DAIG), and Austrian AIDS societies (OEAG) (DAIG 2005) as well as American Guidelines (CDC 2005 a) and b)). In addition, detailed and continuously updated recommendations of the US guidelines are to be found on the HIVATIS website: http://hiv.net/link.php?id=190.

HIV therapy in pregnancy

Starting HIV therapy during pregnancy

It is important to distinguish between women with and without a therapy indication of their own. In the case of a maternal indication, treatment is begun as a rule in week 13 + 0 of gestation, otherwise from week 32 + 0. The assessment of indications for therapy and drug selection is similar to that in non-pregnant patients (chapter ART 2005). Since the CD4 T-lymphocyte count decreases physiologically by approximately 10-20 % in pregnant patients, the threshold values should be adjusted upwards accordingly before treatment is started. Following the recommendations of the German/Austrian guidelines and the CDC (2006 b), antiretroviral therapy in symptom-free patients should begin

- when CD4+ T-cell count is below 200–350/µl (15-20% relative) and/or
- with a viral load of > 50,000–100,000 copies/ml HIV RNA (by RT-PCR or 3.0 version b-DNA).

Before initiating therapy , a resistance test, and, if necessary, subtyping should be carried out (see chapter on Resistance).

When setting up a treatment plan, it is important that:

- AZT (Retrovir™) should be one component of the combination – if the result of the resistance test and the expected toxicity are favorable; and

Efavirenz (Sustiva™, Stocrin™) should be avoided because of possible teratogenic effects in the first trimester, but also the combination of DDI + D4T should not be used, and

Even if maximum suppression of viral activity is achieved during pregnancy, this is no guarantee for the prevention of HIV transmission. Therefore, prophylaxis to reduce perinatal HIV transmission is also recommended in sufficiently treated pregnant patients (see below i).

Table 1: Special features of anti-HIV therapy in pregnancy

Explanation of risk: Only AZT is approved for perinatal transmission prophylaxis
HIV resistance testing, if necessary HIV subtyping
No efavirenz (Sustiva™) in the first trimester (teratogenicity)
No d4T+ddI (Zerit™+Videx™) because of mitochondriopathies
Nevirapine related hepatotoxicity in women with CD4+ T-cell counts > 250/µl
Raised toxicity through combination therapy, therefore monthly controls of lactate, hepatic transaminase levels, viral load, CD4+ T-cell count
Therapeutic plasma drug level measurement (TDM) and possible dose adaptation

Continuation of treatment during pregnancy

More and more HIV-infected women, in whom pregnancy has been diagnosed, have been pretreated with antiretroviral agents.As a rule, if pregnancy is diagnosed **after** the first trimester, the antiretroviral therapy should be continued. Interruption of treatment might give rise to an increase in viral load and a possible deterioration of immune function causing the danger of disease progression and, ultimately, of reduction of the immune status of mother and fetus. AZT should be administered as a component of a combination regimen starting at 32 weeks of gestation at the latest.

Women in whom pregnancy is diagnosed **during** the first trimester should be informed about the benefits and risks of treatment in this period. In cases of reduced immune status, in particular, antiretroviral therapy could be continued even in the first trimester under careful laboratory and ultrasonic controls. However, substances that can have a toxic effect on the embryo should not be administered during early pregnancy (Table 1).

Interruption of treatment in the first trimester

Women who have to discontinue antiretroviral treatment during pregnancy, e.g. because of hyperemesis, should only restart therapy when drug tolerance can be expected. In this case, as in all others, the rule is: withdraw all drugs simultaneously and re-administer them simultaneously, with the exception of NNRTIs.

In other cases – especially if pregnancy is diagnosed very early – the fear of possible embryotoxic effects may lead to an interruption of antiretroviral therapy until the end of the first trimester . There are indications that after interruption of treatment in pregnancy, complete viral suppression is much more difficult in the further course (Liuzzi 2006). A continuously updated summary of the current state of

knowledge about antiretroviral drugs in pregnancy can be found on the internet at the web address http://hiv.net/link.php?id=189.

If treatment is interrupted, all drugs (NRTIs and PIs) should be withdrawn and re-administered simultaneously in order to prevent development of resistance. As it is usually not possible to determine pregnancy duration exactly, the restart is mostly initiated at the gestational age of 13 + 0 weeks. Due to their long half-life, NNRTIs should be withdrawn up to three weeks before NRTIs: alternatively, the NNRTI can be replaced beforehand by a boosted PI. Because of the complicated interruption strategy, however, a therapy containing nevapirin is usually continued in practice.

Combination therapy for the duration of pregnancy

It is becoming more and more common to offer a combination therapy to pregnant patients with a plasma HIV RNA level of only 1,000 –10,000 copies/ml from the second trimester (CDC 2006a) onward or 32 + 0 weeks of gestation. This approach is based on the assumption that any decrease in viral load translates into a lowering of the transmission risk.

With a viral load of less than 1,000 HIV RNA copies/ml, the advantage of cesarean section compared with vaginal delivery can no longer be verifiedShapiro 2004). For this reason, in the USA as well as in some European countries, vaginal delivery is considered an option for women on antiretroviral combination therapy whose HIV status at the time of delivery is less than 1,000 copies/ml and/or undetectable and in whom no obstetric complications are expected.These cases are increasing in Europe, the rates have now reached over 30% (Rodrigues 2006). Since the study data are not yet definitive and C-section is still accepted as being safer (ECS 2005), countries such as Germany still prefer to use this mode of delivery.

Treatment monitoring

In addition to measuring the hemoglobin concentration to exclude an AZT-associated anemia, transaminases for potential hepatic toxicity, and lactate level to detect lactic acidosis early, the CD4+ T-cell number and viral load should be monitored at monthly intervals. If PIs are part of the treatment, it is of particular importance to monitor the blood glucose level closely (El Betuine 2006). Resistences and plasma level are determined at the beginning of and, if appropriate, in case of failure of treatment.

Special aspects of HIV therapy in pregnancy

Because embryotoxicity cannot be excluded and hepatic metabolism is altered in pregnancy, and also in some cases reduced plasma levels, some basic rules must be taken into consideration (CDC 2006 a)) (Table 2). It is important to understand that a detectable plasma viral load always necessitates a resistance test. AZT resistance was verified, for example, in the United States in approximately 17 % of the women during pregnancy and up to 73% of infected neonates, who therefore seem to have an unfavorable prognosis in these cases (Vignoles 2006).

Table 2: Antiretroviral agents in pregnancy

Preferred NRTIs (full placenta transfer)	AZT + 3TC AZT + ddI	AZT is metabolized in the placenta; mitochondriopathy risk: ddC > ddI > d4T > AZT > 3TC > ABC > TDF
Alternative NRTIs (full placenta transfer)	d4T + 3TC	No side-effects for PACTG 332
	Abacavir	Only little published experience
	Tenofovir	No published data in humans
	Emtricitabine	Alternative to 3TC, barely any experience
NNRTIs (full placenta transfer)	Nevirapine	General use in perinatal prophylaxis; Hepatic toxicity ↑ especially in > 250 CD4 cells; enzyme induction, rapid resistance
PIs (minimal placenta transfer)	Nelfinavir	Once frequent use; but unboosted Hyperbilirubinemia, nephrotoxicity
	Indinavir	Only as booster
	Ritonavir	Some experience, plasma level low ↓
	Lopinavir/r	Low plasma levels, only boosted
	Saquinavir SGC	Some experience, solution contraindicated
	Amprenavir	Little experience
	Fosamprenavir	Initial experience; indir. Hyperbilirubinemia, also with neonates
	Atazanavir	Case reports
	Tipranavir	Case reports
	Darunavir	
Entry Inhibitors	T-20	Intial experience (case reports)

Antiretroviral agents in pregnancy

Nucleoside reverse transcriptase inhibitors (NRTIs)

Nucleoside analogs cross the placenta (Chappuy 2004) and can cause toxic damage not only to the mother but also to the child. According to experience to date, the main problems are anemia and, when using combination therapy, lactate acidosis.

On the basis of pregnancies observed to date, it can be maintained that frequently used nucleoside analogs such as AZT, 3TC and d4T, do not increase teratogenicity by more than twofold (Antiretroviral Pregnancy Registry 2004). Most of our experience is related to AZT administration. Follow-ups of more than 20,000 children who had received AZT prophylaxis did not show any serious side effects. An analysis of the causes of death of 223 children, who died within the first five years of life, ruled out drug-related causes (The Perinatal Safety Review Working Group 2000). In other studies, no damage to mitochondrial DNA or neurological development dysfunction in HIV-exposed children after HAART could be detected (Alimenti 2006).

In contrast to these findings, in a prospective study by Barret et al. (2003) on 2,644 ART-exposed non-infected children, neurological symptoms with persistent mitochondrial dysfunction were reported in 0.26 %. Retardation of auditory evoked potentials (Poblano 2004), as well as nonspecific changes in cerebral MRTs in children perinatally exposed to AZT (plus 3TC) (Tardieu 2005) have been interpreted

as a sign of neurotoxicity. 24 months after combined nucleoside exposure, raised lactate values as well as impairment of hematopoeiesis can still be demonstrated in children. Even after eight years, neutrophil granulocytes were reduced in perinatally NRTI-exposed children (ECS 2004). Severe mitochondriopathies have been observedduring a combination therapy of the nucleoside analogues d4T+ddI. Tenofovir proved to be harmless when given for a short time (Rodman 2006).

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

In perinatal prevention, nevirapine has been employed successfully, particularly in combination with AZT. Because of enhanced risk of liver toxicity during the first 18 weeks of treatment in women with a CD4+ T-cell count more than 250/µl, treatment should be monitored closely and at short intervals, especially in the time of dose escalation (Boehringer 2004). Nevirapine in pregnant women with over 250 CD4 cells/µl is only recommended following very careful assessment of the benefit-risk ratio (CDC 2005a)). In a retrospective study of 197 pregnant women, toxic side effects were observed in 5.6%, which led to stopping the treatment in 3.6% (Joao 2006).
Perinatal single and two-dose prophylaxis has resulted in the development of drug resistance (Flys 2005).
If a mother gives birth less than two hours following nevirapine administration, or has not received any prior nevirapine at all, the newborn should receive a dose of nevirapine immediately after birth and a further dose after 48-72 hours (Stringer 2003). Because of embryonic toxicity in the rhesus monkey and also in humans (neural tube impairments, Bristol-Myers Squibb 2004) efavirenz is not used during the first trimester of pregnancy and only after the second in cases with no alternative treatment option providing reliable contraception is practiced after delivery (CDC 2006 b)). Following isolated cases of neural tube defects, which caused the FDA to allocate efavirenz to category D, however, no further cases of teratogenicity due to this substance have been reported (Beckermann 2006)

Protease inhibitors (PIs)

The use of protease inhibitors must be monitored carefully, especially in the later stages of pregnancy (monthly in the third trimester), due to a possible diabetogenic effect (Beitune 2005, Hitti 2006) and hepatic toxicity. Hyperlipidemia also occurs more frequently (Floridia 2006). Presently, most experience relates to nelfinavir (Timmermans 2005). Since Nelfinavir is not boosted, and the plasma level can be reduced (Khuuong-Josses 2006), the substance is now used less often than in the past. Indinavir can lead to hyperbilirubinemia and nephrolithiasis; the plasma levels can be lowered (Kosel 2003). As with indinavir, saquinavir should also be boosted with ritonavir in pregnancy. lopinavir/r plasma levels are also lowered during pregnancy, especially in the third trimester (Mirocknick 2006). With Atazanavir/r, mild hyperbilirubin anemia were describes in neonates (Morris 2005b).

Past conjecture that there are increased deformities under PIs have since been disproved, especially since PIs are scarcely able to cross the placenta due to the molecule size. An increase in premature births in cases of HAART containing PIs (ECS 2004), also failed to find confirmation in other studies to date (Morris 2005a, Tuo-

mala 2005). According to a current study, there may be an increased risk of eclampsia (Suy 2006).
Alfa-fetoprotein levels are said to be increased under PI regimes, but the serum levels of unconjugated oestriol and human choriongonadotropine are not (Einstein 2004).

Entry or fusion inhibitors

T-20 was administered to pregnant women with multiresistant viruses with partial success, in combination with tipranavir also (Wensing 2006). Failures of therapy with perinatal HIV infection are described. There is probably no possibility of crossing the placenta (Brennan-Benson 2006).

FDA classification for drugs in pregnancy

The FDA has classified the potential toxicity of drugs in pregnancy into the categories A-D. All HIV virustatic agents belong to the categories B-D, since "harmlessness through studies on the human being" (= category A) does not apply to any of these drugs.
FDA category B is defined as follows: “Animal studies have revealed no evidence of harm to the fetus; however, there are no adequate and well-controlled studies in pregnant women”. The FDA category B includes ddI, emtricitabine, tenofovir, atazanavir, saquinavir, ritonavir, nelfinavir and enfuvirtide (T-20).
FDA category C is defined as follows: “Animal studies have shown an adverse effect and there are no adequate and well-controlled studies in pregnant women. Use in pregnancy should occur only after careful benefit/risk appraisal.” All other drugs that were not mentioned in category B fall into the FDA category C. Efavirenz falls into category D because of neural tube defects in humans after first trimester exposure.
FDA category D (Efavirenz) is defined as follows: “Adequate well-controlled or observational studies in pregnant women have demonstrated a risk for the fetus. Nevertheless, the benefits of therapy may outweigh the potential risk.” This category applies to efavirenz. For example, the drug may be acceptable if it is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective.

Prevention of perinatal HIV infection

In approximately 75 % of cases, HIV is transmitted prior to, or during the last weeks prior to birth. About 10 % of vertical HIV infections occur before the third trimester, and 10-15 % are caused by breastfeeding.

The probability of HIV transmission to a neonate correlates with the viral load. This also seems to apply to women who are being treated with antiretroviral drugs (Table 3). If the viral load is undetectable using currently available tests, the probability of transmission is indeed extremely low; however, infections have also been described under such circumstances. Likewise, premature births and premature rupture of membranes are associated with an increased infection risk for the child.

For this reason, reduction in the level of plasma viremia and improvement in the immune status of pregnant women are vital prophylactic measures. If a mother is treated with antiretrovirals, these drugs should continue to be taken, if possible, during delivery at the usual scheduled intervals in order to achieve the maximum

effect and to minimize the risk of developing resistance. Viral resistances make up over 20% of the remaining infection rate of less than 2% (Birkhead 2006).

Table 3: Known risk factors for perinatal HIV transmission

High maternal viral load
Low CD4+ T-cell count
AIDS in the mother
Vaginal delivery (at a viral load > 1,000 copies without ART
Premature rupture of membranes of > 4 h
Pre-term infants (< 37 weeks of gestation)
Breastfeeding

For the general prevention of mother-to-child transmission of HIV, pregnant women should be warned not to use intravenous drugs or to have unprotected sex with different partners because of the increased risk of HIV transfer in these cases.

In addition to the indicated or optional antiretroviral therapy of the mother, the following rules should be observed regarding chemoprophylaxis

- Antiretroviral prophylaxis before and during delivery
- Elective cesarean section before onset of labor, because vaginal delivery with a viral load of > 1,000 HIV-RNA copies/ml increases the transmission risk
- Postnatal chemoprophylaxis of the infants (post-exposure prophylaxis)
- No breastfeeding

Antiretroviral transmission prophylaxis

Combination prophylaxis

iIf the viral load is > 10,000 copies/ml, combination prophylaxis should be introduced temporarily from 32 + 0 weeks gestation until immediately after birth (Table 4). In the case of high-risk pregnancies (e.g. multigravidity), the prophylaxis is begun at 29 + 0 weeks of gestation.

A monoprophylaxis or the combination of AZT+3TC is problematic because of the possible development of resistance (Mandelbrot 2001). Therefore, HAART prophylaxis is increasingly being used, with a boosted PI. Combinations containing nevapirin should only be administered after careful consideration of the benefit-risk ratio.

Table 4: Combination prophylaxis with combination therapy containing AZT in cases with a viral load > 10,000 RNA copies/ml, but otherwise only standard risk

After resistance testing starting at 32 + 0 weeks gestation:
2 x 250-300 mg AZT (rarely as a "mono"-prophylaxis at a viral load << 10,000 copies/ml)
+ a second NRTI
+ plus PI/r boosted
During delivery (elective cesarean section from 37+0 weeks gestation to week 37 + 6):
IV infusions of AZT as standard prophylaxis:
2 mg/kg i.v. as a "loading dose" for 1 h to approx. 3 h preoperatively
1 mg/kg i.v. intraoperatively until delivery of the infant
In neonates AZT monoprophylaxis:
2 mg/kg orally every 6 hours *within 6 hours* post partum for 2-4 weeks or
1.5 mg/kg i.v. every 6 hours *within 6 hours* post partum for 10 days

Prophylaxis in ART-pretreated pregnant women

In pregnant women who have already been pretreated with ART, AZT should be integrated into the combination therapy starting at 32+0 weeks gestation. When using combinations containing d4T, this agent should be substituted by another active component because of AZT antagonism. In cases of anemia or AZT resistances, other NRTI are used, e.g. 3TC, DDI, abacavir or tenofovir.

Procedure in cases with additional pregnancy risks

The pregnancy risks mentioned in Table 5 require an intensified prophylaxis. The risk of transmission is reduced here, even in the case of sufficient HIV therapy. In premature infants, for example, perinatal HIV transmissions only occurred when the mothers had received no prophylaxis or only an AZT monoprophylaxis (Aagaard-Tillery 2006).

Intrapartum prophylaxis without antepartum regimens

If the diagnosis of HIV infection is only established at the time of delivery, mother and newborn receive a dual or triple combination prophylaxis with AZT (plus 3TC and/or nevirapine) in cases of highly increased risk (high viral load and/or medical complications during delivery).

Simple prophylaxis

Pregnant women as of week 32 of gestation who do not require therapy thanks to their immune status and who have a low viral load (considerably below 10,000, after CDC below 1,000 copies/ml) and a normal course of pregnancy can be given AZT monotherapy with an elective C-section. This regimen is, however, only administered in 10% of casesl, not only because AZT-resistant viruses have been increasingly identified, but also because the risk (albeit a low one) of resistance formation under monotherapy cannot be neglected. The use of AZT alone during pregnancy should be mentioned here because it remains topical under teratogenic aspects.

Treatment during delivery

Elective cesarean section in cases of uncomplicated course of pregnancy

Cesarean section is carried out swiftly by experienced obstetricians prior to the onset of labor from 37+0 up to 37+6 weeks of gestation using the Misgav-Ladach technique, which reduces bleeding. Blunt preparation and the delivery of the child within the intact amniotic sac are considered ideal (Schäfer 2001). A vaginal delivery in women under long-term HAART with a negative viral load is possible (CDC 2006a).

High-risk pregnancy

Cesarean section in cases of multigravidity should be carried out using the same technique as for a cesarean section in a single pregnancy. In this context, the skill and experience of the operating surgeon are especially important. Cesarean sections in cases of premature infants are also important to avoid hypoxia in the neonate; the special aspects of chemoprophylaxis have been described above.

In cases with a premature rupture of membranes of less than four hours duration, a section is expedient for prophylactic reasons, providing the clinical situation at that stage of delivery still permits. If the rupture of membranes has lasted more than four hours, the advantage of cesarean section compared to vaginal delivery is no longer expected. Nevertheless, vaginal delivery should occur as swiftly as possible, since the HIV transmission risk increases by about 2 % per hour. The extension of the prophylactic scheme (Table 5 and 7) is important. The risks of transmission are lower in the case of undetectable viral load.

Unknown HIV status in cases of known risk

If, at the time of delivery, the HIV status is unknown and the existence of a risk is known, an HIV test can still be offered to the patient . Although specificity is high, it is still considered inadequate. Thus, the combined use of two rapid tests from different manufacturers is ideal. If one of the two tests is negative, there is probably no infection.

Table 5: Risk adapted prophylaxis in the case of complications during pregnancy and delivery

Increased risk	**Mother**	**Child**
Multigravidity	AZT monoprophylaxis poss.	Combination therapy e.g. AZT + 3TC + PI/r
	from week 29 + 0 gestation	
	´Within 6 h post partum	
	AZT 4 x 2 mg/kg orally for 4 weeks (if necessary, after 10 days i.v. shift to roal application	
Early onset of labor	Combination therapy, e.g. AZT + 3TC + PI/r	
	Within 6 h post partum	
	AZT 4 x 2 mg/kg orally 4-6 weeks **plus** 1 single dose nevirapine 2 mg/kg after 48-72 h *,**.	
	AZT dosage for premature birth (PB) < week 35 of gestation: 2 x 2 mg/kg orally or 2 x 1.5 mg/kg i.v. from day 15: 3 x 2 mg/kg orally (for premature birth < week 30 of gestation as of day 29.	
Premature birth	Week 33+0 – 36+6 of gestation**	
	Maternal AZT prophylaxis < 4 weeks	
	In addition to AZT or a combination therapy: nevirapine*	
	As for early onset of labor (see above)	

***see chapter on NNRTIs**
** for premature babies, a triple prophylaxis is also possible (see below): but 3TC should be administered to premature babies only with great reticence

Table 6:Prophylaxis procedure in the case of complications during pregnancy and delivery in cases of highly increased risk

Highly increased risk
Mother
Child
Premature birth < week 33+0 of gesation
Prematurely ruptured membranes
Amniotic infection syndrome
Elevated viral load at the end of pregnancy
In addition to AZT or a combination therapy: nevirapine*
AZT (dosage see above) for 4-6 weeks plus
3TC** 2 x 2 mg/kg for 4-6 weeks plus
nevirapine* 2 mg/kg within 2 to 48 h + 2. Dose 48-72 h post partum (if no NVP pre-delivery or < 2h between intake and delivery).
(If nevirapine pre-delivery, then only 1 after 48-72 h.)
Incision injury of child
Ingestion of hemorrhagic amniotic fluid
Diagnosis: HIV infection only post partum.

***see chapter on NNRTIs**
** 3TC should be administered to premature babies only with great reticence

Therapy of neonates

Postnatal standard prophylaxis

The postnatal transmission prophylaxis should begin, if possible, within the first 6 hours following birth with oral or – in the case of gastrointestinal symptoms – intravenous AZT prophylaxis. In Germany, the duration of the oral standard prophylaxis has been shortened from six to two (to four) weeks (Vocks-Hauck 2001).

Prophylaxis in cases of increased risk (multiple neonates, premature infants)

In multiple-birth neonates without further risk, AZT prophylaxis of four weeks duration is recommended. In addition, premature infants receive nevirapine, which is given either once to the mother before delivery and once to the premature infant, or twice postnatally. If maternal nevirapine administration occurs less than an hour before delivery, then the newborn receives its first dose within the first 48 hours (Stringer 2003). If nevirapine was a part of the combination therapy for the mother, the dose is doubled to 4 mg/kg in newborns because of possible enzyme induction. In addition, newborns receive an extended AZT prophylaxis according to the regimen proposed for premature infants (see below) for the duration of four to six weeks.

Prophylaxis in cases of highly increased transmission risk

In neonates with additional transmission risks, a combination prophylaxis with AZT+3TC is recommended, as well as two doses of nevirapine. However, the pharmacokinetic data available on HAART is extremely limited. A strongly increased risk exists, for example, after premature rupture of membranes, in cases of amniotic infection syndrome, high viral load prior to delivery, lacking transmission prophylaxis and incision injury of the child during cesarean section, as well as in cases where the amniotic fluid sucked from the gastrointestinal or respiratory tract of the newborn is hemorrhagic.

Procedure in cases of no pre- and intranatal prophylaxis

Combination prophylaxis of AZT+3TC should start within the first 6 to 12 hours after delivery. In addition, a perinatal nevirapine prophylaxis with two-fold administration is recommended.

If HIV infection is discovered only after birth, a combination prophylaxis, begun within 48 hours, seems to be far more effective than a prophylaxis, which is initiated only after 3 days (transmission rates 9.2 % vs. 18.4 %, Wade 1998). However, even then, a certain positive effect of AZT prophylaxis as opposed to no prophylaxis can still be verified (18.4 % vs. 26.6 %) (Table 6).Therefore, even late initiation of post-natal prophylaxis (> 3 days) can still make sense.

Further studies for HIV prevention in neonates

A survey of studies about the pharmacokinetics in pregnancy and neonates is given in Table 7 (Ronkavilit 2001 & 2002, Mirochnik 2005).

In order to continuously improve HIV therapy during pregnancy and the chemoprophylaxis of perinatal HIV infection, a thorough documentation of clinical data is necessary. In the US, the “Antiretroviral Pregnancy Registry” is an extensive therapy register that helps to evaluate the potential teratogenicity of antiretrovirals on the basis of “case reports” on HIV-exposed neonates:

Antiretroviral Pregnancy Registry, Research Park, 1011 Ashes Drive, Wilmington NC 28405 Tel. (international) 910-265-0637 or +44-1895-825-005, e-mail: Registry@pharmaresearch.com; http://www.apregistry.com/contact.htm

Table 7: Studies on antiretroviral prophylaxis in neonates

Drug	Average daily dose	Most frequent side effects	Study
AZT Zidovudine Retrovir™	4x2 mg/kg, 2x2 mg/kg in PI*< 35 GW, from 15th day: 3x2 mg/kg* , in PI < 30 GW from 29th day	Anemia,n eutropenia Mitochondriopathy in combination with 3TC	(P)ACTG's 076, 316, 321, 353, 354, 358; HIVNET 012 III PACTG 331(PI)
3TC Lamivudine Epivir™	2x2 mg/kg in neonates (< 30 days)	GI SE, vomiting, Mitochondriopathy in combination Incompatibility in premature infants	PACTG 358
ddI Didanosine Videx®	2x50 mg/m^2 from 14th day	Diarrhea, pancreatitis, mitochondriopathy in combination	PACTG 239,249; HIV-NAT
d4T Stavudine Zerit™	2 x 0.5 mg/kg from 14th day	Mitochondriopathy in combination	PACTG 332, 356; HIV-NAT
ABC Abacavir Ziagen™	1x2-4 mg/kg; > 1 month 2x8 mg/ kg (Study)	Hypersensitivity reaction, mitochondriopathy, lactic acidosis	PACTG 321
NVP Nevirapine Viramune®	1x2-4 mg/kg or 1x120 mg/m^2 for 14 days, thereafter 2x3.5-4 mg/kg or 2x120 mg/m^2 ,maximal 400 mg/m^2	Rash, hepatotoxicity, hyperbilirubinanemia	PACTG 316,356, HIVNET 012
NFV Nelfinavir Viracept®	2x40 mg/kg (Study) from 1 week up to 6 weeks;	GI SE: particularly diarrhea	PACTG 353, 356
RTV Ritonavir Norvir®	1x350 mg/m^2 or 2x350 mg/m^2 for 4 weeks (Study)	Hyperbilirubinemia, gastrointestinal SE	PACTG 354

I=infant; PI = premature infant; MI = mature born infant; SD = single dose; (P)ACTG = (Pediatric) AIDS Clinical Trial Group; HIV-NAT = HIV-Netherlands Australia Thailand Research Collaboration; NN = neonate; GI SE = Gastrointestinal side effect; GW = gestation week

Reference: Except for AZT in mature born infants, the dosage is taken from the studies. Antiretroviral substances that are not approved, should be used in neonates only in the context of studies, if possible.

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11. Antiretroviral Therapy in Children

Tim Niehues and Hermione Lyall

Characteristics of HIV infection in childhood

Children are not small adults. The HIV infection in childhood is different from the infection in adults with regard to transmission, the natural course of viral dynamics, maturity of the immune system and clinical manifestations. Several factors have to be considered when giving antiretroviral drugs to children: children may already have been exposed to AZT and other drugs in utero, the pharmacokinetics of the drugs are age-dependent and children require special attention to help with adherence.

More than 95 % of children are infected by perinatal transmission of the virus from the mother to the child (vertical infection). Transmission by transfusion, sexual transmission and drug abuse are much less prevalent. In most cases (75-90 %) HIV is transmitted peri- or intrapartum. Only a small proportion of children are infected in utero (10-25 %). Transmission by breastfeeding is important in resource-poor settings, but plays a minor role in developed countries, where breastfeeding by known HIV-infected mothers is strongly discouraged. The increasing knowledge about how HIV is vertically transmitted has led to highly effective interventions to prevent transmission and significant reduction of the transmission rate to less than 2 %. However, new infections in HIV-exposed children still occur

- if the HIV status of the mother is unknown;
- if prevention of transmission prophylaxis is incomplete;
- if the mother doesn't have access to transmission prophylaxis during pregnancy.

Without antiretroviral therapy there is a bimodal presentation of vertical HIV infection: in 10-25 % of the children, rapid progression with AIDS-defining symptoms and lethal complications is observed within the first year of life. In 75-90 % there is a much slower disease course with a mean duration of more than 8 years until AIDS-defining symptoms occur. At present, disease progression is mainly influenced by the efficacy of antiretroviral therapy.

At birth, viral load is usually low (< 10,000 copies/ml) and then rapidly rises within the first 2 weeks of life to values above 100,000 copies/ml and only slowly decreases after the age of 4-5 years. These viral dynamics are significantly different from the rapid increase and decrease of the viral load seen in untreated adults within a few months following the acute HIV infection (figure 1).

In children, the higher viral load is associated with the somatic growth of the lymphatic system and the inability of the immature immune system in children to mount an HIV-specific response. When assessing the immune system in infants and children, it is very important to compare the child's CD4 count with the age-appropriate values (e.g. the mean CD4 count for a 6-month-old baby being 3.0×10^9/l). Lymphocyte counts are very high in infancy and decline to adult levels beyond 6 years of age (table 1).

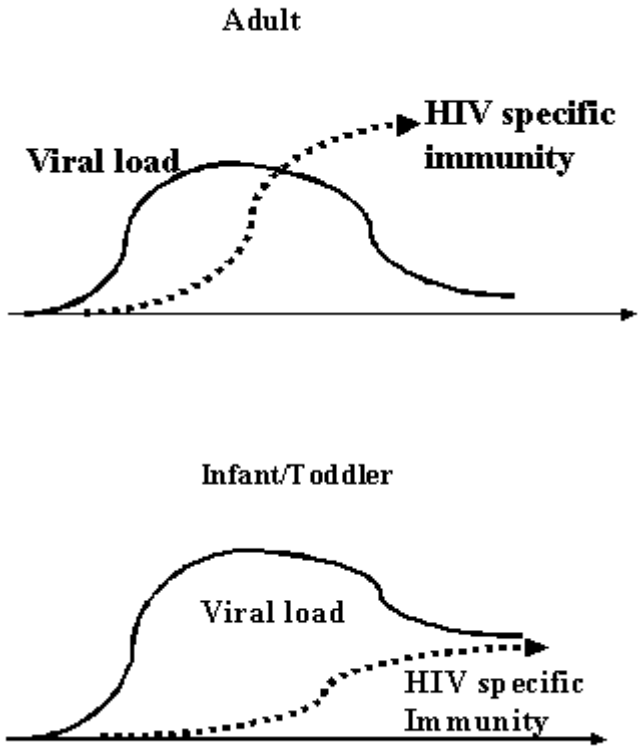


Figure 1: Differences in the natural course of viral load and anti-HIV immunity between adults and infants/toddlers

The spectrum of clinical manifestations in HIV-infected children is different from that of adults. In adults, typical manifestations of the acute HIV seroconversion illness are: fever, sore throat, lymphadenopathy and a mononucleosis-like disease. HIV seroconversion illness has not been described in perinatally-infected children. Symptomatic disease presenting in childhood has been classified according to severity of symptoms (table 2). A new WHO staging has been proposed in 2006(http://www.who.int/hiv/pub/guidelines/en/index.html) . If antiretroviral therapy in children is effective, opportunistic infections become a rarity. However, in children who newly present with HIV (e.g. if HIV status in the mother is unknown and there was no transmission prophylaxis), opportunistic infections can still be observed.

Table 1. 2006 WHO Human Immunodeficiency Virus Pediatric Classification System: Immune Categories Based on Age-Specific CD4 values

Classification of HIV asociated immunodefi-ciency	**Age related CD4 Values**			
	< 11 months	**12–35 months (%CD4+)**	**36 –59 months (%CD4+)**	**>5 years (absolute number per mm3 or %CD4+)**
None or not significant	>35	>30	>25	> 500
Mild	30–35	25–30	20–25	350−499
Advanced	25–29	20–24	15−19	200−349
Severe	<25	<20	<15	<200 *or* <15%

Table 2. WHO clinical staging of HIV/AIDS for children with confirmed HIV infection

Clinical stage 1

Asymptomatic

Persistent generalized lymphadenopathy

Clinical stage 2

Unexplained persistent hepatosplenomegaly
Papular pruritic eruptions
Fungal nail infection
Angular cheilitis
Lineal gingival erythema
Extensive wart virus infection
Extensive molluscum contagiosum
Recurrent oral ulcerations
Unexplained persistent parotid enlargement
Herpes zoster
Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis or tonsillitis)

Clinical stage 3

Unexplained moderate malnutrition or wasting not adequately responding to standard therapy
Unexplained persistent diarrhoea (14 days or more)
Unexplained persistent fever (above 37.5°C intermittent or constant, for longer than one month)
Persistent oral candidiasis (after first 6–8 weeks of life)
Oral hairy leukoplakia
Acute necrotizing ulcerative gingivitis or periodontitis
Lymph node tuberculosis
Pulmonary tuberculosis
Severe recurrent bacterial pneumonia
Symptomatic lymphoid interstitial pneumonitis
Chronic HIV-associated lung disease including brochiectasis
Unexplained anaemia (<8 g/dl), neutropaenia (<0.5 × 10_9 per litre) and or chronic thrombocytopaenia (<50 × 10_9 per litre)

Clinical stage 4
Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy
Pneumocystis pneumonia
Recurrent severe bacterial infections (such as empyema, pyomyositis, bone or joint infection or meningitis but excluding pneumonia)
Chronic herpes simplex infection (orolabial or cutaneous of more than one month's duration or visceral at any site)
Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
Extrapulmonary tuberculosis
Kaposi sarcoma
Cytomegalovirus infection: retinitis or cytomegalovirus infection affecting another organ, with onset at age older than one month
Central nervous system toxoplasmosis (after one month of life)
Extrapulmonary cryptococcosis (including meningitis)
HIV encephalopathy
Disseminated endemic mycosis (coccidiomycosis or histoplasmosis)
Disseminated non-tuberculous mycobacterial infection
Chronic cryptosporidiosis (with diarrhoed)
Chronic isosporiasis
Cerebral or B-cell non-Hodgkin lymphoma
Progressive multifocal leukoencephalopathy
Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy

Diagnosis of HIV infection < 18 months of age

The detection of anti-HIV antibodies does not prove an infection in infants. High titers of anti-HIV IgG are transferred transplacentally from mother to child. Maternal antibodies can be detected in children up to the age of 18 months. Therefore a direct method of detecting HIV is necessary. Identification by HIV DNA PCR is highly sensitive and specific. Detection of HIV can be achieved within the first 48 hours after birth in 38 % of infected children, and within the first 2 weeks in 93 % of children (Dunn 1995). Once a positive HIV PCR is found, a second independent blood sample should soon be taken for repeat PCR analysis. As diverse subtypes of HIV exist, it is advised to test paired samples from mother and infant by HIV DNA PCR. If the mothers virus is not amplified by the primer set used, then another set or another test can be used to avoid a false negative result in the infant. Cord blood is not useful for the diagnosis because maternal cells may be present and may cause a false positive test result. In general, the disappearance of maternal IgG antibodies to HIV needs to be documented before HIV infection can be definitely excluded in the HIV-exposed child. Tests with an increased sensitivity to detect HIV antibodies are not useful as they may detect maternal antibodies up to 28 months of age leading to anxiety and confusion in the affected families (Nastouli 2007). There is a WHO draft for diagnosing HIV in infants aimed at the developing world (http://www.who.int/hiv/paediatric/infantdiagnosis.pdf).

Diagnosis of HIV infection > 18 months of age

HIV infection is diagnosed in an analogous way to adults (see chapter "HIV Testing").

When to initiate antiretroviral therapy

Keep the following facts in mind before starting antiretroviral therapy in children:

- Treatment of HIV-infected children is usually not an emergency.
- Take as much time as needed to decide whether to start with HAART or not.

Commencing antiretroviral therapy too early risks possible long-term side effects and early exhaustion of the limited supply of antiretroviral drugs that can be safely used in children. Therefore, many experts defer treatment in asymptomatic children with a low viral load and without immunodeficiency. The indication for treatment is based on CD4 count, viral load and clinical criteria. There are new WHO guidelines for resource-poor settings (www.who.int/hiv/pub/guidelines/art/en/index.html)

Table 3. PENTA recommendations on when to start antiretroviral therapy
http://www.ctu.mrc.ac.uk/penta/guidelines.htm

Infants
1. Clinical Start all infants with CDC stage B or C (AIDS) disease. 2. Surrogate marker Start all infants with CD4 % < 25–35 %. Strongly consider starting with a VL > 1 million copies/ml. Many experts treat all infants, whether symptomatic or not (with the aim of preventing HIV encephalopathy or other forms of disease progression).
Children aged 1–3 years
1. Clinical Start all children with stage C disease. 2. Surrogate marker Start all children with a CD4 % < 20 %. Strongly consider starting with a VL > 250,000 copies/ml.
Children aged 4–8 years
1. Clinical Start all children with stage C disease. 2. Surrogate marker data Start all children with a CD4 % < 15 %. Strongly consider starting with a VL > 250,000 copies/ml.
Children aged 9–12 years
1. Clinical Start all children with stage C disease. 2. Surrogate marker data Start all children with CD4 < 15 %, but with less urgency than in a younger child. Strongly consider starting with a VL > 250,000 copies/ml.
Adolescents aged 13–17 years

1. Clinical
   Start all adolescents with stage C disease.
2. Surrogate marker data
   Start all adolescents with an absolute CD4 count between 200 and 350 cells/mm^3.

In a meta analysis of 17 studies (Dunn D; HIV Paediatric Prognostic Markers Collaborative Study Group; HPPMC cohort) with 3,941 children who received no therapy or AZT monotherapy, viral load and CD4 cell counts proved to be independent prognostic markers for the end stage, AIDS or death (Dunn 2003). From this large cohort of children, a computer program has been generated which can be used to give the risk of progression to AIDS or death within 6/12 months according to the age and either CD4 count or viral load in the child ("PENTA Calculator" http://www.ctu.mrc.ac.uk/penta/hppmcs/calcProb.htm). Updated guidelines for treatment from Europe and the United States were published in 2004 (PENTA 2004 http://www.ctu.mrc.ac.uk/penta/; http://aidsinfo.nih.gov/guidelines/). The PENTA guidelines use the HPPMC cohort data to optimize timing of starting treatment at different ages, according to CD4 count / viral load, in order to maintain the 1-year risk of progression to AIDS at < 10 % and death at < 5 %. (tables 3, 4).

Table 4. US Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection (http://aidsinfo.nih.gov/guidelines);

A. Indications for Initiation of antiretroviral therapy in children < 12 months of age

Clinical Category		CD4 Cell Percentage	Plasma HIV RNA Copy Number [1]	Recommendation
Symptomatic (Clinical category A, B, or C)	*OR*	< 25 % (Immune category 2 or 3)	Any Value	Treat
Asymptomatic (Clinical category N)	*AND*	≥ 25 % (Immune category 1)	Any Value	Consider Treatment [2]

[1] Plasma HIV RNA levels are higher in HIV-infected infants than older infected children and adults. Because overall HIV RNA levels are high and overlap between infants who have and those who do not have rapid disease progression, HIV RNA levels may be difficult to interpret in infants < 12 months of age.

[2] Because HIV infection progresses more rapidly in infants than older children or adults, some experts would treat all HIV-infected infants < 6 months or < 12 months of age, regardless of clinical, immunologic or virologic parameters.

B. Indications for Initiation of Antiretroviral Therapy in Children ≥ 1 Year of Age

Clinical Category		$CD4^+$ Cell Percentage		Plasma HIV RNA Copy Number	Recommendation
AIDS (C)	**OR**	< 15 % (Immune Category 3)		Any value	Treat
Mild-Moderate Symptoms (A or B)	**OR**	15-25 % [1] (Immune Category 2)	**OR**	≥ 100,000 copies/ml [2]	Consider treatment
Asymptomatic (N)	**AND**	> 25 % (Immune Category 1)	**AND**	< 100,000 copies/ml [2]	Many experts would defer therapy and closely monitor clinical, immune, and viral parameters

[1] Many experts would initiate therapy if CD4 cell percentage is between 15 to 20 %, and defer therapy with increased monitoring frequency in children with CD4 cell percentage 21 % to 25 %.

[2] There is controversy among pediatric HIV experts regarding the plasma HIV RNA threshold warranting consideration of therapy in children in the absence of clinical or immune abnormalities; some experts would consider initiation of therapy in asymptomatic children if plasma HIV RNA levels were between 50,000 to 100,000 copies/ml.

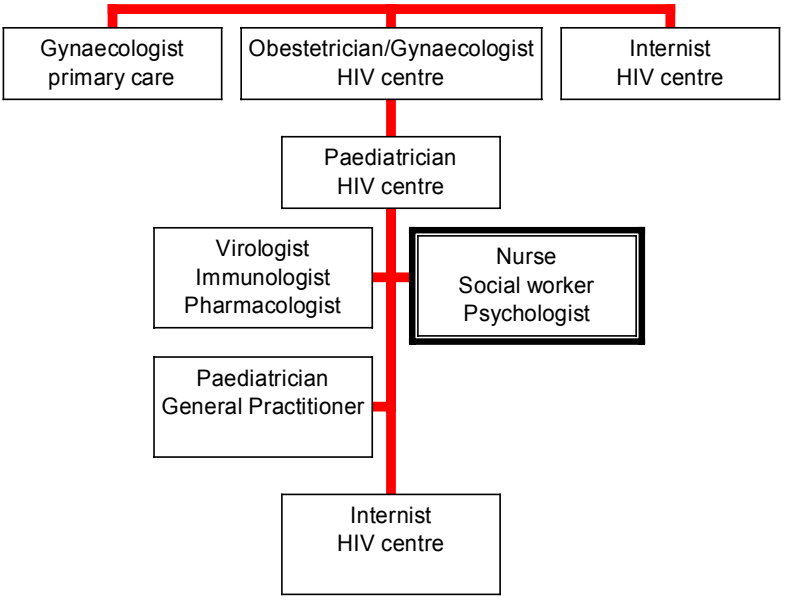
General considerations for treatment of HIV-infected children

The treatment of children with antiretroviral drugs is becoming increasingly complex. A successful treatment requires an interdisciplinary approach to the children and their families.

Antiretroviral therapy cannot be successful without good adherence to treatment. In the prospective PACTG 377, trial adherence was defined as having not missed a single medication dose over the last 3 days. According to this definition, only 70 % of children were found to be adherent (125 children within an observation period of 48 weeks; Van Dyke 2002). These data show that continuous motivation of children and their care providers is of high importance. The modalities of the daily intake of the medication need to be discussed in detail and adjusted to the daily and weekly routines of the family activities. Clear treatment goals need to be set, e.g. 90 % of the prescribed doses. Education of the patient and the family regarding the antiretroviral drugs is necessary. Sometimes a brief period of hospitalization at the start of antiretroviral therapy is useful to educate the patient and access the tolerability of the treatment regimen. Adherence is particularly problematic in adolescence. In this age group, adherence often needs a close follow up including other health care professions such as psychologists and social workers. Peer support may also be helpful for young people. Sometimes periods off ART, despite the risk of ill health, have to be accepted in this group of patients until the young person is ready to restart therapy themselves. A promising approach to increase adherence in children and adolescents is the availability of once-daily regimens: In the PACTG Study P1021 a once-daily regimen with Emtricitabine, Didanosine and Efavirenz was studied over ≥96 weeks in 37 treatment-naïve children (age 3 to 21 years) (McKinney 2007). This regimen resulted in a relatively high percentage of children having VL below

detection limit (70% after 2 years), but unfortunately the study lacked a comparator arm, e.g a twice-daily regimen.Underdosing has been shown to be a problem in day to day practice (Menson, 2006). Dosing by weight instead of body surface area (given as an alternative in some old guidelines) may result in underdosing and simply ongoing growth may not be adjusted for. This underlines the importance of frequent follow up especially for infants and toddlers on therapy when they are growing very fast and will need recalculation of their doses every 4-6 weeks. Particular genotypes are associated with hypermetabolism of of NNRTI's and PI's. Plasma levels of NNRTI's and PI's can be measured (pharmacologic drug monitoring) to detect interindividual differences in drug metabolism and lack of adherence. to exclude dosage that is too low and to prevent toxicity.

Figure 2: Interdisciplinary care for children and families who are affected by HIV



Obviously, regular physical examination and laboratory tests are necessary to monitor antiretroviral therapy in HIV children. Only a physician who is experienced in the care of HIV-infected children and the use of antiretroviral therapy will be able to provide adequate care. Before medication is initiated or changed, the decision should always be based on at least 2 independent blood samples. Infections and vaccinations may influence viral load and CD4 cell count. Therefore, it is not recommended to base decisions on data that have been gathered within 14 days of an infection or vaccination.

Strategy

At present, eradication of HIV cannot be achieved by the existing therapy. In some children, viral load remains below detection level for years and subsequently there are no more HIV-specific antibodies detectable in these children. Even in these children, ultra-sensitive assays can still detect HIV (Persaud 2004). Therefore risks and benefits of antiretroviral therapy have to be balanced in each child. Interruption or incomplete adherence may cause more harm than deferring the therapy. The decision to start antiretroviral therapy has fundamental consequences for the children and families. From this point on, it usually means that children need to take the medication for life. Structured treatment interruptions have not been tested in childhood and adolescence in controlled studies. A retrospective analysis of unplanned treatment interruptions in children demonstrated a significant decline of CD4 percentages by 6.6 % per year (Gibb 2004). PENTA (**P**ediatric **E**uropean **N**etwork for **T**reatment of **A**IDS) is currently undertaking a randomised paediatric study of CD4 guided treatment interruptions (PENTA 11).

Table 5 shows the current treatment concept for choosing antiretroviral drug combinations. In the American PACTG 338-study on 297 children, it has been shown that a PI-containing combination is more effective than a dual combination of 2 NRTI's. It appears useful to start with a combination that includes two substance classes (2NRTI's + PI or 2 NRTI's + NNRTI) in order to spare one or two substance classes for future change of antiretroviral therapy. If there is not full viral suppression on treatment, development of cross-resistance to NNRTIs and PIs is very likely. Therefore, sparing substance classes may be useful for a better long-term efficacy. It has been controversial whether all HIV infected infants should receive HAART. In the PACTG 256 study, an aggressive approach with inclusion of 3 substance classes (NRTI + NNRTI + PI) led to a highly effective and long-lasting virus load reduction (72 % of patients over 4 years), especially if therapy was started at an early age (< 3 months) (Luzuriaga 2004). Moreover, in the South African Study CHER, which examined the influence of early versus deferred HAART in infants, there is a much higher mortality in the deferred treatment arm (unpublished). Especially in the context of encephalopathy and high mortality rates these data suggest to start all infants on HAART what ever their CD4 count and whether or not they have any symptoms. Whether such early treatment in infancy needs to be continued long term beyond 1 or 2 years fo age is also being examined in the CHER trial.

As there are only small numbers of children and adolescents with HIV in Europe it is highly recommended to include all children who receive antiretroviral therapy in multicenter clinical trials (e. g. PENTA (**P**ediatric **E**uropean **N**etwork for **T**reatment of **A**IDS), http://www.pentatrials.org, Tel. Dr. Diana Gibb ++ 44 20 7670 4709; Lynda Harper ++ 44 20 7670 4791). The PENPACT 1 study with participation both of the PENTA and the PACTG group has now completed recruitment and results will be available in 2009 to This trial aims to answer the question whether initial therapy in children is more effective with 2 NRTI + PI or with 2 NRTI + NNRTI.

Table 5. Treatment concept in HIV-infected children

Regime	Recommendation
NRTI* 1 + NRTI 2 + PI** or NRTI 1 + NRTI 2 +NNRTI ***	Include children in multicenter clinical trials (e.g. PENPACT 1)

* = Nucleoside Reverse Transcriptase Inhibitor (Zidovudine (AZT), Didanosine (DDI), Lamivudine (3TC), Stavudine (D4T), Abacavir (ABC), Emtricitabine (FTV), Tenofovir).

** = Protease Inhibitor (Nelfinavir (NFV), Lopinavir/r (LPV/RTV), Atazanavir (ATV) Indinavir (IDV), Amprenavir (APV). Ritonavir as booster drug).

*** = Non-nucleoside Reverse Transcriptase Inhibitor (Nevirapine (NVP), Efavirenz (EFV)).

In the placebo-controlled American CNAA3006 study on children who had already received antiretroviral therapy, a triple NRTI therapy was shown to be more effective than a therapy consisting of 2 NRTI's (Saez-Llorens 2001). However, this study was carried out on children who were already on antiretroviral therapy and were not treatment naive. Data in adults suggest that a triple NRTI strategy is less effective than a therapy combination including PI or NNRTI. At present there are no data on triple NRTI therapy as initial therapy for children.

Classes of Antiretrovirals

In the following paragraphs the different antiretroviral classes that are currently used in children are introduced with emphasis on Pediatric issues and in particular daily dosage, relation to food intake (unless the drug can be taken independent of meals) and side effects. All drugs can lead to nausea, vomiting, fever, headache, diarrhea, rash and anorexia.

Nucleos(t)ide analog reverse transcriptase inhibitors (NRTIs)

NRTIs have been used for over 15 years in the treatment of HIV-infected children. The combination of 2 NRTIs as part of HAART is effective and well tolerated. Severe side effects are rare but potentially life-threatening, such as lactic acidosis and hepatic steatosis. Other side effects are neuromuscular dysfunction, cardiomyopathy, pancytopenia, pancreatitis and neuropathy. All of these effects are probably related to mitochondrial toxicity caused by NRTIs. Due to pharmacologic and antiviral antagonism as well as synergistic neurotoxicity, the following combinations are not recommended: AZT + D4T, DDI +D4T (not first line), and FTC + 3TC. The less mitochondrially toxic NRTI's include 3TC, ABC, FTC and TDF.

Zidovudine (ZDV, AZT, Retrovir™) is available as syrup, capsules, tablets and concentrate for injection or intravenous infusion. Dosage is 180 mg/m² orally every 12 hours. Maximum dosage is 300 mg every 12 hours.

Lamivudine (3TC, Epivir™) is available as oral solution and tablets. Dosage is 4 mg/kg every 12 hours, maximum dosage is 150 mg every 12 hours. In older children and adolescents (> 35 kg body weight) combination with Zidovudine (Combivir™) or Abacavir (Kivexa™/US: Epzicom™) can be used and daily pill burden reduced. In adults, lamivudine shows antiviral activity against hepatitis B virus. In

HIV negative children with chronic Hepatitis B early initiation of Lamivudine appears to achieve a high HBe and HBs conversion rate(Choe 2007). There are no data in HBV and HIV coinfected children. A once-daily regimen in combination with abacavir has been shown to be as effective as twice daily (Bergshoeff, 2005) (PENTA 13 Trial).

Didanosine (DDI, Dideoxyinosine, Videx™) is available as oral solution and tablets. Dosage is 200 mg/m^2 once daily. Maximum dosage is 400 mg (body weight $\geq$ 60 kg) or 250 mg (body weight < 60 kg). It should be taken on an empty stomach. NB need to dose adjust DDI with TDF

Abacavir (ABC, Ziagen™) is available as oral solution and tablets. Dosage is 8 mg/kg every 12 hours, maximum dosage is 300 mg twice daily or 600 mg once daily. In the PENTA 5 trial, the NRTI back bone of ABC+3TC showed a better efficacy regarding viral load suppression than AZT+ABAC and AZT+3TC. There is a potential risk of a fatal hypersensitivity reaction. If ABC hypersensitivity occurs and the drug is stopped, it should not be restarted as, rarely, deaths have occurred in adults upon rechallenge HLA B5701 appears to be associated with hypersensitivity and HLA testing before starting ABC is useful, an alternative NRTI should be used in HLA B5701 positive children.In the PENTA 15 study the pharmacokinetics, feasibility and acceptability of dosing ABC or ABC in combination with 3TC once daily in children aged 3 months to <36 months is being assessed.

Emtricitabine (FTC, Emtriva™) is available as capsules and oral solution. Dosage is 6 mg/kg is . The administration of capsules results in a 20 % higher plasma level. Emtricitabine can be given once daily. Maximum dosage is 200 mg once daily.

Tenofovir (TDF, Viread™) is currently only available as tablets (300mg). In 18 children and adolescents between 6 and 16 years of age, a dosage of 200 mg/m^2 once daily was well tolerated (Hazra 2004). It should be taken with meals. There are no controlled trials regarding the efficacy of tenofovir in children. Tenofovir has been shown to have metabolic renal and bone side effects which may be significant for children and should be monitored closely. Tenofovir is also effective for treatment of HBV. In children co-infected with HIV and HVB who require treatment for HIV the NRTI backbone of TDF+FTC (Truvada) should be considered as this will be effective against both viruses.

Stavudine (D4T, Zerit™) is available as oral solution and capsules. Dosage is 1 mg/kg every 12 hours. Maximum dosage is 40 mg every 12 hours. It should be taken on an empty stomach. D4T is not recommended for first-line therapy as it has a high risk of causing lipoatrophy.

Non nucleoside reverse transcriptase inhibitors (NNRTIs)

These drugs have a low genetic barrier to resistance. Within a few weeks suboptimal dosing or adherence can lead to cross-class resistance mutations affecting all available NNRTIs. NNRTIs exist in palatable liquid preparations which are easier for children to tolerate than the liquid PI solutions. It has to be kept in mind that single dose nevirapine exposure as part of the perinatal transmission prophylaxis may affect subsequent treatment response, if NNRTIs are used in an initial regimen for infants (Lockman 2007).

Efavirenz (EFV, Sustiva™) is available as capsules and oral solution. Dosage is 200 mg (body weight 10-15 kg), 250 mg (15-20 kg), 300 mg (20-25 kg), 350 mg (25-33 kg), 400 mg (33-40 kg), 600 mg (> 40 kg) once daily. Maximum dosage is 600 mg once daily. It should be taken on an empty stomach. High fat meals should be avoided. When using the solution, a 20 % higher dosage than for capsules is necessary. Central nervous system symptoms (somnolence, insomnia, abnormal dreams, confusion, abnormal thinking, concentration, amnesia, agitation, depersonalization, hallucinations, euphoria) appear to be more common in adults than in children. Skin rash is observed in < 10 % of the patients and is rarely severe, it usually disappears within days despite continuation of efavirenz. Efavirenz may cause raised lipids in some patients.

Nevirapine (NVP, Viramune™) is available as tablets and suspension. Dosage is 150 mg/m^2 once daily for 14 days, followed by 150 mg/m^2 every 12 hours, if liver function tests are normal. In a retrospective analysis, once-daily application – 300 mg/m^2 after week 2 – was as effective as twice-daily (Verweel 2003). The most common side effect of nevirapine, in up to 16 % of children during the first weeks of treatment, is a skin rash, which may be quite severe (8 %) and require hospitalization. Life-threatening complications (Steven Johnson Syndrome, toxic epidermal necrolysis) are rare. Hepatotoxicity may also occur, and fatal cases have been reported in adults, but this appears to be less common in children.

Protease inhibitors (PIs)

All protease inhibitors can be used in combination with 2 NRTIs. PIs differ from each other in respect to their tolerability and side effects. As with adults, dyslipidemia is associated with the use of protease inhibitors (Lainka 2002). It includes elevated total cholesterol, triglycerides (TG), and low density lipoprotein cholesterol (LDL-c) and decreases in high density lipoprotein cholesterol (HDL-c) In lipodystrophy, there is a loss of subcutaneous fat (lipoatrophy) and/or a deposition of fat tissue subcutaneously or in visceral stores (lipohypertrophy) including the presence of dorsocervical fat accumulation ("buffalo hump") and increased waist-to-hip ratio. Lipoatrophy is marked by thinning of subcutaneous fat in the face, buttocks, and extremities associated with a prominent appearance of peripheral veins. The body habitus changes usually occur gradually over months to years. The exact prevalence of lipodystrophy in children is unknown and there are no clear diagnostic criteria. Lipodystrophy and dyslipidemia coexist, their interconnection is unclear. Other substance classes such as NRTIs (e.g. stavudine) and NNRTIs (efavirenz, not nevirapine) may also play a role in the pathogenesis of lipodystrophy. Insulin resistance is another side effect which may present with or without fasting hyperglycemia, with new onset diabetes mellitus and exacerbations of pre-existing diabetes. Moreover, PIs may influence bone mineral density and metabolism (Mora 2004). Taken together, the long-term consequences of PI-containing antiretroviral therapy for growth and development of the child are currently not known.

Lopinavir / Ritonavir (LPV/r, Kaletra™) is a co-formulation of lopinavir and ritonavir, in which ritonavir acts as a pharmacokinetic enhancer (booster). It is available as capsules, tablets and oral solution. In therapy-naive and -experienced chil-

dren, the combination of LPV/r and NRTI or NNRTI shows a high efficacy (Saez-Llorens 2003, Fraaij 2004). The dosage is 230-300mg/m2 (most centres use the higher dose) or 13 mg/kg lopinavir/3.25 mg/kg ritonavir twice daily (bodyweight 7 - < 15 kg), 11 mg/2.75 mg (15-50 kg), 533 mg/133 mg (> 50 kg). It should be taken with meals. The dosage of LPV/r may need to be increased by up to 30 % when combined with a NNRTI, and therapeutic drug monitoring is useful in this situation.

Nelfinavir (NFV, Viracept™) is available as tablets and powder. It is well tolerated in most children. The dosage is 55 mg/kg every 12 hours, but in infants < 3 months 75 mg/kg every 12 hours is required. Maximum dosage is 1,250 mg every 12 hours. Some older children require 1,500 mg every 12 hours, more than the adult dose. Therapeutic drug monitoring is useful. In the PENTA 7 trial in newborns and infants below the age of 3 months, combination of nelfinavir with D4T and DDI was poorly absorbed with poor plasma levels and consequently poor viral load suppression (Aboulker 2004). It should be taken with meals. The most common side effect is diarrhea, which rarely causes discontinuation of the drug. To facilitate the administration of nelfinavir, the tablets can be crushed or readily dissolved in water. In the PENTA 5 study, nelfinavir powder was only poorly tolerated.

In May 2007 a contamination of NFV with a genotoxic/carcinogenic agent ethyl mesylate (also known as methane sulfonic acid ethylester) occurred, which is a by-product of manufacture and was found in some batches of nelfavinavir manufactured in Europe. Children were either switched to an other agent or NFV from the manufacturer in the US was imported. International registeries of children in Europe treated with Nelfinavir, or exposed to Nelfinavir whilst in utero are going to be set up to follow children for any side effects of possible exposure.

Amprenavir (APV, Agenerase™) is not recommended for children < 4 years of age. It is available as capsules and oral solution. Capsule dosage is 20 mg/kg every 12 hours, for the oral solution 22.5 mg/kg every 12 hours. The maximum dosage is 1,200 mg every 12 hours. The dosage of amprenavir needs to be increased by 30 % in case of combination with NNRTI. In 5 children, who were intensively pretreated, amprenavir in combination with delavirdine showed good efficacy (Engelhorn 2004). The most common side effects are nausea, vomiting, diarrhea and headaches. The prodrug of amprenavir is fosamprenavir, which is currently used for antiretroviral therapy in adults at a dosage of 1,400 mg twice daily (without ritonavir) or 1,400 mg + ritonavir 200 mg once daily. It should be taken with meals. There is no pediatric dose. The drug is currently under investigation for use in HIV-infected children. Fosamprenavir is usually prescribed with ritoanvir boosting to increase bioavailable levels.

Ritonavir (RTV, Norvir™) is available as oral solution or capsules. However, most children do not tolerate the taste of the oral solution. The dosage is 350-400 mg/m² every 12 hours, maximum dosage 600 mg every 12 hours. It should be taken with meals. Today, ritonavir is almost exclusively used as a drug to boost other protease inhibitors, and for this purpose, the dosage is 75 mg/m² every 12 hours.

Indinavir (IDV, Crixivan™) is available as capsules. Dosage is 500 mg/m² every 12 hours in combination with ritonavir 750 mg/m² every 12 hours. It should be

taken on an empty stomach. Side effects include nephrolithiasis, especially at high plasma levels.

Saquinavir (SQV, Invirase™ hard gel capsule or Fortovase™ softgel capsule). Dosage in children is unknown. There is very limited experience with 50 mg/kg every 12 hours. Saquinavir should only be used in combination with ritonavir because of poor bioavailability. It should be taken with meals.

Atazanavir (ATV, Reyataz™) is available as capsules. It should be taken with meals. Atazanavir could be an interesting drug for use in children in the future, because of its once-daily application and lower incidence of dyslipidemia. At present, there is no approved dosage for children. Phase I and II studies are underway. Some patients develop jaundice. Better levels of atazanivir are obtained with ritonivir boosting.

Tipranavir (TPV, Aptivus™) is available as 250mg soft gel capsules. It should be taken with meals. At present, there is no approved dosage for children and it has been associated with significant hepatotoxicity in adults. Phase I and II studies in children are being conducted.

Fusion inhibitors

Fusion inhibitors prevent the fusion of the virus with the target cell. In adults, randomized studies have proven an effect of T-20 (the first drug of this substance class) within salvage treatment protocols.

Enfuvirtide (T-20, Fuzeon™) can be used in children older than 6 years of age. The drug is injected subcutaneously at a dosage of 2 mg/kg every 12 hours. A study with 14 children showed no severe side effects, but after a 2-year treatment duration only 6 out of 14 children stayed on this therapy (Church 2004). Reasons for treatment discontinuations were aversion to injections, local injection site reactions, inefficient viral load suppression, thrombocytopenia and edema. There are no controlled studies on the use of T-20 in children.

Drug interaction

There are a great number of interactions, which may complicate antiretroviral therapy when it is co-administered with other drugs. In particular, tuberculosis and atypical mycobacterial treatment may interact with ART, so close monitoring and expert advice should be sought.

Monitoring of therapy efficacy and therapy failure

A good treatment response is documented by a permanent suppression of the viral load below the detection limit. Not all children achieve complete viral suppression, and development of resistance is not uncommon due to the selection pressure of the anti-HIV immune response as well as antiretroviral therapy. There is no commonly used definition of treatment failure in children treated with antiretroviral drugs. Therefore, it is also not certain when to change antiretroviral therapy. In the PENPACT 1 study, this important question is being addressed: children are ran-

domized to change a failing treatment at either low or high viral rebound (> 1,000 or > 30,000 copies/ml) Alternatively, therapy failure can be defined by a decrease in CD4 cell counts, e.g. a decrease by at least a third of the absolute CD4 cell number in less than 6 months. In children with relatively low CD4 cell counts of less than 15 %, a decrease by more than 5 % may already be significant for therapy failure. The use of clinical criteria, such as toxicity of the drugs, a progression within the CDC classification, an increased susceptibility to infections, encephalopathy and failure to thrive, may all indicate treatment failure.

Many children with multi-disciplicnary support do now manage to maintain longterm (> 5 years) viral suppression on first line therapy, and the longer this can be maintained on first line therapy the better. Indeed over the last few years as more treatments have become available for children they have been increasingly successful with treatment. The most common cause of treatment failure is insufficient adherence, which can be found in up to 25-30 % of children. Assessment of adherence may be difficult as questionnaires may not be reliable. Determination of plasma levels and resistance tests (e.g. reoccurrence of wild type) are other options to assess adherence and monitor antiretroviral therapy more effectively.

Change of therapy

There are no systematic data on how and when to change therapy in HIV-infected children. The suppression of viral load that can be reached by a second or third regimen depends on the preceding therapy and the resistance status. The longer and more intensive pretreatment has been, the lower the viral load reduction that can be expected. When a new antiretroviral drug combination is introduced, the age of the child, the availability of appropriate formulations (e.g. solution for infants), side effects and interactions with other drugs are all taken into account. At present, it is unclear whether dyslipidemia and lipodystrophy can be influenced by a change from a PI-containing regimen to an NNRTI-containing HAART (McComsey 2003). In adults, randomized and prospective trials have shown that a change of antiretroviral therapy guided by resistance tests leads to a better treatment response. In children there is a smaller prospective study (Englund 2004). Usually, the initial treatment regimen contains a double NRTI backbone (e.g. AZT + 3TC or AB

C + 3TC). When changing therapy, it appears useful to introduce a backbone with two new NRTI's and one new substance class into the treatment combination. A mega-HAART therapy combining five to six antiretroviral drugs has not been systematically investigated in children. In single cases, it may be useful to introduce up to five drugs if treatment failure has occurred despite multiple different drug regimens.

Supportive therapy and prophylaxis

Opportunistic infections have become rare in perinatally infected children who experience immune reconstitution with successful HAART. In most of these HIV infected children respiratory and other infections are not more common than in healthy children. HIV infected children who are treated with HAART and who are clinically stable can even be given live varicella virus vaccine and show a specific response, which is an impressive sign of successful immune reconstitution (Arme-

ninan, 2006). In the vast majority of stable treated children treatment with i.v. immunoglobulins and PCP prophylaxis is no longer required (Nachman 2005b).

However, there are still life-threatening infections and deaths from HIV, if perinatal HIV infection is unrecognised or HAART has not yet led to immune reconstitution. A description of such infections in adults is given in other chapters of this book. An excellent and detailed guide for treatment of children with opportunistic infections can be found at

http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5314a1.htm.

Conclusion

In many aspects, HIV infection in children is different from HIV infection in adults. The ongoing growth and development of children, their viral dynamics and immaturity of the immune system result in a different response to HIV in children compared to adults. This has important consequences for diagnosis and treatment of HIV in children. The aim of the therapy is to reach maximum efficacy while avoiding long-term side effects. Sustained success in the treatment of children with HIV infection can be achieved by:

- a multidisciplinary approach;
- standardized treatment protocols;
- participation in multicenter trials;
- development of new drugs and strategies for children.

In developed countries, the clinical picture of HIV infection in children has now changed from an often fatal to a treatable chronic infection. This picture is entirely different in developing countries, where the majority of children do not have access to HAART (Prendergast 2007). According to the WHO, 380,000 children died from HIV infection or its sequelae in the year 2006, a disease that can be treated and, more importantly, prevented.

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Part 3

AIDS

12. Opportunistic Infections (OIs)

Christian Hoffmann

OIs in the HAART era

In Western industrialized countries, many OIs have become rare today. This is particularly true for those infections that are associated with severe immunodeficiency, such as CMV and MAC disease. The incidence of these OIs has now been reduced to less than one tenth of their frequency in the pre-HAART era. However, HAART has not only lowered the incidence, but also changed the course of OIs quite considerably. While survival times after the first AIDS illness were seldom more than three years, many patients now live with AIDS for ten years and longer. Our own study demonstrates this: while 5-year survival after an episode of cerebral toxoplasmosis was 7 % in the years 1990-1993, it climbed to 29 % by 1994-1996. This rate has risen to approximately 78 % since 1997 (Hoffmann 2007).

More than half of the patients who develop AIDS today are unaware of their HIV infection status. Due to various reasons, the remainder of patients, with a few exceptions, was not treated with antiretroviral drugs until AIDS was diagnosed. These patients often present late, usually in a very serious condition. AIDS remains life threatening, and a severe PCP does not become less critical because of the overall improvement in long-term survival. The acute danger remains. Therefore, every HIV clinician should be familiar with the diagnosis and therapy of OIs, even today.

Although much has improved in recent years, many problems remain. There is still no adequate treatment available for diseases such as PML or cryptosporidiosis, and resistance will become an increasing problem with other infections. HAART does not always lead to immediate improvement, and may even complicate things because of the atypical course of disease under HAART, as well as with immune reconstitution. For this reason, we have included a separate sub-chapter on immune reconstitution syndrome (IRIS). There are still no guidelines for OI prophylaxis in many countries, and the US recommendations, last published in December 2004 (Benson 2004), cannot always be simply adopted elsewhere, as seroprevalence rates often differ. In addition, it is becoming clear that nearly every type of prophylaxis or maintenance therapy can be discontinued when a sufficient level of immune reconstitution has been reached.

In many places, diagnostic problems recur again and again for many OIs, perhaps with the exception of larger HIV centers, in which laboratory doctors and pathologists “voluntarily” work with HIV and its complications. Those unfamiliar with the pathogens will not recognize them! Therefore, we only recommend that any specimens be sent to specialized laboratories (for German centers, see http://www.rki.de). Further advice, if needed, can also be sought from a specialized clinician or a clinical HIV center.

The most important rule remains true even today for almost all OIs: the poorer the immune status of the patient, the earlier the invasive diagnostic procedures should be! The primary aim should not be to spare patients investigations involving un-

pleasant procedures. If nothing can be found the first time around, diagnostic tests must be repeated. Treatment should be initiated as rapidly as possible.

The second rule: in many cases, a number of OIs can largely be excluded if the immune status is known. Knowledge of the current status is therefore important! Table 1 shows cut-offs for CD4 cells, below which particular infections can be expected. The occurrence of OIs above the cut-off values is usually the exception.

Table 1. Cut-offs for CD4 T-cells, above which particular AIDS illnesses are improbable. These CD4 counts are only reference values; exceptions are possible.

No cut-off	Kaposi's sarcoma, pulmonary TB, HZV, bacterial pneumonia, lymphoma
< 250/μl	PCP, esophageal candidiasis, PML, HSV
< 100/μl	Cerebral toxoplasmosis, HIV encephalopathy, cryptococcosis, miliary tuberculosis
< 50/μl	CMV retinitis, atypical mycobacteriosis

The third rule: if not already in place, HAART should be started as quickly as possible in the presence of an OI. Immune reconstitution is the best protection against relapses. It will also protect against further OIs. However, the optimal start is still not clear. Occasionally, it may be better to wait for a few days or even weeks with acute OI therapies which are often toxic and highly interactive. This applies to PCP, CMV retinitis, or toxoplasmosis. On the other hand, treatment of esophageal candidiasis or a herpes infection is usually no reason to delay HAART. For some OIs, such as PML or cryptosporidiosis, which have no specific therapy, HAART is the only hope. In these cases in particular, there is no time to lose.

The following is intended as a relevant practical overview, and will not include clinical rarities. The literature cited refers to interesting reviews and almost exclusively to controlled and, if possible, randomized studies.

OI reviews

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Pneumocystis pneumonia (PCP)

PCP is still one of the most frequent OIs. This interstitial pneumonia, from which most patients died in the early years of the HIV epidemic, is caused by pneumocysts. In the last 20 years, knowledge about this organism has significantly progressed, especially through DNA analysis (detailed review in: Thomas 2004). Although Pneumocystis was previously classified as a protozoan, it was established in 1988 that it is in fact an unusual type of fungus (Edman 1988). In the 1990s, it was recognized that every host, whether rat, mouse, monkey or human, has its own specific pneumocysts. It also became clear that the species *Pneumocystis carinii*, first described by the Italian Antonio Carini in 1910, does not occur in humans at all, but only in rats. The species that affects humans is no longer referred to as *P. carinii*, but is named *P. jiroveci* after the parasitologist Otto Jirovec. The term "carinii" has now been removed from the name for the pneumonia, although the abbreviation, PCP, remains the same (Stringer 2002).

The majority of patients diagnosed with PCP are not pre-treated with antiretroviral drugs, even today, and many of these do not know of their HIV infection status (or do not want to). PCP is a life-threatening disease, which should be treated by an HIV specialist. It often requires mechanical ventilation and still continues to have a high fatality rate. Older patients have a particularly high mortality risk (Benfield 2001). The relapses that were frequently seen in the past have become rare, thanks to HAART and prophylaxis. Scar tissue formation may result in susceptibility to recurring pneumothoraces. PCP may also rarely occur in relation to an immune reconstitution syndrome (see below).

Extrapulmonary pneumocystis infection is very rare. Although it can principally be located anywhere (kidneys, abdomen, meninges, bones, middle ear), it preferably affects the liver. Disseminated cases are also possible, but are usually first diagnosed on post mortem.

Signs and symptoms

The classic triad of PCP symptoms consists of: dry cough, subfebrile temperatures and gradual onset of dyspnea on exertion (Ask patients specifically! Respiratory rate!). A subacute course is typical. This often allows differentiation from bacterial pneumonia (Productive cough! Dyspnea less likely! Acutely high fever and pain!). Often there is significant oral thrush. Weight loss of several kilograms in the weeks before is also common. Symptoms may be even more subtle in cases with suboptimal prophylaxis (rare).

Often, weeks or sometimes even months may go by before the diagnosis of PCP is made. It is important to note that decompensation – as with all interstitial pneumonias – often occurs more quickly than expected. It is not rare that a patient suddenly requires ventilation after weeks of antibiotic therapy (even broad spectrum antibiotics don't help!) prescribed by the primary health care provider. A patient with significant exertional dyspnea or resting dyspnea must be sent to hospital immediately.

Diagnosis

If there is clinical suspicion of PCP, physical examination (Respiratory rate? Unremarkable auscultation? Oral thrush?) should be followed without delay by a chest x-ray and, if possible, high resolution computed tomography (HR-CT) of the lungs. The chest x-ray often shows relatively characteristic findings with a butterfly-shaped (perihilar) interstitial infiltrate. In the early stages, the focus is on the mid and lower fields. Indistinct, diffuse changes are more easily visible on HR-CT than on chest x-ray. A CT scan also allows a fairly certain distinction from other pulmonary infections (Hidalgo 2003).

However, if nothing pathological is visible on CT (experience of radiologist?), rapid initiation of treatment is justified even without a definitive diagnosis – particularly in the presence of the classic triad of symptoms, low CD4 cell count and no previous prophylaxis. There is almost always partial respiratory insufficiency, which should be confirmed by arterial blood gas analysis. Lactate dehydrogenase (LDH) is often elevated and may have limited use as a parameter for the course of disease. A high LDH is an unfavorable sign and reflects, even if not precisely, the severity of the PCP. In contrast, CRP is usually normal, provided there are no other concurrent infections.

Sputum specimens are generally not useful (review: Cruciani 2002), so that a bronchoalveolar lavage (BAL) is usually necessary. This can lead to confirmation, even several days after the start of therapy; but, it is not essential to wait for the BAL to start treatment. However, Pneumocystis can be easily missed, so that specimens should always be sent to an experienced laboratory. The laboratory must be alerted to the suspicion of PCP. Performing an early BAL also allows for the timely diagnosis of co-infections (CMV, pneumococci). It should be noted that respiratory insufficiency can deteriorate with BAL. Full blood count, transaminases and kidney function must be monitored during treatment and baseline values should be determined beforehand.

Newer diagnostic approaches include antibody testing (Bishop 2003) and measurement of S-adenosylmethionine, a substance that pneumocysts require but cannot produce. S-adenosylmethionine levels are reduced in patients with PCP (Skelly 2003). It is currently not foreseeable, whether these tests, which spare patients the discomfort of bronchoscopy, will be available as routine diagnostic tests in the future.

Treatment

General

Treatment should be initiated immediately if there is clinical suspicion. In cases of mild PCP (BGA: $PO_2 > 70$-80 mm Hg), ambulatory treatment can be attempted; oral medication can even be administered in very mild forms. This may well be possible in cooperation with a competent HIV nursing service. If such monitoring is not possible, if respiratory deterioration occurs, and in every case with resting dyspnea, immediate hospitalization is advised. If ventilation becomes necessary, patients have a poor prognosis, even today. Non-invasive methods (such as CPAP)

may be beneficial if used from an early stage. This helps particularly in prevention of pneumothoraces (Confalonieri 2002).

Initiation of HAART is usually postponed in ART-naïve patients until the PCP has resolved. In some countries, HAART and PCP-therapy are often administered concurrently. A general recommendation cannot be given at present. A retrospective study showed improved survival in patients who began HAART while hospitalized (Morris 2003). Disadvantages of this approach include possible cumulative toxicities and allergies, which may necessitate discontinuation of both PCP and HIV treatment (Watson 2002).

Drugs

Acute therapy should last for 21 days. The drug of choice is co-trimoxazole. The dose of three 960 mg tablets three times daily is only possible in milder cases. However, these higher oral doses are also associated with poor gastrointestinal tolerability. All severe cases should be treated intravenously in hospital. Due to possible clinical deterioration, which is probably a result of the bursting of pneumocysts in the alveoli, 20-40 mg prednisone bid should always be simultaneously co-administered with the PCP therapy for 5-10 days. Physicians should not hesitate to use steroids especially with worsening blood gases. The mortality risk is halved in patients with severe PCP and significantly less patients need intubation (Briel 2006). Clinical deterioration during the first week of treatment is still not uncommon. Initial treatment should be re-evaluated after one week at the earliest, and only after exclusion of co-infections such as CMV.

On high doses of co-trimoxazole, full blood count, electrolytes, renal function parameters and transaminases have to be monitored at least three times a week. The main problems in addition to myelotoxicity, liver and kidney problems include a rash that usually occurs after the middle of the second week of treatment, often accompanied by drug fever. Patients should be examined daily for skin changes. If such an exanthema occurs, one can attempt to interrupt treatment for one or two days, and then continue with half the dose under antihistamines and steroids. Otherwise, co-trimoxazole must be discontinued and replaced with alternative treatments.

All alternatives to co-trimoxazole are less effective. In cases of intolerability or history of sulfonamide allergy, intravenous pentamidine is recommended as the drug of second choice. An induction therapy is administered over the first few days (200-300 mg in 500 ml 5 % glucose or 0.9 % NaCl), and half the dose can then be given from day 6. This treatment is very toxic, which is why we have not used it for many years. Severe decompensations of electrolyte and blood glucose levels (both hyper- and hypoglycemia) are possible, as well as pancreatitis, arrhythmia and renal failure. Initially, blood glucose, electrolytes and renal parameters should be monitored daily.

In very mild cases of PCP, inhalative treatment with daily pentamidine inhalations (300-600 mg daily for three weeks) can be attempted (Arasteh 1990, Montgomery 1995). However, the experiences have not all been positive (Conte 1990, Soo 1990), and the current US guidelines advise against inhalatory acute therapy (Benson 2004). Instead of pentamidine, treatment with atovaquone suspension (better than the tablets used in the past) or a combination of clindamycin and primaquine is

possible. However, data on these alternative therapies is only available for mild to moderately severe cases of PCP (Hughes 1993, Dohn 1994, Toma 1998). Primaquine is no longer licensed in many countries, although it can be supplied through international pharmacies. A recently published analysis of the studies on the second-line therapy of PCP came to the conclusion that clindamycin plus primaquine was the best combination; but the sample size for both groups was small (Benfield 2006).

In the past few years, we have used many alternative substances (intravenous pentamidine, atovaquone, clindamycin, primaquine) in exceptional cases only. Instead, we have changed to treating with high dose co-trimoxazole for as long as possible (every day with co-trimoxazole is a good day!). A 10-day initial therapy is achievable in almost all patients, most of whom are then already significantly better. If exanthema or toxicity forces the interruption of co-trimoxazole between day 10 and 14, daily pentamidine inhalation is called into question in the third and last week of acute therapy. As this is not toxic, it can usually be started in parallel to HAART. However, a study on this strategy has not yet been published.

Prophylaxis

Patients with less than 200 CD4 cells/µl (CD4 cells < 14 % of the total lymphocyte count) are at risk and need prophylaxis, ideally with co-trimoxazole. Daily dosing may be slightly more effective than giving the dose three times weekly (El Sadr 1999). Gradual introduction over 14 days is supposed to prevent allergies, but is cumbersome (Para 2000).

When a moderate allergy to co-trimoxazole occurs, desensitization is possible (Leoung 2001), and should definitely be attempted. Although dapsone and pentamidine inhalations are almost equally effective (Bozzette 1995, Bucher 1997), co-trimoxazole prophylaxis is better for preventing bacterial infections such as enteritis and pneumonia (DiRienzo 2002). More importantly, co-trimoxazole also provides reliable protection for toxoplasmosis.

Pediatric co-trimoxazole suspension can be used for desensitization, by slowly increasing exposure within six days from 12.5, 25, 37.5, 50 and 75 to 100 % of the dose in the 480 mg tablet. In a study of almost 200 patients, no cases of severe allergy occurred, and there was a reduction of fever and headaches. Approximately three quarters of all patients are thus able to "tolerate" co-trimoxazole again. However, re-exposure should only be attempted after an interval of eight weeks (Leoung 2001).

Monthly inhalation of pentamidine is a well-tolerated alternative. Coughing may occur, asthma attacks are rare, and pneumothoraces even rarer. A suitable inhalation system should be used after administration of a beta-sympathomimetic to dilate the bronchi (e.g. Respigard II™, not Pariboy™!). The loading dose (300 mg tid for the first 5 days) conventionally used in the past is no longer a universal standard. In patients with pulmonary disease, inhalation is probably less effective.

All other options are problematic. Dapsone has poor gastrointestinal tolerability, is quite myelotoxic and often leads to elevation of LDH. LDH, an important diagnostic parameter, can therefore not be utilized under treatment with dapsone (Ioannidis 1996). Atovaquone was of similar efficacy to co-trimoxazole, dapsone and pentamidine in two multicenter studies (El-Sadr 1998, Chan 1999), and since then, is

considered to be a good alternative. The oral suspension has better tolerability than the tablet formulation (Rosenberg 2001). A significant disadvantage of atovaquone for long-term prophylaxis is the disproportionately high cost.

PCP prophylaxis regimens can be discontinued fairly safely with sufficient immune reconstitution: more than 200 CD4 cells/µl for three months (Schneider 1999, Wewerling 1999, Lopez 2001). In individual cases, PCP has been described after stopping prophylaxis with CD4-cell counts greater than 200/µl (Degen 2002, Mussini 2003). By stopping therapy, not only are the side effects and costs reduced, but resistances are also prevented: the proportion of co-trimoxazole resistant bacteria increases continuously in HIV patients (Martin 1999).

Treatment/Prophylaxis of PCP
(daily doses, if not specified otherwise)

Acute therapy		Duration: always at least three weeks
Severe to moderately severe PCP	Co-trimoxazole	Co-trimoxazole 4-5 amp. à 480 mg tid **plus** prednisolone 2–2–0 tbl. à 20 mg (5-10 days)
Mild PCP	Co-trimoxazole	Co-trimoxazole 3 tbl. à 960 mg tid
Alternatives	Pentamidine	Pentamidine 200-300 mg i.v. for 5 days (4 mg/kg), then halve dose In very mild cases: daily inhalations with 300 mg
	Atovaquone	Atovaquone suspension 5-10 ml bid (750–1500 mg bid)
	Clindamycin + Primaquine	Clindamycin 1 amp. à 600 mg i.v. q 6-8 h plus primaquine 1 tbl à 30 mg qd
Prophylaxis		Below 200 CD4+ T-cells/µl; after PCP episode
First choice	Co-trimoxazole	Co-trimoxazole 1 tbl. à 480 mg qd or Co-trimoxazole 1 tbl. à 960 mg 3 x/week
Alternatives	Pentamidine	Pentamidine inhalation 300 mg 1-2 x/month
	Dapsone	Dapsone 2 tbl. à 50 mg qd
	Dapsone + Pyrimethamine	Dapsone 1 tbl. à 50 mg qd **plus** pyrimethamine 2 tbl. à 25 mg/week **plus** leucovorin 2 tbl. à 15 mg/week
	Atovaquone	Atovaquone suspension 5 ml bid (750 mg bid)

The worldwide use of co-trimoxazole has also affected pneumocysts. Resistance analyses were previously difficult, as this organism, even almost 100 years after its discovery, can still not be cultured. However, today it is possible to sequence sections of the genome encoding for dihydropteroate synthetase (DHPS). DHPS is an important enzyme involved in the folate metabolism of many organisms, and is targeted by sulfonamides such as sulfamethoxazole (SMX) and dapsone. The first mutations in the DHPS gene in pneumocysts were discovered in 1997. A larger study showed DHPS mutations in 43 %, in contrast to the gene region for dihydrofolate reductase (DHFR), targeted by trimethoprim (TMP), which did not show a single relevant mutation. This deficient selection pressure associated with TMP – a suspicion that has to be analyzed, that trimethoprim is not effective against pneumocysts (Ma 1999), even DHFR-mutations have since been proven (Nahimana

2004). Overall, the frequency of sulfa resistance mutations has considerably increased in recent years, and correlates significantly with the duration of prior prophylaxis and its failure (Helweg-Larsen 1999, Kazanjian 2000, Nahimana 2004).

It is still not clear, whether DHPS mutations should also affect decisions on PCP therapy (Stein 2004). In a study on 144 PCP patients, DHPS mutations correlated with higher mortality rates (Helweg-Larsen 1999). In a further study, however, a trend was discovered (Crothers 2005). A working group in the US observed mostly low-level resistance, which could be overcome with high sulfonamide doses (Kazanjian 2000). It should be stressed that resistance tests for pneumocysts are still in the experimental stage (Beard 2004).

The sequencing of the genome has uncovered other possibly relevant findings: it seems highly likely that PCP is caused by a new infection, rather than reactivation as previously assumed (Stringer 2002, Wakefield 2003). Asymptomatic HIV infected patients with frequent detection of pneumocysts may be reservoirs (Wakefield 2003), in addition to HIV negative patients on corticosteroids (Maskell 2003) and those with active PCP. However, other authors doubt patient-to-patient transmission (Wohl 2002), and isolation of PCP patients is still not recommended (Thomas 2004).

An Italian working group has repeatedly stressed in recent years that the effect of PIs on pneumocysts detectable in vitro has clinical relevance and patients on PIs have better protection from PCP than patients on NNRTIs (Atzori 2003). However, these effects have not yet been demonstrated in larger patient groups.

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Cerebral toxoplasmosis

Although the incidence in Europe has been reduced to a quarter as a result of HAART (Abgrall 2001), cerebral toxoplasmosis remains the most important neurological OI in HIV infected patients in many areas of the world.

Cerebral toxoplasmosis results from the reactivation of a latent infection with *toxoplasma gondii*, an intracellular parasite that infects birds, mammals and humans. Prevalence rates vary considerably worldwide (Porter 1992). Whereas *toxoplasma gondii* is relatively rare in the USA, prevalence rates in regions within central Europe are as high as 90 %. Toxoplasma has an affinity for the CNS. Extracerebral organ manifestations (heart, muscle, liver, intestine, lung) are rare and often only detected at autopsy.

Cerebral toxoplasmosis is potentially life threatening, and treatment is complicated. In severe cases, there may be residual neurological syndromes with significant disabilities (hemiparesis!) or a susceptibility for seizures. In our own cohort, 37% were left with a neurological deficit (Hoffmann 2007). It should be noted that relapses may occur even after long periods of time due to intracerebral persistence.

The patients presenting with cerebral toxoplasmosis these days are different from earlier. Often, the HIV infection is not known when the diagnosis is made, or patients are not under regular routine care. In our own analysis of 140 cases between 1990 and 2004, 62% of patients in the period 1990-1996 had already had other AIDS-associated illnesses; in 1997, it was just 26 %. The proportion of patients with simultaneous diagnosis of HIV and toxoplasmosis increased from 20 to 49 % (Hoffmann 2007). In the last few years in particular, no further improvements in the prognosis have been observed – toxoplasmosis remains dangerous, especially in the first few months after diagnosis.

Signs and symptoms

Clinical symptoms depend on the localization of lesions, with acute or peracute onset within a few days. The major signs include focal neurological deficits such as paresis, speech problems or sensory loss (Porter 1992). A febrile psychosyndrome with confusion is also frequently an early sign. It is not unusual to see an epileptic seizure as the initial presentation, in the absence of other symptoms. Headaches with fever or subfebrile temperatures are suspicious. Meningitic signs, however, are less typical. Atypical manifestations in the presence of IRIS have been described (Ghosn 2003).

A fairly rare, but important manifestation is Toxoplasma chorioretinitis. It causes impairment of vision, is an important differential diagnosis to CMV retinitis and may occur on its own (Rodgers 1996).

Toxoplasma chorioretinitis should be treated in the same way as cerebral toxoplasmosis.

Diagnosis

Cerebral toxoplasmosis seldom occurs above a CD4 count of 100 cells/µl; over 200 CD4 cells/µl it is very rare (Bossi 1998). In contrast, it should always be expected below 100 CD4 cells/µl. A CT or MRI scan of the head should be performed promptly (not a week later!) in every case of focal neurological deficit, but also if seizures occur in significantly immunocompromised patients. An MRI is superior to a CT scan and almost always shows more visible lesions. A third of cases have either solitary, several (2-5) or multiple lesions, respectively. In approximately nine out of ten cases, ring enhancement is found around the lesions, often accompanied by edema. Hemorrhage may occasionally occur.

For all radiologically detected lesions, the most likely diagnosis is cerebral toxoplasmosis. In addition, the most important differential diagnosis is an "atypical" cerebral toxoplasmosis. The more lesions there are, the more likely the diagnosis of toxoplasmosis. However, the distinction between a bacterial abscess or cerebral lymphoma is not always simple radiologically. Other rare differential diagnoses include PML, infarcts, tuberculomas and cryptococcomas. "HIV-unrelated" diseases such as brain tumors or vascular disease should also be considered.

A brain biopsy is not obligatory. Before it comes to this, on suspicion of toxoplasmosis, a trial of treatment is justified. Response to therapy then confirms the diagnosis. However, if the patient does not improve clinically within one week, or even worsens, stereotactical brain biopsy cannot be avoided, and in this case should not be postponed.

The cerebrospinal fluid (CSF), which also does not necessarily have to be analyzed if there are clear radiological findings (several lesions with contrast enhancement), usually shows moderate pleocytosis and slightly elevated total protein. Our experience with Toxoplasma PCR from CSF has not been good. A negative result (frequent!) never excludes toxoplasmosis.

An updated serology should be available for every patient. Up to 97 % of patients with cerebral toxoplasmosis have IgG antibodies, and so a negative result, which should be repeated in another laboratory if there is any doubt, makes toxoplasmosis unlikely. It has not yet been properly validated whether the IgG titers are a diagnostic help (Derouin 1996). IgM is rarely positive, and therefore usually does not help; likewise PCR from the blood (review: Bretagne 2003).

Treatment

Treatment of cerebral toxoplasmosis is not simple. The most frequently used combinations are usually effective (resistance has not yet been convincingly described), but require modification in approximately half of the patients due to side effects – particularly allergic reactions. Sulfadiazine and clindamycin are presumably equally effective in combination with pyrimethamine (Dannemann 1992). However, one large European study demonstrated a trend, though not significant, in favor of sulfadiazine (Katlama 1996). Co-trimoxazole can also be considered. The studies to date have not produced any evidence for the superiority of one particular regimen (Dedicoat 2006).

We recommend using sulfadiazine and pyrimethamine for an initial attempt as oral treatment. Arguments for using clindamycin (instead of sulfadiazine) include sul-

fonamide allergy and severely ill patients, who have difficulty swallowing pills. Because of the high rate of allergies under sulfadiazine, some clinicians completely oppose this treatment. We do not share this view; after all clindamycin is also allergenic and can be problematic (pseudomembranous colitis).

A so-called "loading dose" for pyrimethamine during the first few days has been postulated since the first study (Leport 1988). It has not yet been proven whether this is necessary. Even the doses used are variable: in the USA 200 mg is recommended for the first day (followed by 50-75 mg depending on the body weight); here, 100 mg is often given for three days, followed by 50 mg. It should be noted that, in contrast to clindamycin, pyrimethamine is also active in the presence of an intact blood brain barrier, and is sometimes therefore the only effective substance.

Due to the myelotoxicity of pyrimethamine, which inhibits transformation of folic acid to folinic acid, it is important to substitute with folinic acid (unfortunately expensive!) from the start. Folic acid (cheap!) itself is ineffective, as it cannot be converted in the presence of pyrimethamine (Luft 2000).

Good results are also reported with intravenous co-trimoxazole, with administration of the same dosages as for PCP (Canessa 1992). In two randomized studies on patients with ocular or cerebral toxoplasmosis, co-trimoxazole was as effective as sulfadiazine/pyrimethamine (Torre 1998, Soheilien 2005).

If allergies or intolerance to both sulfonamides and clindamycin occur, a combination of atovaquone plus pyrimethamine is an alternative therapy (Chirgwin 2002). This is also the case for azithromycin plus pyrimethamine (Bosch-Driessen 2002), however the data are vague.

Acute therapy lasts from four to (better) six weeks duration, possibly even longer for the alternative therapies. The success can be assessed clinically in the first 14 days. Often an improvement can be observed within a few days. A patient that has not even partially improved clinically after two weeks of adequate therapy (did he take the pills?), or has even deteriorated, probably does not have toxoplasmosis! If this occurs, the diagnosis has to be reviewed and an urgent brain biopsy must be organized. Changing the toxoplasmosis therapy is not useful in such cases and just costs valuable time.

A control MRI is recommended for stable patients after two weeks at the earliest. Significant resolution of lesions is often only visible after four weeks. In cases of increased intracranial pressure or extensive edema, steroids are given (8 mg dexamethasone q 6-8 h). Administration of steroids should be for a limited duration (beware aspergillosis!). All treatment combinations require initial monitoring of blood count, glucose, transaminases and renal parameters at least three times weekly. Maintenance therapy with the reduced dose should only be initiated if lesions have resolved by at least 75 %.

Prophylaxis

Exposure Prophylaxis: IgG-negative patients can protect themselves from initial infection – they should avoid eating raw or only briefly cooked meat (lamb, beef, pork, game). However, it has not been proven, despite widespread opinion, that HIV patients can infect themselves by mere contact with cats, the definitive host of *toxoplasma gondii*. The only study that has seriously investigated this to date could

not prove endangerment as a result of proximity to cats (Wallace 1993). Nevertheless, hygiene measures should be taken (e.g. use gloves for the cat litter box!).

Primary Prophylaxis: All IgG-positive patients with less than 100 CD4 cells/µl require primary prophylaxis. The drug of choice is co-trimoxazole. In cases of allergy, desensitization may be considered (see PCP). Alternatives are dapsone plus pyrimethamine or high-dose dapsone alone. Primary prophylaxes can be discontinued if CD4 cells are above 200/µl for at least three months on HAART.

Treatment/prophylaxis of cerebral toxoplasmosis
(daily doses, if not specified otherwise)

Acute therapy		Duration: always at least four weeks
First choice	Sulfadiazine + Pyrimethamine	Sulfadiazine 2-3 tbl. à 500 mg qid **plus** pyrimethamine 2 tbl. à 25 mg bid (for 3 days, then halve dose) **plus** leucovorin 3 x 1 tbl. à 15 mg/week
First choice	Clindamycin + Pyrimethamine	Clindamycin 1 amp. à 600 mg i.v. qid or 1 tbl. à 600 mg qid **plus** pyrimethamine 2 tbl. à 25 mg bid (for 3 days, then halve dose) **plus** leucovorin 3 x 1 tbl. à 15 mg/week
Alternative	Atovaquone + Pyrimethamine	Atovaquone suspension 10 ml bid (1500 mg bid) **plus** pyrimethamine 2 tbl. à 25 mg bid (for 3 days, then halve dose) **plus** leucovorin 3 x 1 tbl. à 15 mg/week
Maintenance therapy		
	As for acute therapy	As for acute therapy, but halve dose Discontinue if > 200 CD4 cells/µl for > 6 months (if MRI is normal or without contrast enhancement)
possibly	Co-trimoxazole	Co-trimoxazole 1 tbl. à 960 mg qd
Primary prophylaxis		
Standard	Co-trimoxazole	Co-trimoxazole 1 tbl. à 480 mg qd
Alternative	Dapsone	Dapsone 2 tbl. à 50 mg qd
Alternative	Dapsone + Pyrimethamine	Dapsone 1 tbl. à 50 mg qd **plus** pyrimethamine 2 tbl. à 25 mg/week **plus** leucovorin 2 tbl. à 15 mg/week

Secondary Prophylaxis: In the absence of immune reconstitution, lifelong maintenance therapy is necessary, as otherwise a recurrence occurs. It usually consists of half the dose of the acute therapy (Podzamczer 2000). However, clindamycin is presumably less suitable, as it cannot cross the intact blood-brain barrier (Luft 2000). Even co-trimoxazole does not seems to be as effective for secondary prophylaxis, but should be considered because it is simple. However, it definitely requires higher doses than those used to treat PCP (Ribera 1999, Duval 2004). With sufficient immune reconstitution (at least three months above 200 CD4 cells/µl), secondary prophylaxis can be stopped (Benson 2004, Miro 2006).

An updated MRI scan should be available. If there is enhancement, it may mean that lesions have become active even after years – and there is a risk of a recur-

rence. We have seen a recurrence even after five years, despite CD4-cell levels being around 200/µl.

This and other cases (Stout 2002, Ghosn 2003) have shown that quantitative measurement of CD4 cells on HAART does not always reflect the quality of the Toxoplasma-specific immune response. Studies have shown that the Toxoplasma-specific immune response remains poor in approximately 10-20 % of patients on HAART, despite good CD4-cell counts (Fournier 2001, Miro 2003).

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CMV retinitis

Infections with cytomegalovirus are widespread. In many European countries, seroprevalence is around 50-70 %, and above 90 % in homosexual men. In severely immunocompromised individuals (CD4-cell count below 50/µl), reactivation of CMV infection can lead to retinitis. In the past, CMV retinitis was a common AIDS-associated illness, leading to blindness in up to 30 % of patients. It occurs mainly in untreated patients, who are often first diagnosed with HIV infection on presentation (Jacobson 2000). An inflammatory CMV retinitis with severe vitritis, is also possible in the course of an IRIS. If CMV retinitis is not diagnosed and treated promptly, vision is always at risk. Impairment of vision is almost always associated with lesions, which are no longer reversible even with adequate treatment. This is why CMV retinitis remains a dangerous illness and threat to vision, even in the HAART era, although the prognosis has been significantly improved by HAART (Goldberg 2003, Salzberger 2005, Thorne 2006).

Other manifestations of disseminated CMV infection are rare (approx. 15 %), and can affect every organ. Pneumonias, esophagus (ulcers), colon (colitides) and CNS (encephalitides) are most frequently involved, although sinusitides may also occur (Jutte 2001). The clinical signs depend on the organ affected; diagnosis is often difficult and may only be possible on histology (Goodgame 1993). There is insufficient data on the treatment, so that systemic therapies are usually chosen analogous to treatment for CMV retinitis (Whitley 1998).

Signs and symptoms

Any visual impairment occurring peracutely or acutely, such as blurred vision or floaters – especially unilaterally – should prompt immediate ophthalmological examination of the patient. Today, not tomorrow! Symptomatic CMV retinitis is an emergency – once there is a black spot in the visual field, it will be permanent. Usually retinal detachment and macular edema, more rarely cataract-like changes are responsible for the visual disturbances (Thorne 2006). CMV treatment regimens can generally only prevent the progression, but cannot reverse anything.

Eye pain, burning, increased production of tears and conjunctival irritation are not typical. Many patients suffer from systemic symptoms such as fever and weight loss.

Diagnosis

Diagnosis is made by fundoscopy. Assessment of the usually peripheral, whitish exudates is dependent on the experience of the ophthalmologist. Unfortunately, incorrect diagnoses that are ill fated due to the valuable time (and retina) lost are no exception. Therefore, if the ophthalmologist remains undecided: start with oral ganciclovir if necessary and transport the patient to a larger clinical center with ophthalmologists who are experienced in HIV! It is essential that they also receive information about the immune status. In cases where the CD4-cell count is less than 100/µl, chorioretinitis caused by *toxoplasma gondii* is the most important differential diagnosis. CMV retinitis can almost be excluded at CD4-cell counts above

100/µl, and other viral infections (HSV, VZV) or even neurosyphilis should then be considered.

CMV lesions may also be confused with cotton wool spots, which are not rare in HIV infected patients with high HIV viral load. Multiple small lesions without hemorrhage or exudates are almost always cotton wool spots, and almost never CMV retinitis! Bilateral involvement is also usually the exception. Vitritis is rare, except with immune reconstitution syndrome.

CMV serology (IgG almost always positive, IgM variable) is not helpful for diagnosis. CMV PCR or, if not available, determination of pp65 antigen in the blood may be more useful in contrast. CMV retinitis is unlikely with a negative PCR or pp65 antigen result. The higher the levels of CMV viremia, the higher the risk of CMV disease. A positive PCR increases the mortality risk by 3-5-fold (Casado 1999, Nokta 2002) and is also associated with a poor prognosis (Deayton 2004, Jabs 2005, Wohl 2005).

As with *toxoplasma gondii*, there have been efforts to determine the antigen-specific immune response more precisely (Jacobsen 2004), although such testing is not yet routine.

Treatment

CMV treatment in the presence of retinitis should always be initiated promptly and strictly monitored by fundoscopy (once a week in the beginning; photodocumentation is advisable). Initially, an intensive induction therapy is administered for two to three weeks, until there is scar formation of the lesions. HIV clinicians and ophthalmologists should make contact at least once a week during the induction therapy. Induction therapy is followed by maintenance therapy at a reduced dose.

There have been significant developments for CMV treatment in the past few years (see below).

HAART has dramatically improved the prognosis of patients. All patients should therefore, if this has not already happened, start HAART as soon as possible. This can restore CMV-specific immune responses (Komandouri 1998), so that CMV viremia may disappear even without specific therapy after a few weeks (Deayton 1999, O'Sullivan 1999). In the absence of symptoms, we would not specifically treat an isolated CMV viremia, HAART is usually sufficient. The situation is of course different for retinitis, as immune reconstitution may take several months.

Systemic treatment

Valganciclovir is the treatment of choice, a prodrug of ganciclovir with good oral absorption. Because of the potential for myelotoxicity, regular blood counts are necessary. Intravenous ganciclovir, as well as other systemic options (see below) have become unimportant and are only used for recurrences. Oral ganciclovir is obsolete.

If there is intolerability or resistance to valganciclovir (Drew 1999), i.v. foscarnet is an alternative option. The substance is nephrotoxic, and can cause very painful penile ulcers. Very intensive hydration of the patient is therefore necessary.

There are no direct comparative studies available for cidofovir. The benefit of the long half-life (once weekly dosing possible) is outweighed by the considerable

nephrotoxicity (Plosker 1999). We observed creatinine elevations in every second patient treated, despite the fact that a strict infusion plan was closely followed (see Drugs section).

New drugs, such as maribavir, will take a while to come onto the market. CMV retinitis has become rare in the field of HIV infection, and progress is slower in transplantation medicine, where the current need for new CMV drugs might be greater (maribavir is undergoing Phase II studies).

In one analysis of three large studies, patients with CMV retinitis, who had received additional treatment with G-CSF (filgrastim) in the years 1990-1997, had improved survival rates. In particular, there was a reduction of bacterial infections. The reason for this positive effect remains unclear. Administration of filgrastim is not generally recommended (Davidson 2002).

Local treatment

Several options for local treatment of CMV retinitis have been tested (review in: Smith 1998). Although such treatments can be administered by experienced ophthalmologists, and complications (infections, hemorrhage) are rare, few disadvantages remain. Weekly intravitreal injections of ganciclovir or foscarnet, or pellet implantation (Vitrasert™, must be replaced every 6-9 months) do not protect from infection of the contralateral eye or from extraocular manifestations (Martin 1999). The same is true for fomivirsen (Vitravene™), an antisense-oligonucleotide for intravitreal injection, which is astonishingly effective even with multiresistant CMV strains (Perry 1999). These local treatments have become less important since HAART and valganciclovir, and some have been taken off the market.

Prophylaxis

Primary Prophylaxis: In the prospective studies that have been performed, no primary prophylaxis regimen has been convincing. There is also no effective vaccine. Therefore, the most important method for prevention in patients with CD4 counts less than 200 cells/µl is still fundoscopy every three months. With good immune reconstitution, intervals between examinations can be extended. It is important to perform a fundoscopy in severely immunocompromised patients prior to starting HAART. This allows detection of smaller lesions, which may later present with severe inflammation during the course of immune reconstitution.

Secondary Prophylaxis: After approximately three weeks of acute therapy, but at the earliest with scar formation of lesions, a reduced dose secondary prophylaxis (maintenance therapy) should begin, preferably with oral valganciclovir (Lalezari 2002). However, the drug is not only extremely expensive (three weeks of induction therapy cost around 4,500 Euro – the manufacturer demands a high price for the savings in nursing or hospital care), but also just as myelotoxic as ganciclovir infusions.

Treatment/prophylaxis of CMV retinitis
(daily doses, if not specified otherwise)

Acute therapy		Duration: always at least three weeks
Treatment of choice	Valganciclovir	Valganciclovir (Valcyte™) 2 tbl. à 450 mg bid
Alternative	Ganciclovir	Ganciclovir 5 mg/kg i.v. bid
Alternative	Foscarnet	Foscarnet 90 mg/kg i.v. bid
Alternative	Ganciclovir + Foscarnet	Half of the doses above
Maintenance therapy		Discontinue when > 100-150 CD4 cells/µl > 6 mo
Treatment of choice	Valganciclovir	Valganciclovir (Valcyte™) 1 tbl. à 450 mg bid
Alternative	Foscarnet	Foscarnet 120 mg/kg i.v. qd on 5 days/week
Alternative	Cidofovir	Cidofovir (Vistide™) 5 mg/kg i.v. qd every 14 days (plus probenecid hydration according to protocol, see Drugs section)
Primary prophylaxis		Not recommended

Discontinuation of secondary prophylaxis as quickly as possible, is therefore also desirable and practical for this OI (MacDonald 1998, Tural 1998, Jouan 2001). According to US guidelines, it should occur at the earliest after six months of maintenance therapy and with an immune reconstitution above 100-150 CD4 cells/µl. However, we have even successfully stopped ganciclovir at lower CD4-cell counts, if both HIV and CMV PCR in blood were below the level of detection. One study showed that stopping after 18 months of HAART/maintenance therapy can be safe above 75 CD4 cells/µl (Jouan 2001). Following discontinuation, patients should receive ophthalmological checks at least once a month initially.

The previously required life-long daily infusions of ganciclovir or foscarnet via port, pumps and nursing service are luckily now a thing of the past. If there are relapses under oral valganciclovir, we recommend re-induction and maintenance therapy with foscarnet or possibly with cidofovir.

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Candidiasis

Candidiasis is an infection with yeast-forming fungi. Of the 150 Candida species known to date, only approximately 20 cause disease. By far the most frequent species is *C. albicans*. Other species such as *C. tropicalis*, *C. glabrata* and *C. krusei* are rare, but may respond less readily to treatment with azoles. Although it is commonly assumed that azole resistance is a problem particularly with albicans strains, this has not been the case to date (Sanglard 2002).

Candidiasis is an important indicator of immunodeficiency and should be seen as a reason to consider starting HAART, even with a good immune status. Esophageal candidiasis and even oral thrush often occur following other OIs. Fever, which is not a classic symptom of candidiasis, is a particular indication to be on the alert. If immune status is good, it must be remembered that there are also other reasons for thrush – alcoholism and steroid treatment are just two. In addition to candidiasis of the oropharynx and esophagus, vaginitis is a frequent problem in women (also occurring in healthy individuals). Candidemia occurs only rarely in HIV-infected patients, even with severe immunodeficiency.

Signs and symptoms

The oropharynx is usually affected, with taste disturbances and sometimes, a burning sensation on the tongue. White, non-adherent plaques on the buccal mucosa, tonsillar ring and tongue confirm the diagnosis. Involvement of the tongue alone is rare. Occasionally, there may be atrophic candidiasis, which presents only with an erythematous mucosa.

Candida esophagitis usually occurs with oropharyngeal involvement, but in about one third of cases there is no oral thrush. It often presents with dysphagia ("drinking is ok, but food can't go down") and retrosternal pain. Some patients complain of nausea, although vomiting occurs only rarely.

Diagnosis

Diagnosis in the oropharynx can be made based on the clinical appearance. A swab is not usually required. Characterization by culture or even determination of drug susceptibility (beware laboratory uncertainty!) is only advised if one treatment attempt with fluconazole or itraconazole has failed. Oral candidiasis is not to be confused with oral hairy leukoplakia (OHL). In contrast to candidiasis, the whitish, hairy plaques of OHL, on the sides of the tongue, cannot be scraped off. OHL is not caused by fungi but by EBV, and is an important disease marker for HIV, even if it is harmless and does not require treatment.

Candida esophagitis can also initially be diagnosed clinically. Dysphagia, retrosternal pain and oral candidiasis make the diagnosis very probable. Empiric fluconazole therapy reduces costs (Wilcox 1996). Upper GI endoscopy is only required if complaints persists after treatment with fluconazole. To distinguish fluconazole-resistant esophageal candidiasis from herpes or CMV esophagitis, samples of lesions should always be taken. In contrast, determination of serum antibodies or antigen is always unnecessary.

Treatment

With relatively good immune status and presentation for the first time, treatment with topical antimycotics (gargle, rinse mouth and then swallow!) can be attempted. However, systemic treatment is usually necessary. This is more effective and prevents relapses for longer (Pons 1997). Fluconazole is the treatment of choice, and one week of oral treatment is usually sufficient (Sangeorzan 1994). If symptoms persist for more than a week, a swab should be taken and the fluconazole dose may be increased up to 800 mg for the second attempt.

Itraconazole should only be used if the second treatment attempt fails and non-albicans strains have been found. It will be effective in approximately two thirds of cases (Saag 1997). Itraconazole suspension is as effective as fluconazole (Graybill 1998). Because of the unreliable plasma levels and numerous interactions, we do not primarily use itraconazole.

Promising antimycotics have been developed in recent years. However, they should only be used in clear cases of fluconazole resistance. There is no evidence to show superiority of any particular antimycotic (Pienaar 2006). Voriconazole is expected to be as effective as fluconazole, but is possibly not tolerated as well (Ruhnke 1997, Ally 2001). Like amphotericin B, it can be used for treatment of multi-azole resistant mycoses. Caspofungin or micafungin, two antimycotics belonging to the new class of echinocandins, also have good efficacy (Keating 2001, Villanueva 2001, Arathoon 2002, de Wet 2004). Both agents, which can only be administered intravenously, were as efficacious and well-tolerated as fluconazole for treatment of Candida esophagitis in randomized studies (Villaneuva 2001, de Wet 2004). The same is true of the new drug posaconazole (Vaszquez 2006).

A HAART regimen should be initiated when such mycoses occur, particularly with multiresistant strains, as these usually disappear with sufficient immune reconstitution (Ruhnke 2000).

Prophylaxis

No survival benefit has been demonstrated for any Candida prophylaxis to date (McKinsey 1999, Rex 2000, Goldmann 2005). In the largest randomized study a reduction in oral candidiasis episodes as well as in invasive candidiasis was observed on long-term prophylaxis (Goldman 2005). The hypothesis that long-term prophylaxis will lead to the selection of resistant non-albicans strains (Vazquez 2001) was not confirmed in this study. Azole resistant candida species were not seen more frequently in the long-term therapy group. But: check the mouth of every immunocompromised patient at every visit!

Treatment/prophylaxis of candidiasis (daily doses)

Acute therapy		Duration: 5-10 days
In mild cases	Topical	e.g. amphotericin B 1 lozenge qid or nystatin suspension 1 ml qid
Treatment of choice	Fluconazole	Diflucan™ or fluconazole CT/Stada™ 1 x 1 cap à 100 mg for oral candidiasis Diflucan™ or fluconazole CT/Stada™ 1 x 1 cap à 200 mg for esophageal candidiasis (twice the dose on the first day in each case)
Alternative	Itraconazole	Sempera™ 1-2 cap. à 100 mg bid or Sempera™ suspension 10-20 ml bid (1 ml = 10 mg)
Prophylaxis		Not recommended

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Tuberculosis

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Tuberculosis (TB) has greater impact on morbidity and mortality in HIV-1-infected individuals than all other opportunistic infections (OI) (Unaids 2006). In fact, the rising incidence of TB in many regions of the world is closely related to the HIV epidemic. Approximately 1/3 of the 40 million people infected with HIV-1 worldwide are co-infected with bacilli of *Mycobacterium tuberculosis* (MTB) complex (*M. tuberculosis, M. africanum*, *M. bovis*, *M. canetti* or *M. microti*). The prevalence of HIV in TB patients in Africa has been reported to be about 40% (Corbett 2003) and the incidence of TB is more than 8 times higher in HIV-positive than in HIV-negative people (Corbett 2006). Recently, co-infection of the two pathogens has become more noticeable in Eastern Europe and in Asia (Field 2004, Sonnenberg 2004, Steinbrook 2004, Surendran 2004). In addition, there is increasing concern that HIV-1 will enhance the spread of multidrug resistant (MDR) TB in these regions (Kruuner 2001) as MDR TB is already 10 times more frequent in Eastern Europe than in Africa (Dye 2002, Morozova 2003).

Despite a steadily increasing prevalence of HIV-1 infection in Western Europe and North America in recent years, the incidence of TB has continuously declined in countries where antiretroviral therapy (ART) against HIV-1 are available (Kirk 2000, Girardi 2000). However, clinical management of MTB-HIV co-infected patients is complicated due to a wide range of drug interactions, overlapping side effects of ART and antituberculous medications and low compliance caused by pill burden.

Interaction of HIV and MTB

HIV and MTB infections have synergic influence on the host immunoregulation. Indeed, HIV infection impairs cell-mediated immunity largely through depletion of CD4+ lymphocytes. The impaired immunity leads to increased number of cases of primary TB and reactivation TB in HIV-infected people. In turn, TB may accelerate the progression of HIV infection by increasing viral replication and intensifying immunodepression effect of HIV. It is likely that TB enhances immunodeficiency related to HIV infection (Toossi 2003). The incidence of primary TB and reactivation TB is increased in HIV-infected patients in comparison with HIV-seronegative individuals (Havlir 1999, Badri 2001). The factors that lead to TB reactivation in HIV infection have not been determined in detail and the pathogenesis of TB is not always dependent on the stage of immunodeficiency. The incidence of post-primary TB is increased from 5 % to 30 % in HIV-1 infected subjects. The risk of active TB in patients with latent TB infection (LTBI) is approximately 8% per year in HIV-infected patients compared with a lifetime TB risk of 5 to 10% in HIV-seronegative individuals (Unaids 2006). Despite adequate TB therapy, the morbidity and mortality is increased in HIV-seropositive patients with TB in comparison with HIV-seronegative patients with TB (Manas 2004, Whalen 2000). While most OI, including all other mycobacteria diseases (i.e. *M. avium* complex mycobacteriosis), occur in the advanced stages of HIV infection, HIV-infected pa-

tients can develop TB at any stage of immunodepression regardless of the levels of circulating CD4+ T lymphocytes (Ackah 1995). More than 50% of pulmonary TB cases occur in patients with more than 200 CD4+ T cell/µl in the peripheral blood (Badri 2001). Recently, it has been shown that the risk of TB is already significantly increased in the first year after HIV-antibody seroconversion, (Sonnenberg 2005). However, the incidence of disseminated TB is much higher in patients with advanced immunodeficiency (Wood 2000) and TB is the leading cause of death among people with HIV infection, accounting for one-third of deaths due to AIDS worldwide.

Clinical manifestations

In the early stages of HIV infection, generic clinical manifestations of TB are fever, fatigue, night sweats and weight loss and they resemble TB in HIV-seronegative patients.

Pulmonary TB

As in HIV-seronegative patients, typical lesions of pulmonary TB in HIV patients with more than 200 circulating CD4+ T cell /µl are upper-lobe lung infiltrates (with or without cavities) and tuberculous granulomas are always present in these lesions. Cough and haemoptysis are frequent. Undefined lung opacities are often present on chest x-ray as well as enlarged mediastinal lymph nodes. As immunodeficiency progresses, atypical pulmonary presentations or tuberculous pleuritis become more frequent. Bronchopulmonary symptoms, such as cough and haemoptysis are often absent when TB occurs in the advanced stages of HIV infection. Because CD4+ T lymphocytes are required for granuloma formation, these typical lesions are usually absent on histopathological examination of tissue from AIDS patients (Nambuya 1988).With the progression of immunodeficiency, haematogenous and lymphatic spread of mycobacteria is more common leading to miliary or disseminated TB (Elliott 1993) or localized extrapulmonary TB (Mayanja-Kizza 2001).

Extrapulmonary TB

Extrapulmonary TB occurs predominantly in HIV-MTB co-infected patients with CD4+ T cell count less than 200/µl. The most common localization of extrapulmonary TB is cervical lymph nodes. The involved nodes are enlarged, hard and generally not painful on palpation. The formation of abscesses and draining fistulas as well as fever and malaise are common.

Tuberculous meningitis often presents with unspecific prodromal symptoms such as headache, nausea and vomiting followed by elevated temperature and clinical signs of meningeal irritation. The basal meninges are usually involved and cranial palsies of III and VI nerves are common. Mono-, hemi- or paraparesis as well as loss of consciousness and seizures can occur. In any patient with symptoms and signs of meningitis, a lumbar puncture should be performed without delay.

Other extrapulmonary localizations include pericarditis, osteoarthritis, urogenital tract and skin TB. Tuberculous lesions may involve adrenal glands causing Addison's disease. Practically, every organ can be involved.

Miliary or disseminated TB

Clinical manifestations depend on multiple small granular lesions (lat. milium effusum) and their localization. Lungs may be involved and micro-nodular opacities are evident on chest x-ray. On radiological criteria alone, these lesions cannot be distinguished from pulmonary cryptococcosis. Miliary dissemination of TB can also involve abdomen. In febrile patients with abdominal pain and ascites, peritoneal TB must be included in the differential diagnosis. Liver and spleen lesions may be detected by echography.

Diagnosis

Diagnostic steps in the management of an HIV-infected patient with suspected TB do not differ from those used for HIV-seronegative patient (Lange 2004). In the differential diagnosis, TB has to be distinguished from mycobacteriosis caused by atypical mycobacteria (i.e. *M. avium* complex), cryptococcosis, histoplasmosis, sarcoidosis, lymphoma, and solid malignant neoplasia.

The diagnosis is made on clinical, radiological and microbiological grounds. Radiographic exams are very helpful as part of diagnostic procedure in case of suspected TB.

Radiographic images of pulmonary TB are often unspecific and can vary substantially. Pulmonary TB can mimic a variety of other pulmonary diseases and can be present without evident changes of chest x-ray. However, typical chest x-ray findings are undefined single or multiple opacities in upper lobe, with or without cavities inside opacities, and enlarged mediastinal lymph nodes. Calcifications and fibrosis scaring may be either a sign of healed pulmonary TB or a clue of reactivated disease. In miliary TB, chest x-ray shows disseminated micro-nodular opacities. Patients with pulmonary TB and low CD4+ T cell count often present with pleural effusion without evident chest x-ray pulmonary infiltrates. In case of doubt, a chest CT scan should be recommended whenever possible. If extrapulmonary TB is diagnosed, lung radiographic imaging as well as abdominal echography should be performed to identify possible pulmonary disease, liver and spleen abscesses, bowel thickening or ascites.

When pulmonary TB is suspected, three sputum samples should be collected on consecutive days for mycobacteria culture test and microscope analysis. If patients are unable to cough deeply and cannot produce sputum, an attempt should be made by inhalation of 3% hypertonic sodium chloride steam to induce sputum. Alternatively, early morning gastric aspirate can also be examined for mycobacteria. The acidic gastric aspirate should be rapidly buffered in phosphate solution even before transportation to laboratory. Anyway, if enough sputum is not produced or mycobacteria are not found by culture test and microscope examination of sputum but the suspicion of TB remains high, bronchoscopy is usually indicated. Bronchial secretions or bronchoalveolar lavage fluid obtained by bronchoscopy are not better than sputum as biological samples for diagnosis of TB in patients with HIV infection (Conde 2000) but bronchoscopy may be very helpful in the differential diagnosis between TB and other diseases (Narayanswami 2003) particularly since coexistence of more than one pulmonary disease is rather frequent in patients with HIV infection. Furthermore, histopathological examination of transbronchial biopsies collected by bronchoscopy may show typical tuberculous granulomas in case of TB.

On the day after bronchoscopy, sputum should be sampled for analysis as the diagnostic yield is higher following the intervention even if no mycobacteria were detected in lavage fluid.

Sputum and other collected biological materials should always be culture tested. The gold standard test for diagnosis of TB is culture identification of MTB after incubation of biological samples in liquid or solid media. Roughly, liquid media take less time than solid media for the result: 2 to 4 weeks of incubation and 3 to 5 weeks of incubation, respectively. A mycobacteria culture test is to be considered negative only if no mycobacteria are identified after 6 to 8 weeks of incubation. Atypical mycobacteria usually grow much faster than MTB and can be often identified within two weeks of incubation. All new clinical isolates of MTB should undergo antibiotic sensitivity test.

Sputum and other collected biological materials (bronchial secretions and lavage fluid) have to be analysed by microscopy to detect the presence of MTB which appear as acid-fast bacilli (AFB) after staining. The sensitivity and specificity of microscope analysis of sputum are poor. Approximately, the presence of at least 5,000-10,000 mycobacteria/microscope-slide is necessary for a routine microscope result of AFB positive smear. Approximately 50 % of all patients with culture positive pulmonary TB has AFB negative smear on three consecutive sputum samples. AFB positive smear is present in approximately 5% of cases where pulmonary lesions are not visible on standard chest x-ray (Ackah 1995). In addition, discrimination between MTB and atypical mycobacteria is not possible by acid-fast staining. While HIV-seropositive patients with more than 200 circulating CD4+ T cell /µl with typical lesions of pulmonary TB have the same percentage of AFB-positive smear as HIV-seronegative patients, in patients with TB and advanced stages of HIV infection the likelihood of AFB positive smear is decreased.

For the diagnosis of extrapulmonary TB, biological samples such as heparinised venous blood, bone marrow aspirate, cerebrum-spinal fluid, urine, pleural fluid, pericardial fluid and peritoneal fluid should be analysed by culture test. Biopsies of lymph nodes, pleura, peritoneum, synovia and pericardium are also suitable for diagnosis of extrapulmonary TB as AFBs and typical tuberculous granuloma may be detected through histological examination of tissue lesions.

Indeed, acid-fast staining is rapid but is not very sensitive neither specific and culture test is very sensitive and specific but takes more than 2 weeks for results. In the past few years, bio-molecular analysis were designed to get more rapid results and presently mycobacteria nucleic acid (DNA or RNA) can be detected in biological samples by routine Polymerase Chain Reaction (PCR) test. MTB PCR test is faster than culture test and more sensitive and specific than acid-fast staining. PCR test is especially helpful for differentiation of mycobacteria species when AFBs are present and visible on microscope slide. In this circumstance, MTB PCR test sensitivity is higher than 95%. Unfortunately, sensitivity of MTB PCR test is decreased to about 40-77 % if sputum samples are AFB negative (Barnes 1997). Because in case of AFB negative smear the use of PCR test can yield false negative results, PCR test results should always be questioned.

In extrapulmonary TB, for example tuberculous meningitis, where microscope analysis is often negative but a rapid diagnosis is needed, MTB PCR test should be performed in the initial routine evaluation. For PCR analysis, biopsy samples

should not be fixed in formalin but rather be preserved in "HOPE" (Hepes-glutamic acid buffer-mediated organic solvent protection effect) media (Olert 2001).

In case of suspected TB, a tuberculin skin (TS) test, also known as purified protein derivative (PPD) test, is recommended. Positive TS (or PPD) test shows an immunological memory to previous or ongoing contact with MTB that is MTB infection and not active TB. Positive TS test results may be found also in patients who were BCG-vaccinated or who had contact with atypical mycobacteria. On the other side, TS test give usually false negative results in MTB-HIV co-infected patients with CD4+ T cell count less than 200/μl (Fisk 2003). TS test should only be administered intradermally, into the top layer of skin of forearm, according to the method described by Mendel and Mantoux. The standardized dose that is recommended by WHO and IUATLD is 2 Tuberculin Units (TU)/0.1ml PPD RT23/Tween 80. In the United States of America and other countries, the standardized dose is 5 TU/0.1ml PPD-S, which is thought to be similar in strength. After 48-72 hours since intradermal injection, the diameter of induration (not redness) in the site of injection is measured along the short axis of forearm (Sokal 1975). TS test is considered positive if induration diameter is 5 mm or more. In HIV-infected patients, an induration $\geq$ 5 mm is positive according definition of IDSA (Jasmer 2002). The IDSA guidelines for interpretation of TS test result are based on results of clinical studies that were conducted with 5 TU PPD-S in the USA and therefore cannot be directly applied to other countries where different antigens are used.

Recently, new tests, called Interferon (IFN)-γ blood test, have been developed for the diagnosis of MTB infection. As of today, two IFN-γ blood tests are available: ELISPOT (T-SPOT-TB Test) and ELISA (Quantiferon-Gold-in-tube Test); they detect the secretion of IFN-γ by peripheral blood mononuclear cells induced by specific MTB peptides, ESAT-6 and CFP-10. These tests are more sensitive and specific than TS test for diagnosis of MTB infection in patients with immunodeficiency (Chapman 2002, Dheda 2005, Ferrara 2006,). However, in patients with advanced immunodeficiency, a substantial proportion of ELISA test results are indeterminate hence clinical usefulness of these assays still need to be evaluated in patients with HIV infection and low CD4+ T cell count.

Therapy

First-line drugs include rifampin (RMP), rifabutin (RB), isoniazid (INH), ethambutol (EMB) and pyrazinamide (PZA). INH and RMP are the most potent of these drugs. Second-line drugs include streptomycin, amikacin, capreomycin, prothionamide, moxifloxacin, levofloxacin, cycloserine and linezolid. Streptomycin is not orally available, is delivered i.v. or i.m. and it should only be included in the treatment regimen if one of first-line drugs is contraindicated (drug resistance, allergy, toxicity, etc.).

In uncomplicated cases, pulmonary TB, both in HIV-seronegative and HIV-seropositive patients, can be treated successfully with standard 6 month course. To avoid the development of drug resistance, active TB should always be treated initially with a combination of four drugs (initial phase). Standard initial phase therapy is 2 month course of RMP, INH, EMB and PZA, followed by continuation phase therapy of 4 month with RMP and INH. Drug doses are listed in Table 1. Anyway,

in the initial phase the four drugs should have to be administered until culture test results show drug susceptibility of MTB isolates.

Hospitalization is indicated to prevent the spread of the infection to others until the contagious period has been resolved with drug therapy. As long as AFBs are detected in the sputum or in the bronchoalveolar lavage, the patient should be treated in isolation. The duration of the contagious period of a patient with pulmonary TB depends on the extent of pulmonary lesions and cavities. Sputum should be regularly collected (in the initial phase every week) and evaluated for the presence of AFBs (by microscopy) and viable MTB (by culture test) until the end of treatment. The contagiousness of a patient is very low once AFBs are repeatedly absent in smears. When at least three sputum samples obtained on different days are AFB negative, the patient may be discharged. However, viable MTB can usually be cultured from sputum for a few weeks after microscope test has become AFB negative. Patients with MDR TB should be kept in isolation until sputum cultures turn negative.

Failure of therapy occurs in the presence of drug resistance, poor drug compliance or insufficient treatment duration (Sonnenberg 2001, Korenromp 2003). If sputum cultures were still positive after the initial phase of treatment, or in case the initial phase regimen was different from standard therapy and not including RMP and INH, the duration of therapy should be extended to 9 months or longer (that is continuation phase should be extended to 7 months or longer). Treatment is longer than standard 6 month course even for AIDS patients, cavitary pulmonary TB and tuberculous meningitis. Despite successful initial therapy, recurrence of TB occurs more often in HIV-seropositive than HIV-seronegative individuals (Sonnenberg 2001).

Drug adverse events

The most frequent and important adverse events of antituberculous drugs are listed in Table 1.

Since INH often induces peripheral polyneuropathy the drug should always be co-administered with pyridoxine (B6 vitamin) to prevent the development of the neural side effect.

Before and during therapy with EMB, colour vision should be examined and monitored as this drug may affects optic nerve (II pair of cranial nerves). Dosages of EMB and PZA need to be adjusted in patients with renal insufficiency. In patients with liver disease (including drug induced hepatitis), the choice of first-line drugs is limited as RMP, INH and PZA can worsen the liver injury. In these cases, a combination of EMB, streptomycin, cycloserine, moxifloxacin and/or linezolid may be administered. Since this second-line therapy is no different from that of MDR TB, these patients should be treated in specialized centres. Audiometric monitoring should be performed when streptomycin is used.

Following the start of antituberculous therapy, liver enzymes, serum creatinine and complete blood count should be monitored on a regular basis (e.g. in the initial phase every week, then every four weeks). Hyperuricemia is common when PZA is used. A mild, polyarthralgia can be treated with allopurinol and non-steroidal antiphlogistic drugs. Arthralgia can also be induced by RMP and RB.

Table 1: Antituberculous drug doses, side effects and drug interactions

Antituberculous drugs	Recommended daily dose	Common side effects	Drug interactions	Comments
Rifampin (RMP) Also available for i.v. injection	10 mg/kg > 50 kg: 600 mg < 50 kg: 450 mg	Elevation of liver enzymes, toxic hepatitis; allergy, fever; gastrointestinal disorders: anorexia, nausea, vomiting, abdominal pain; discoloration (orange or brown) of urine, tears and other body fluids; thrombopenia.	Many drug interactions: induces cytochrome p450, reduces effectiveness of oral contraceptive pill; (for ART drug interactions see table 3).	Monitor LFTs*.
Rifabutin (RB)	300 mg/day	Gastrointestinal discomfort; discoloration (orange or brown) of urine and other body fluids; uveitis; elevated liver enzymes; arthralgia.	Weaker inductor of cytochrome p450 than rifampin; (for ART drug interactions see table 3).	Monitor LFTs; generally preferred instead of rifampin in patients treated with ART drugs (see table 3).
Isoniazid (INH) Also available for i.v. or i.m. injection	5 mg/kg maximum 300 mg/day, administer vitamin B6	Peripheral neuropathy; elevated liver enzymes, toxic hepatitis; CNS** side effects: psychosis, seizurs.	Avoid ddC, d4T, ddI.	Avoid administration if preexisting liver damage; avoid alcohol.
Ethambutol (EMB)	40-55 kg: 800 mg/day 56-75 kg: 1.2 g/day 76-90 kg: 1.6 g/day	Optic neuritis; hyperuricemia; peripheral neuropathy (rare).	Antiacids may decrease absorption.	Baseline screen for visual acuity and colour perception, (repeated monthly); contraindicated in pts with preexisting lesions of optic nerve.
Pyrazinamide (PZA)	30 mg/kg/day maximum 2.0 g/day	Arthralgia, hyperuricemia, toxic hepatitis, gastro-intestinal discomfort		Hyperuricemia: uricosuric drug (allopurinol); monitor LFTs.

Streptomycin i.v./i.m. administration only	0.75-1 g/day < 50 kg: 0.75 g/day > 50 kg: 1 g/day maximum cumulative dose 50 g	Auditory and vestibular nerve damage; renal damage; allergies, nausea, skin rash, leukopenia, thrombopenia, pancytopenia, hemolytic anemia.	Audiometry; cumulative dose should not be exceeded; monitor renal function; should not be used in pregnancy.
Amikacin i.v./i.m. administration only	1 g/day maximum cumulative dose 50 g	Auditory and vestibular nerve damage;	Audiometry; cumulative dose should not be exceeded; monitor renal function; should not be used in pregnancy.
Capreomycin i.v./i.m. administration only	15 - 30 mg/kg/day max 1 g/day > 50 kg: 1 g < 50 kg: 0.75 g maximum cumulative dose: 50 g	Renal damage, Bartter-like syndrome, auditory nerve damage.	Audiometry; cumulative dose should not be exceeded; monitor renal function; should not be used in pregnancy.
Prothionamide	0,75 –1 g/day	CNS disorders; liver damage, gastrointestinal discomfort	Slowly increase dosage; monitor LFTs
Moxifloxacin Also available for i.v. injection	400 mg/ day	Gastrointestinal discomfort, headache, dizziness, hallucinations.	Similar activity as rifampin, drug resistance is still rare.
Levofloxacin Also available for i.v. injection	500 or 1,000 mg/day	Gastrointestinal discomfort, CNS disorders, tendon rupture (rare).	Not approved for treatment in children; in adults rather use moxifloxacin.

Ciprofloxacin Also available for i.v. injection	500 BID or 750 mg/day	Gastrointestinal discomfort, CNS disorders, tendon rupture (rare).		Not approved for treatment in children; in adults rather use moxifloxacin.
Cycloserine	10-15 mg/kg day maximum 1,000 mg/day	CNS disorders, anxiety, confusion, dizziness, psychosis, seizures, headache.	Aggravates CNS side effects of INH and prothionamide.	Contraindicated in epileptics; CNS side effects occur usually within the first 2 weeks.
Linezolid	600 mg BID	Thrombopenia, anemia, CNS disorders.		Evidence for clinical use relies on case reports; expensive.

*LFTs: Liver function tests.

** CNS: Central nervous system.

Patients who exhibit severe side effects should always be hospitalized for diagnosis and treatment. Drugs that could possibly be responsible for a given side effect are stopped. Reintroduction of the same drug must be avoided if visual dysfunction occurs on EMB therapy or renal failure, shock or occurs on RMP therapy and vestibular dysfunction occurs on streptomycin therapy. With the exception of RMP (in case of shock or thrombocytopenia), EMB and streptomycin, other drugs can be reintroduced one by one when symptoms resolve, beginning with the drug that is least likely to cause the adverse effect. All drugs should be restarted at low dosages and dosages should be increased stepwise (Table 2). When no adverse effects occur after 3 days, additional drugs can be added. The drug that is most likely to be responsible for an adverse effect should be the last to be restarted if no alternative is available.

If toxic hepatitis occurs, all drugs should be stopped until the serum bilirubin and liver transaminases (aminotransferase) have normalized. In many cases, it is possible to reintroduce the causative drug (usually INH, RMP or PZA) with increasing dosage without further hepatic complications.

In all cases, when second-line drugs are used it is usually necessary to prolong the standard duration of treatment.

Table 2: Reintroduction of antituberculous drug following drug adverse event

Drug	Day 1	Day 2	Day 3
INH	50 mg	300 mg	5 mg/kg/day (max 300 mg/day)
RMP	75 mg	300 mg	10 mg/kg/day (max 600 mg/day)
PZA	250 mg	1,000 mg	25 mg/kg/day (max 2 g/day)
EMB	100 mg	500 mg	25 mg/kg/day for 2 months then 15 mg/kg/day
Streptomycin	125 mg	500 mg	15 mg/kg/day (max 1 g/day)

ART and TB therapy

Independently on the status of ART, uncomplicated non-cavitary pulmonary TB in HIV-infected patients can be treated using standard 6 months course with a similar success rate as HIV-seronegative individuals (Burman 2001, Chaisson 1996, Hung 2003). If the therapeutic response is delayed (e.g. when sputum cultures are still MTB positive after 2 months of the initial phase), the duration of TB therapy should be extended to at least 9 months.

A few issues must be considered regarding simultaneous ART and TB therapy.

Paradoxical reaction: Following initiation of antituberculous therapy, patients already treated with ART present paradoxical reactions (increasing lymphadenopathy, fever or increasing pulmonary infiltrates) five times more often than ART naïve patients (Narita 1998, Breen 2005). An acute exacerbation of TH1 immune response against mycobacteria antigens seems to be responsible for the paradoxical reaction in ART experienced HIV-MTB co-infected patients (Bourgarit 2006).

Adherence: Adherence to therapy is very difficult due to the large number of ART and antituberculous pills administered simultaneously and overlapping toxicities. The most important factor for the success of antituberculous treatment is drug adherence for the entire duration of therapy. In case of poor compliance, development of drug resistance and relapses are common. The WHO recommends that all patients with TB should therefore be enrolled in therapeutic programs based on directly observed therapy (DOT).

Drug interactions: There are many pharmacological interactions between ART and antituberculous drugs (Table 3 and 4). Both RMP and protease inhibitors (PIs) are metabolized by cytochrome P450 3A. As RMP and PIs serum levels are unpredictable when they are administered simultaneously, concomitant therapy with PIs and RMP is generally not recommended (exception: ritonavir ± saquinavir and ritonavir-hyper boosted lopinavir) (OARAC DHHS Panel Guidelines, October 2006) (Table 3). Either the combination of 2 nucleoside reverse transcriptase inhibitors (NRTIs) with the non-nucleoside reverse transcriptase inhibitor (NNRTI) efavirenz or the suboptimal combination of 3 NRTIs are possible therapeutic options for treating HIV infection during TB treatment with RMP. As an alternative to RMP, RB (another rifamycine) can be co-administered with PIs as it is a weaker inductor

of cytochrome P450-3A than RMP. Anyway, RB dosage adjustments have to be considered (table 4). There are not yet available clinical data on the use of rifamycines with enfurvirtide or tenofovir, but their combination may be safe to use as both drugs are not metabolized by cytochrome P450-3A.

Table 3: Recommendations for co-administering ART with Rifampin*

Drug	Antiretroviral dosage adjustment	Rifampin dosage adjustment
Amprenavir	Should not be co-administered	
Fosamprenavir	Should not be co-administered	
Atazanavir	Should not be co-administered	
Darunavir	Should not be co-administered	
Indinavir	Should not be co-administered	
Nelfinavir	Should not be co-administered	
Ritonavir	None	None (600 mg/day)
Saquinavir	Should not be co-administered	
Lopinavir/ritonavir	Should not be co-administered	
Saquinavir/ritonavir	400 mg BID/400 mg BID	None (600 mg/day)
Tipranavir	Should not be co-administered	
Efavirenz	600-800 mg/day	None (600 mg/day)
Nevirapine	Should not be co-administered	
Delavirdine	Should not be co-administered	

* OARAC DHHS Panel Guidelines, October 2006 (modified)

Priority: Treatment of active TB always has clinical priority over the treatment of HIV. When TB occurs in ART naïve patients with advanced immunodeficiency (i.e. less than 100 CD4+ T cells/µl) the risk of mortality is high and simultaneous treatment of both infections is indicated (Dean 2002). Even in this situation, it is recommended that antituberculous therapy be started first and the initiation of ART be delayed for at least two weeks. Providing the antituberculous therapy is tolerated, ART should be introduced. However, patients need to be monitored closely as the risk of paradoxical reaction is high and there are some overlapping toxicities.

In patients with CD4+ T cell count of 100 - 200/µl who develop TB, antituberculous therapy must be started as soon as possible and the initiation of ART can be delayed for at least two months; by this time, the number of antituberculous drugs has been reduced to two for the continuation phase.

When TB occurs at CD4+ T cell count higher than 200/µl, completion of antituberculous treatment is usually recommended before the initiation of ART.

Patients who are already on ART when TB develops should remain on antiviral treatment, although ART should be modified depending on the compatibility with antituberculous drugs (Dean 2002).

Patients with advanced immunodeficiency remain at high risk of developing TB despite ART (Lawn 2005a, b, Bonnet AIDS 2006) as the function of immune system is not fully restored by ART (Sutherland 2006, Lange 2003).

Table 4: Recommendations for co-administering ART with Rifabutin*

Drug	Antiretroviral dosage adjustment	Rifabutin dosage adjustment
Amprenavir	None	Decrease 150 mg/day or 300 mg 3x/week
Fosamprenavir	None	Decrease 150 mg/day or 300 mg 3x/week
Atazanavir	None	Decrease 150 mg every other day or 150 mg 3x/week
Darunavir	None	Decrease 150 mg every other day or 150 mg 3x/week
Darunavir/ritonavir	None	Decrease 150 mg every other day or 150 mg 3x/week
Indinavir	Increase 1,000 mg TID	Decrease 150 mg/day or 300 mg 3x/week
Indinavir/ritonavir	None	Decrease 150 mg every other day or 150 mg 3/week
Nelfinavir	Increase 1,000 mg TID	Decrease 150 mg/day or 300 mg 3x/week
Ritonavir	None	Decrease 150 mg every other day or 150 mg 3x/week
Saquinavir	Should not be co-administered	
Lopinavir/ritonavir	None	Decrease 150 mg every other day or 150 mg 3x/week
Saquinavir/ritonavir	None	Decrease 150 mg every other day or 150 mg 3x/week
Tipranavir	None	Decrease 150 mg every other day or 150 mg 3x/week
Efavirenz	None	Increase 450-600 mg/day or 600 mg 3x/week
Nevirapine	None	None (300 mg/day)
Delavirdine	Should not be co-administered	

* OARAC DHHS Panel Guidelines, October 2006 (modified)

Therapy of latent TB infection (LTBI)

Persons with LTBI do not have any symptom or sign, have inactive MTB bacteria in their body and usually have a positive reaction to the TS test. Diagnosis is based on positive TS test or positive IFN-γ blood test. They are infected with MTB, do not have active TB disease, are not infectious and cannot spread TB infection to others. Experts recommend treatment for LTBI to prevent TB disease. According to USA Centres for Disease Control and Prevention (CDC) Guidelines (2006) for the treatment of LTBI, persons included in high-risk groups (HIV-infected persons, recent contacts of a TB case, persons with fibrotic changes on chest x-ray consistent with old TB, patients with organ transplants, persons who are immunosuppressed for other reasons, e.g. therapy with prednisone or TNF-α antagonists) should be given treatment if their reaction to the TS test is ≥5mm. In addition, treatment of LTBI should be offered to persons included in other high-risk groups (recent arrivals from

high-prevalence countries, injection drug users, employees of health care facilities, mycobacteriology laboratory personnel, children < 4 years of age, or children and adolescents exposed to adults in high-risk categories) if their reaction to the TS test is ≥10 mm.

For the treatment of LTBI, a 9 month course of INH (300 mg daily) and pyridoxine is usually recommended. Alternatively, treatment with RMP (600 mg daily) could be offered. A recent Cochrane review showed that short course (2 months) multidrug regimens (RMP+PZA) were much more likely to require discontinuation of treatment due to adverse hepatic effects in comparison to INH monotherapy (Woldehanna 2004). Generally, RMP+PZA regimens should not be offered for the treatment of LTBI (CDC Guidelines, 2006).

HIV-infected patients with LTBI have higher risk of developing active TB than HIV-seronegative persons. The efficacy of prophylactic INH treatment to prevent TB in HIV-infected patients with LTBI has been demonstrated in several randomized and controlled studies (Bucher 1999, Elzi 2007). However, ART naïve patients with negative TS test do not benefit from either primary (Bucher 1999) or secondary chemoprophylaxis of TB (Churchyard 2003). In addition, chemoprophylaxis with INH has no positive effect on the overall mortality of these patients (Woldehanna 2004). Offering prophylactic INH chemotherapy to all HIV-infected subjects in a country with high incidence of TB reduced TB incidence only from 11.9 to 9.0 per 100 person/year (Grant 2005). Although ART has beneficial effect on the prognosis of HIV-positive patients with active TB, the effects of ART on HIV-positive patients with LTBI are so far unknown.

Drug resistant TB: Multidrug resistant (MDR) TB and Extensively drug resistant (XDR) TB

MDR TB means TB caused by MTB isolates resistant to at least RMP and INH, two of the best antituberculous drugs. Despite declining numbers of TB cases in many industrialized nations in recent years, the proportion of MDR TB is rising in many countries. In Germany, in 2004, 13.9 % of all MTB isolates were resistant against one of the first-line drugs; 2.5 % of the MTB isolates were MDR (RKI 2006). In the future, an increase in the number of patients with drug resistant TB is expected worldwide. In some areas, such as the Baltic region, the rate of INH resistant MTB isolates is already greater than 25 % (Morozova 2003). Under these circumstances, selection of the correct drug regimen for treatment of LTBI and active TB becomes problematic.

Where possible, patients with MDR TB should be treated in specialized centres with second-line antituberculous drugs and should not be discharged before repeated sputum cultures give MTB negative result. Depending on susceptibility drug test results, a combination of EMB, streptomycin, cycloserine, moxifloxacin and/or linezolid may be administered.

XDR TB is defined by the WHO (Global Task Force on XDR TB) as TB resistant to at least RMP and INH and also resistant to fluoroquinolones (moxifloxacin and levofloxacin) and to at least one of the injectable drugs (capreomycin, kanamycin and amikacin) (Report WHO/HTM/TB/2006.375, World Health Organization, Geneva, 2006).

The term XDR TB was first used in March 2006 by the USA CDC in a report on MDR TB compiled after laboratory surveillance from a number of countries (CDC report, Nature Medicine volume 13, number 3, 295-298, March 2007). This lethal MTB strain blazed in 2005 across Tugela Ferry, a small village in South Africa. The MTB strain, dubbed XDR for its extensively drug resistance, does not respond to known TB drugs and killed 52 out of 53 infected individuals (all of which were HIV-positive) all of them within weeks of diagnosis. Since then, XDR MTB isolates have appeared in every part of the world. Population data demonstrated that in the USA, Latvia and South Korea prevalence of XDR TB is 4%, 19% and 15% of all MDR TB cases, respectively.

Some cases have shown that cure is possible by treatment based on susceptibility drug test. Successful therapy depends greatly on the extent of the drug resistance, the severity of active TB and whether the patient's immune system is weakened.

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Atypical mycobacteriosis (MAC)

Atypical mycobacterioses are usually synonymous for infections with *Mycobacterium avium complex* (MAC). Although MAC is by far the most frequent pathogen, numerous other atypical mycobacterioses exist that cause a similar disease pattern, such as *M. celatum*, *M. kansasii*, *M. xenopi* or *M. genavense*. MAC bacteria are ubiquitous and can be found in diverse animal species, on land, in water and in food. Exposure prophylaxis is not possible; isolation of infected patients is not necessary. While MAC may be detectable in the sputum or stool of asymptomatic patients (colonization), only patients with less than 50 CD4 cells/µl develop disease (Horsburgh 1999). This used to include up to 40 % of AIDS patients in the pre-HAART era (Nightingale 1992).

The infection has now become very rare in industrialized countries (Karakousis 2004). However, it remains important, as it has developed into a completely new disease in the HAART era. It previously occurred mainly with a chronic, disseminated course of disease, often in patients with wasting syndrome. MAC infections under HAART are now almost always localized and related to an immune reconstitution syndrome. The disease now occurs with manifestations that were previously never seen (see below).

Signs and symptoms

The symptoms of *disseminated* MAC infection are unspecific. When the CD4-cell count is less than 100/µl, fever, weight loss and diarrhea should always lead to consideration of atypical mycobacteriosis. Abdominal pain may also occur. As described above, disseminated MAC infection has now become rare.

Localized forms are far more frequent. These include, above all, lymph node abscesses, which may occur practically everywhere. We have seen abscesses in cervical, inguinal and also abdominal lymph nodes, some of which developed fistulae and resolved only slowly even after surgical intervention. Any abscess appearing whilst on HAART (with severe immunosuppression) is highly suspicious of MAC! In addition to skin lesions, localized forms include osteomyelitis, particularly of the vertebrae, and septic arthritis (observed: knee, hand, fingers).

Diagnosis

Diagnosis of the disseminated form is difficult. Blood cultures (heparinized blood) should always be sent to a reference laboratory. Although atypical mycobacteria usually grow more rapidly than TB bacteria, the culture and differentiation from TB may take weeks. In cases presenting with anemia, bone marrow aspiration is often successful. If atypical mycobacteria are detected in the stool, sputum or even BAL, it is often difficult to distinguish between infection requiring treatment and mere colonization. In such cases, treatment should not be initiated if general symptoms are absent. This is also true for *Mycobacterium kansasii* (Kerbiriou 2003).

Laboratory evaluations typically show elevated alkaline phosphatase (AP) - a raised AP with poor immune status is always suspicious of MAC. Similarly, MAC infection should be considered in any cases of anemia and constitutional symptoms. Cytopenia, particularly anemia, often indicates bone marrow involvement. Ultra-

sound reveals enlargement of the liver and spleen. Lymph nodes are often enlarged, but become apparent due to their number rather than their size (Gordin 1997). Here, differential diagnoses should always include TB or malignant lymphoma.

Direct specimens should always be obtained for localized forms, as identification of the organism from material drained from the abscess is usually successful.

Treatment

Treatment of MAC infection detected from culture is complex. Similarly to TB, monotherapy does not suffice. Since 1996, many clinicians prefer the combination of a macrolide (clarithromycin=C or azithromycin=A), rifabutin=R and ethambutol=E (Shafran 1996). In the past, this treatment was given lifelong; today it is generally considered sufficient to treat for at least six months and until an increase in the CD4-cell count to above 100/µl has been achieved. After publication of data indicating that rifabutin may be omitted from the regimen (Dunne 2000), the randomized ACTG 223 Study demonstrated survival benefit with the triple combination C+R+E compared to C+E and C+R – mortality rates were halved in the triple combination arm (Benson 2003).

Due to the high potential for interactions, however, rifabutin can be discontinued after several weeks when clinical improvement is observed. The clarithromycin dose should not exceed 500 mg bid. In at least two randomized studies, there was a significantly higher number of deaths in treatment arms with a higher clarithromycin dose, for reasons that remain unclear (Chaisson 1994, Cohn 1999). Instead of clarithromycin, azithromycin can also be given, which may be cheaper in some countries and which interacts less with cytochrome P450 enzymes. Azithromycin and clarithromycin have comparable efficacy in combination with ethambutol (Ward 1998).

In disseminated illnesses, treatment should be monitored through regular blood cultures. Cultures must be negative after 8 weeks, at the latest. In the localized from, the response can be assessed better clinically. Every MAC therapy has a high potential for side effects and drug interactions. The concomitant medications, including HAART, should be carefully examined – dose adjustments are frequently required and there may be contraindications (see Drugs section).

Reserve drugs such as amikacin, quinolones or clofazimine are only required in rare cases today. It is important to perform resistance testing for all atypical mycobacterial infections with species other than *M. avium complex*.

We have generally stopped treatment of localized MAC infections when the abscess has healed – this usually takes several months. In individual cases, steroids may be helpful temporarily. However, there are no specific guidelines for treatment of local MAC infections.

Prophylaxis

In the US, large placebo-controlled trials have shown that the macrolides, clarithromycin and azithromycin, as well as rifabutin, significantly reduce MAC morbidity and mortality when used for primary prophylaxis in severely immunocompromised patients (Havlir 1996, Nightingale 1992, Pierce 1996, Oldfield 1998). Prophylaxis also saves costs (Sendi 1999). However, MAC infections are more rare

in Europe. As a result, and because of concerns over compliance and development of resistance, few patients in Europe receive primary MAC prophylaxis (Lundgren 1997).

For patients failing currently available HAART regimens and without new treatment options, prophylaxis with a macrolide should be considered at low CD4-cell counts (below 50/µl). Weekly dosing with azithromycin is convenient for patients and has comparable efficacy to daily rifabutin (Havlir 1996).

Primary prophylaxis and maintenance therapies (see Treatment) can be discontinued quite safely at CD4-cell counts above 100/µl (Currier 2000, El Sadr 2000, Shafran 2002, Aberg 2003). It is possible that even partial viral suppression suffices for MAC-specific immune reconstitution (Havlir 2000). Complete recovery as a result of immune reconstitution is possible (Aberg 1998).

Treatment/prophylaxis of MAC (daily doses, if not specified otherwise)

Acute therapy		
Treatment of choice	Clarithromycin + ethambutol + possibly rifabutin	Clarithromycin 1 tbl. à 500 mg bid plus ethambutol 3 tbl. à 400 mg qd plus rifabutin 2 tbl. à 150 mg qd
Alternative	Azithromycin + ethambutol + possibly rifabutin	Azithromycin 1 tbl. à 600 mg qd plus ethambutol 3 tbl. à 400 mg qd plus rifabutin 2 tbl. à 150 mg qd
Maintenance therapy		As for acute therapy, but without rifabutin Discontinue if > 100 CD4 -cells/µl > 6 months
Primary prophylaxis		Consider for CD4 cells < 50/µl Discontinue if > 100 CD4 cells/µl > 3 months
Treatment of choice	Azithromycin	Azithromycin 2 tbl. à 600 mg/week
Alternative	Clarithromycin	Clarithromycin 1 tbl. à 500 mg bid

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Herpes simplex

Herpes simplex infections are a frequent problem for HIV patients. With a significant immune deficiency (under 100 CD4 cells/µl), chronic courses of infection are possible. Two viruses should be distinguished.

HSV-1 is transmitted by contact with mucosal membranes (kissing), and causes itchy perioral blisters on the lips, tongue, gums or buccal mucosa.

HSV-2 is sexually transmitted and leads to herpetiform lesions on the penis, vagina, vulva and anus. These lesions significantly increase the risk of transmission of HIV (Freeman 2006, Ouedraogo 2006).

In severe cases, other organs may be affected. These include the esophagus (ulcers), CNS (encephalitis), eyes (keratoconjunctivitis, uveitis) and respiratory tract (pneumonitis, bronchitis). In such cases and with persistence for a period of more than four weeks, herpes simplex infection is AIDS-defining.

Signs and symptoms

The blisters itch and burn. Oral involvement may impair food intake. In cases of genital or anal herpes (proctitis!), urination and defecation can be very painful. Extensive lesions may occur with severe immunosuppression. Regional lymph nodes are often enlarged. The clinical symptoms of disseminated herpes infections depend on the organs affected.

Diagnosis

Diagnosis of oral, genital or perianal herpes can often be made clinically. If in doubt, a swab can be taken, placed in viral culture media and rapidly transported to the laboratory. Organ manifestations are usually diagnosed histologically. In HSV encephalitis, the diagnosis is difficult, as cerebrospinal fluid often does not help. Serologies are only useful if they are negative (seldom), thus making HSV infection improbable.

Treatment

Each treatment, whether topical, oral or systemic is more effective the earlier it is started. For patients with a good immune status and only discrete lesions, topical treatment with acyclovir cream or ointment is adequate. Penciclovir cream is probably as effective as acyclovir (Chen 2000) and allegedly less irritant, although significantly more expensive.

The nucleoside analog acyclovir remains the treatment of choice for systemic treatment. Acyclovir inhibits the DNA polymerase of herpes viruses. Resistances are rare, despite the fact that this agent has been used since 1977 (Levin 2004). Acyclovir is well tolerated and effective against both HSV-1 and HSV-2. Severe cases with mucocutaneous or organ involvement should be treated intravenously. As CNS levels are lower than in plasma, the dose should be increased to treat encephalitis. If acyclovir is to be given intravenously, renal blood values should be checked.

Valacyclovir and famciclovir are equally effective alternatives to acyclovir (Ormrod 2000, Conant 2002), though more expensive (more than 100 Euro/week!) and not licensed for treatment of immunocompromised patients. The advantage is their improved oral bioavailability – they require less frequent dosing. They should be used when acyclovir is not effective. For stubborn herpes lesions, we have had good experience with famciclovir, a prodrug of penciclovir (Vinh 2006). Brivudin remains a good alternative for HSV-1 and VZV. However, it is possible that this dihydropyrimidine dehydrogenase inhibitor causes mitochondrial toxicity and even reduces the efficacy of HAART (U. Walker 2005, personal communication). Foscarnet should only be used in exceptional cases.

Newer drugs that, unlike acyclovir, do not inhibit DNA polymerase but helicase, another herpes virus enzyme, have been more effective than acyclovir and well tolerated in animal studies – their value remains to be shown (Kleymann 2002+2003).

A local anesthetic that can be produced by the pharmacist can be prescribed in addition for painful mucocutaneous lesions. Unfortunately, the approved tetracaine solution (Herviros™) has been taken off the market. Some pharmacists can, however, make-up something similar.

Prophylaxis

Primary prophylaxis is not recommended. However, a meta-analysis showed that on acyclovir the risk of both HSV and HZV disease was reduced by more than 70 % and even mortality was decreased by 22 % (Ioannidis 1998): this is however, relative in the age of HAART. Nevertheless: it can make sense, even today, to treat persistent recurrences with long-term low dose acyclovir or valcyclovir (DeJesus 2003, Warren 2004).

Treatment/prophylaxis of HSV infection (daily doses)

Acute therapy		Duration: 7-14 days
1st choice	Acyclovir	Acyclovir 1 tbl. à 400 mg 5x/day
Severe cases		Acyclovir ½-1 amp. à 500 mg tid (5-10 mg/kg tid) i.v.
Alternatives	Valacyclovir	Valacyclovir 2 tbl. à 500 mg tid
Alternatives	Famciclovir	Famciclovir 1 tbl. à 250 mg tid
Alternatives	Brivudin	Brivudin 1 tbl. à 125 mg qd
Prophylaxis		Not recommended

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Herpes zoster

Herpes zoster is the reactivation of an earlier infection with varicella virus, which subsequently resides lifelong in the spinal ganglia. Herpes zoster episodes occur even in HIV patients with relatively good immune status, and are also seen during immune reconstitution (Martinez 1998). With more advanced immunodeficiency, herpes zoster tends to become generalized. In addition to involvement of one or more dermatomes, dangerous involvement of the eye (affecting the ophthalmic branch of the trigeminal nerve, "herpes zoster ophthalmicus", with corneal involvement) and ear (herpes zoster oticus) may occur. Most feared is involvement of the retina with necrotizing retinitis. The neurological complications include meningoencephalitis, myelitis and also involvement of other cranial nerves (Brown 2001).

Signs and symptoms

There are often prodromal signs with headache, malaise and photophobia, accompanied only rarely by fever. The affected areas are initially hypersensitive, and then become pruritic and/or painful within hours or days. Pain can precede lesions by several days. Lesions often show segmental (always unilateral!) erythema with herpetiform blisters within one or more dermatomes. Lesions ulcerate, are often hemorrhagic, and gradually dry up. They should be kept dry and clean to avoid bacterial superinfection.

Involvement of several dermatomes often leaves treatment-resistant pain syndromes with zoster neuralgia. Post-herpetic neuralgia can be assumed if pain persists even after more than a month (Gnann 2002).

Diagnosis

Cutaneous involvement usually allows clinical diagnosis of herpes zoster. However, in untypical locations (the extremities!) and in complicated cases, the diagnosis can be difficult. Typical cases do not require further diagnostic tests. If there is uncertainty, a swab may be taken from a blister and sent to the laboratory in viral culture media. An immunofluorescence assay is presumably more reliable. VZV encephalitis is only detectable through analysis of CSF by PCR. Herpes zoster oticus should be considered in cases of unilateral, peracute hearing loss, which is not always visible from the outside. Either examine the ear yourself or consult an ENT specialist! For visual impairment the same rules apply as for CMV retinitis – refer to the ophthalmologist as quickly as possible!

Treatment

Monosegmental zoster can be treated on an outpatient basis with oral acyclovir. Rapid initiation of treatment is important. Systemic therapy is always necessary, and doses are higher than for HSV. Lesions dry up more rapidly if calamine lotion is used, which also relieves pain. Wear gloves! Lesions are highly infectious initially, and unvaccinated individuals without a history of chickenpox, especially pregnant women, should not come into close contact with a case of herpes zoster.

Analgesics (novaminsulfone, or better still tramadol) should be given generously. Any complicated, multi-segmental or facial herpes zoster should be treated with intravenous therapy, which can also be done well in ambulatory care with a competent nursing service.

As with HSV, several alternatives for treatment include valcyclovir, famciclovir and brivudin (see HSV). The unpleasant post-herpetic neuralgia allegedly occurs less frequently under these drugs than under acyclovir in HIV-negative patients (Gnann 2002). However, valcyclovir, famciclovir and brivudin have not been tested widely in HIV patients, and are not licensed for treatment of immunocompromised patients. They are also substantially more expensive than the numerous acyclovir formulations. Acyclovir resistance may occur in the thymidine kinase gene, but is rare (Gershon 2001, Saint-Leger 2001). In these cases, foscarnet can be given.

Pain management of post-herpetic neuralgia is a challenge. Carbamazepine or gabapentin only partially help. Steroids are not advised (Gnann 2002).

Prophylaxis

Varicella vaccination, previously contraindicated in HIV patients, seems to be fairly safe and effective thesedays for patients with more than 400 CD4 cells/µl, as shown in a placebo-controlled study (Gershon 2001), and should be considered if VZV serology is negative. In individuals with negative serology and exposure to VZV (highly infectious!), administration of hyperimmunoglobulin (2 mg/kg i.v.) may be attempted in individual cases. Long-term primary prophylaxis is not advised. However, long-term low-dose therapy can be useful for persistently recurring episodes.

Treatment/prophylaxis of VZV infection (daily doses)

Acute therapy		Duration: at least 7 days
1st choice	Acyclovir	Acyclovir 1 tbl. à 800 mg 5x/day
Severe cases		Acyclovir 1-2 amp. à 500 mg tid (10 mg/kg tid) i.v.
Alternatives	Valacyclovir	Valacyclovir 2 tbl. à 500 mg tid
Alternatives	Famciclovir	Famciclovir 2 tbl. à 250 mg tid
Alternatives	Brivudin	Brivudin 1 tbl. à 125 mg qd
Prophylaxis		Not recommended

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Progressive multifocal leukoencephalopathy

PML is a severe demyelinating disease of the central nervous system. It is caused by JC virus (JCV), a polyoma virus found worldwide. JCV was named after the initials of the first patient, from which this simple DNA virus was first isolated in 1971 (Major 1992). JC therefore has no connection, as is often wrongly assumed, with Jakob-Creutzfeld syndrome. As seroprevalence is high, at up to 80 %, latent persistent infection is assumed. Only impaired cellular immunity leads to reactivation of JCV and manifestation of disease. It seems certain that JCV reaches the CNS via leukocytes, and affects mainly oligodendrocytes and therefore the cells comprising the myelin sheaths. Destruction of these is macroscopically apparent as multifocal demyelination. The main focus of disease is the white matter of the cerebral hemispheres, but the cerebellum and in some cases the grey matter may also be affected. Severe immunodeficiency is frequently seen, but not obligatory for development of PML. In contrast to CMV or MAC infection, PML does not always indicate the final stages of HIV infection. Although CD4 cells are usually below 100/µl at manifestation of disease, PML may also occur at above 200 CD4 cells/µl. The decrease in incidence is not as marked as with other OIs. After cerebral toxoplasmosis, it is now probably the second most common neurological OI (Antinori 2001).

Prognosis was poor in the pre-HAART era. The median interval between the onset of the first symptoms and death was between 3 and 6 months. Patients usually died of secondary complications after being bedridden for many weeks. The prognosis is slightly better at CD4-cell counts above 200/µl (Berger 1998). Disease progression seems to be much slower under HAART, and even complete remission seems possible (Albrecht 1998). However, these effects are not as impressive as for other OIs: in a Spanish study of 118 PML patients on HAART, 64 % were still alive 2.2 years after diagnosis (Berenguer 2003). Complete remissions are not the rule, even under sufficient HAART. They mainly happen in inflammatory PML, which occurs in the course of an immune reconstitution syndrome (Du Pasquier 2003, Hoffmann 2003).

Signs and symptoms

Although there is a broad spectrum of PML symptoms due to the variety of localized areas of demyelination, the clinical signs and course of disease have several common characteristics. In addition to cognitive disorders, which may range from mild impairment of concentration to dementia, focal neurological deficits are very typical of PML. Mono- and hemiparesis are observed most frequently, as well as speech and even visual deficits. We have seen several blind patients with PML. These deficits may be isolated and initially present as discrete changes in coordination, rapidly leading to considerable disabilities. Epileptic seizures may occur. Loss of sensibility, fever, and headache are rare and are usually more typical of cerebral toxoplasmosis.

Diagnosis

Clinical suspicion of PML should be rapidly confirmed radiologically. However, on CCT the (hypodense) lesions are not clearly seen. MRI is much more sensitive for

detecting both the number and size of lesions and usually shows high signal intensity lesions in T2-weighted imaging and in FLAIR sequence, which are hypointense in T1-weighted imaging and usually show no gadolinium enhancement or mass effect. HAART may result in inflammatory courses that can involve significant enhancement (see Immune reconstitution syndrome). Exclusion of grey matter is typical – since this is a leukoencephalopathy. Also of note: lesions are almost always asymmetrical!

MRI often allows distinction from cerebral toxoplasmosis or lymphoma. However, the huge, extensive lesions covering an entire hemisphere that are often shown in textbooks are not always present. Every PML starts small – very discrete, localized, solitary lesions can occur and certainly do not exclude the diagnosis. PML can occur everywhere in the brain, and there are no typically susceptible areas. Lesions are often parieto-occipital or periventricular, but the cerebellum may also be involved. It is important that the images are assessed by a radiologist or clinician familiar with PML. Even then, it is difficult to distinguish PML from HHV-6 infection (Caserta 2004) or HIV associated leukoencephalopathy (Langford 2002).

Clinicoradiological diagnosis is therefore not definitive. Examination of cerebrospinal fluid is important. Generally, if there is no other co-infection, unspecific inflammatory signs are absent, although the total protein content is usually slightly elevated. Pleocytosis is rarely seen, and more than 100/3 cells make PML unlikely. CSF should always be tested for JCV, or sent to a JCV-experienced laboratory. Newer PCR methods have a sensitivity of around 80 % and a specificity of over 90 %.

The diagnosis is very probable in cases of clinicoradiological suspicion and positive JCV PCR. In such cases, brain biopsies are superfluous. Nevertheless, negative PCR does not safely exclude PML. Levels of JCV viral load may vary significantly and do not correlate with the extent of lesions (Eggers 1999, Garcia 2002, Bossolasco 2005). Unfortunately, JCV PCR is even less useful in the age of HAART– many patients with PML have a low or undetectable JCV CSF viral load under HAART (Bossolasco 2005). Stereotactic brain biopsy may therefore become necessary in individual cases.

Treatment

A specific PML treatment is not available. Numerous strategies such as foscarnet, interferon, immune stimulants, steroids, or cytosine arabinoside (Hall 1998) are not effective. Cidofovir and camptothecin are two further drugs being discussed. It is feared that these drugs will have a similar fate in controlled studies. Camptothecin is an alkaloid cytostatic, which inhibits topoisomerase I, a nuclear enzyme that is required for DNA and therefore also JCV replication (O'Reilly 1997). Currently, only data from case studies and a small series of patients exist (Vollmer-Haase 1997, Royal 2003). In the small, usually uncontrolled studies described to date, cidofovir has had positive effects in some, but not all cases (De Luca 2001, Gasnault 2001, Herrero-Romero 2001, Marra 2002, Wyen 2004). So far, a real benefit has not been proven. Our own experience has been rather disappointing and, in a retrospective analysis of 35 patients, cidofovir was even associated with a poorer prognosis. However, this chiefly reflects that the study was not controlled and that cidofovir was mainly used in cases of progressive disease (Wyen 2004). Cidofovir

should therefore only be used in exceptions if HAART or optimization is not possible, or patients deteriorate clinically despite sufficient HAART.

In our view, the absolute priority at present should be to optimize ART in cases of PML. In 1998, we were able to show that prognosis significantly improved under HAART (Albrecht 1998). This has been confirmed by several other groups (Clifford 1999, Dworkin 1999, Gasnault 1999, Tantisiriwat 1999). As synergism between HIV and JCV has been demonstrated in vitro, maximal HIV suppression should at least be achieved. Although progression of disease has been described under sufficient antiretroviral therapy, HAART often remains the only real hope for patients today.

Prophylaxis

There is none. Exposure prophylaxis is also not possible.

Treatment/prophylaxis of PML

Acute therapy		
Treatment of choice	HAART	The most important goal is maximal HIV suppression and immune reconstitution!!!
Experimental	Cidofovir	Cidofovir 5 mg/kg i.v. every 7-14 days (plus probenecid/ hydration per protocol, see Drugs section)
Prophylaxis		Not available

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Bacterial pneumonia

Bacterial pneumonia occurs even with relatively good immune status (above 200 CD4 cells/µl). It is not as closely associated with immunodeficiency, and the decrease in incidence since the beginning of the HAART era has been more moderate than for other OIs. Only recurring, radiologically and culturally detected acute pneumonia (more than one in the last 12 months) is considered AIDS-defining. As with HIV negative patients, community-acquired pneumonia should be distinguished from nosocomial pneumonia. Evaluation of travel history is important, particularly for community-acquired pneumonia.

The bacteria that are most frequently found to cause community-acquired pneumonia in HIV infected patients are *Pneumococcus* and *Hemophilus influenza*. *Mycoplasma* is important to consider, particularly in younger patients. *Klebsiella*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* are other common pathogens. Legionella are rare. I.v. drug users develop community-acquired pneumonia significantly more often than other patient groups.

Nosocomial pneumonia is often caused by hospital germs (Klebsiella, Staphylococcus, Pseudomonas). In such cases, treatment depends on local resistance patterns and experience (Gant 2000, Vogel 2000).

Signs and symptoms/ Diagnosis

Acute, usually high, fever and productive cough are typical. Breathing may be painful because of accompanying pleuritis, but real dyspnea is rare. Auscultation almost always allows distinction from PCP. If something can be heard, PCP is unlikely! Chest radiography secures the diagnosis. CRP is significantly elevated, LDH often normal. Blood cultures should be taken at body temperatures above 38.5˚C and before starting treatment. Sputum culture is a simple method allowing determination of etiology in approximately half of all cases – however, its overall utilization remains controversial (Cordero 2002).

Treatment

General

Treatment of bacterial pneumonia in HIV infected patients is similar to that in HIV-seronegative patients. Therapy should always begin empirically, without waiting for sputum or blood culture results. Many HIV infected patients with bacterial pneumonia can be treated as outpatients. Patients with poor immune status, high fever (above 39.5˚C), poor compliance, signs of organ failure, CNS disorders (confusion) and poor vital signs (tachypnea, tachycardia, hypotonia), as well as older patients (above 65 years), should be hospitalized immediately.

Sufficient hydration is important in all patients. If patients remain in ambulatory care, this means that they must drink a lot (more than 2 l daily). The use of supportive therapy with expectorants or mucolytics such as N-acetylcysteine or antitussives is controversial. On adequate therapy, improvement can be expected within 48-72 hours. If patients, especially the severely immunocompromised, have a persistent fever, the treatment must be reconsidered after 72 hours at the latest. It

should be noted that the current first-line therapies are not effective against *Pseudomonas aeroginosa*!

Medication

Different drugs are possible for ambulatory treatment. Even an attempt with penicillin may be justified in some circumstances – depending on local rates of *Pneumococcus* and *Hemophilus influenzae* resistance. HIV infected patients frequently develop allergic reactions.

Aminopenicillins are effective against *Hemophilus influenza* and various gram negatives. However, when combined with clavulanic acid, which is active against beta-lactamase-producing bacteria, they are associated with more gastrointestinal complaints.

Newer oral cephalosporins have a broader spectrum against gram negatives, while at the same time having good efficacy against Pneumococcus and Hemophilus. They are, however, comparatively expensive.

Macrolides are advantageous for atypical bacteria such as Mycoplasma, Chlamydia and Legionella – but the proportion of macrolide-resistant Pneumococcus is increasing (14 % in Germany). Weaknesses also exist in the Hemophilus strains.

For quinolones, it should be noted that ciprofloxacin has no or only weak efficacy against many important pathogens. Therefore only newer quinolones should be used.

If patients are hospitalized, intravenous administration is possible initially. In these cases, at least two antibiotics should be combined.

Targeted treatment after isolation of the pathogen, and, in particular, treatment of nosocomial pneumonias, should depend on local resistance patterns and the recommendations of the in-house microbiologist.

Prophylaxis

The Pneumovax™ vaccine provides effective protection. It should be utilized in all HIV patients with adequate immune status (above 200 CD4 cells/µl).

Empiric treatment/prophylaxis of community-acquired bacterial pneumonia (daily doses) - there may be significant differences in price!

Outpatient		Duration: 7-10 days
Mild	Amoxicillin + clavulanic acid	1 tbl. à 875/125 mg tid
Mild	Clarithromycin	1 tbl. à 500 mg bid
Mild	Roxithromycin	1 tbl. à 300 mg qd
Mild	Cefuroxim	1 tbl. à 500 mg bid
Mild	Cefpodoxim	1 tbl. à 200 mg bid
Mild	Moxifloxacin	1 tbl. à 400 mg qd
Inpatient		
Severe	Piperacillin (+ tazobactam)	1 bottle à 4.5 g i.v. tid **plus**
	+ macrolide	roxithromycin 1 tbl. à 300 mg qd **or** clarithromycin 1 tbl. à 500 mg bid
Severe	Ceftriaxon	1 infusion à 2 g qd i.v. **plus**
	+ macrolide	roxithromycin 1 tbl. à 300 mg qd **or** clarithromycin 1 tbl. à 500 mg bid
Severe	Cefuroxim	1 infusion à 1.5 g tid i.v. **plus**
	+ macrolide	roxithromycin 1 tbl. à 300 mg qd **or** clarithromycin 1 tbl. à 500 mg bid
Prophylaxis	Vaccination (pneumococcal polysaccharide)	Pneumovax 23® pre-filled syringe i.m.

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Cryptosporidiosis

Cryptosporidiosis is a parasitic intestinal disease with fecal-oral transmission. It is mainly caused by the protozoon *Cryptosporidium parvum* (2 genotypes exist, genotype 1 is also known as *C. hominis*), and may affect both immunocompetent and immunocompromised hosts (review in: Chen 2002). First described in 1976, cryptosporidia are among the most important causes of diarrhea worldwide. the main sources of infection for this intracellular parasite are animals, contaminated water and food. The incubation period lasts approximately 10 days. While diarrhea almost always resolves within a few days in healthy hosts or in HIV infected patients with CD4-cell counts greater than 200/µl, cryptosporidiosis is often chronic in AIDS patients, and may become life threatening in severely immunocompromised patients (below 50 CD4 cells/µl) due to loss of water and electrolytes (Colford 1996). Chronic, and not acute, cryptosporidiosis is AIDS-defining.

Signs and symptoms

The watery diarrhea can be so severe that it leads to death as a result of electrolyte loss and dehydration. 20 bowel movements daily are not uncommon. Tenesmus is frequent, and there is often nausea and vomiting. However, the symptoms are highly variable. Fever is usually absent. The biliary ducts may occasionally be affected, with elevation of biliary enzymes. Pancreatitis is also possible.

Diagnosis

When sending in stool samples, it is important to specifically inform the laboratory of the clinical suspicion. Otherwise cryptosporidia are often overlooked. If the laboratory is experienced and receives the correct tip, just one stool sample is usually sufficient for detection. Antibodies or other diagnostic tests are, in contrast, not helpful. The differential diagnosis should include all diarrhea-causing pathogens.

Treatment

No specific treatment has been established to date. Diarrhea is self-limiting with a good immune status; therefore, poor immune status should always be improved with HAART – and this often leads to resolution (Carr 1998, Miao 2000). To ensure absorption of antiretroviral drugs, symptomatic treatment with loperamide and/or opium tincture (controlled drug prescription, to the maximum doses!) is advised. If this is unsuccessful, treatment with other anti-diarrheal medications, perhaps even sandostatin, can be attempted. Sufficient hydration is important – this may even require infusions.

We have seen good results in individual cases with the antihelminthic agent nitazoxanide (Cryptaz™ or Alinia™). Nitazoxanide was effective in a small, randomized study and is possibly the first drug with real efficacy for treating cryptosporidia (Rossignol 2001). In the American Expanded-Access Program (EAP), almost two thirds of the patients responded to treatment (Rossignol 2006). In June 2005, nitazoxanide was licensed for cryptosporidia-associated diarrhea. There is no approval for AIDS patients, either in the USA or in Europe, and this is unlikely to change in the near future. Already licensed in the USA for the treatment of diarrhea, an alter-

native, rifaximine (Xifaxan™ 2400 mg), a non-absorbable rifampicin derivative, will possibly be available soon. Data on AIDS patients with cryptosporidiosis are very promising (Gathe 2005).

If immune reconstitution cannot be achieved and the health insurance provider refuses, options become very limited: paromomycin, a nonabsorbed aminoglycoside antibiotic, is available in powder and tablet form, and has been used by many clinicians since a small, uncontrolled study showed a favorable effect on diarrhea (White 2001). In the only double-blind randomized study to date, however, there was no advantage over placebo (Hewitt 2000). There is possibly an effect in combination with azithromycin (Smith 1998).

Treatment/prophylaxis of cryptosporidiosis (daily doses)

Acute therapy		
Symptomatic	Loperamide +	Loperamide 1 cap à 2 mg 2–6 times daily **or**
		loperamide solution 10 ml (10 ml = 2 mg) 2–6 times daily **and/or**
	opium tincture	opium tincture 1 % = 5–15 drops qid
Symptomatic	Octreotide	Sandostatin solution for injection 1 amp à 50 µg s.c. bid or tid (increase dose slowly)
Curative attempt	Nitazoxanide	Nitazoxanide 1 tbl. à 500 mg bid
Curative attempt	Rifaxmin	Xifaxan™ 2 tbl. à 200 mg bid
Curative attempt	Paromomycin + Azithromycin	Humatin Pulvis™ 1 Btl. à 1 g tid plus 1 tbl. à 600 mg od
Prophylaxis		Exposure prophylaxis: no tap water

Prophylaxis

There is no generally accepted prophylaxis, although retrospective analyses have reported a protective effect of rifabutin and clarithromycin (Holmberg 1998). In our opinion, it is more important that patients, at least in countries with hygiene problems, do not drink tap water. Contact with human and animal feces should be avoided. We have observed that patients mainly become ill during the summer months, often after swimming in rivers. Cryptosporidia are resistant to most disinfectants. In hospital, however, the usual hygiene measures (gloves!) are adequate. Patients need not be isolated, but should not be put in the same room as other significantly immunocompromised patients.

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Cryptococcosis

Infections with the yeast *Cryptococcus neoformans* are feared, even though they are rare in Europe. In the USA and Southeast Asia, they are much more frequent and belong to the most important AIDS-defining illnesses worldwide. *C. neoformans* is probably transmitted via inhalation. Bird droppings are an important reservoir. The pulmonary infection may remain subclinical in immunocompetent patients, but is almost always followed by disseminated disease in HIV infected patients. Apart from the lungs, the main manifestation after hematogenic spread is in the CNS. CSF examination is therefore obligatory in every suspected case. However, isolated skin manifestations and lymphadenitis also occur. Organ involvement, such as in the urogenital or gastrointestinal tract, is rare.

Cryptococcosis almost always occurs with severe immunodeficiency. In a collection of 114 cases, 87 % had less than 100 CD4 cells/µl; the median CD4-cell count was 30/µl (Weitzel 1999). In addition, crytococcosis is relatively frequently seen in association with an IRIS.

Cryptococcosis is fatal if untreated. Treatment is lengthy, complicated and should be managed only on an inpatient basis. Relapses were frequent in the pre-HAART era (at least 15 %). Thesedays, they are rarer. The prognosis has improved considerably and mortality has decreased from 64 to 15/100 patient years – although early mortality has remained the same (Lortholary 2006).

Signs and symptoms

The CNS manifestation with encephalitis is the most frequent (approx. 80 %). Patients complain mainly of headache and fever. Clouding of consciousness (confusion) rapidly progresses over a few days. Disorders of gait, hearing or vision as well as paresis, particularly of the cranial nerves, may occur - intracranial pressure is almost always increased! However, meningeal symptoms are usually absent. In the course of an immune reconstitution syndrome, clinical symptoms are often atypical and characterized by extensive abscesses (Manfredi 1999).

Pulmonary disease leads to symptoms of atypical pneumonia with unproductive cough and chest pain. Skin lesions can initially resemble molluscum contagiosum, and later become confluent in the form of larger ulcerative lesions.

Diagnosis

Cryptococcosis is life threatening, and the mortality rate is between 6 and 25 % (Saag 2000). There is no time to lose - in every suspected case (e.g. positive cryptococcal antigen test), rapid examination of the lungs and CNS in particular should be initiated. Usually, the chest x-ray does not reveal much; therefore, an HRCT scan must be performed if pulmonary involvement is suspected. The spectrum of morphology on the image is very variable: diffuse small lesions similar to tuberculosis may occur, but there can also be sharply defined infiltrates reminiscent of bronchopneumonia. Cavitation and bronchiectasis may also be present. Every attempt should therefore be made to clearly identify the causative organism by BAL.

An MRI scan of the head should always be performed if there are neurological symptoms. However, in contrast to toxoplasmosis and cerebral lymphoma, it usually does not reveal much, and isolated or multiple mass lesions (cryptococcomas) are very rare. Nevertheless, intracranial pressure is often increased (fundoscopy: papillary edema?).

The most important test for cryptococcosis is lumbar puncture (after fundoscopy and MRI!). Diagnosis can be made via India ink stain in almost all cases. CSF must be examined even in cases with pulmonary or other manifestations to exclude CNS involvement. Cryptococcal antigen in the blood (titer > 1:8) is a good parameter and should always be determined. Blood cultures are also often positive. With cutaneous involvement, the diagnosis is usually made from a biopsy.

Treatment

Meningitis immediately requires a combination of antimycotics during the acute phase of treatment, followed by maintenance therapy with fluconazole (Saag 2000).

Combination prevents resistance and allows reduction of acute therapy to 4-6 weeks. The choice of combination is not clearly defined. In Germany, combination therapy with the three antimycotics amphotericin B, flucytosine and fluconazole is often used for meningitis. The triple therapy leads to complete remission of meningitis in around 80 % of cases (Weitzel 1999), and therefore possibly a slightly higher rate than under dual therapy with amphotericin B and flucytosine as favored in the United States (van der Horst 1997).

However, recent data is raising questions as to the superiority of triple therapy. In one smaller, randomized study of 64 patients in Thailand, the combination of amphotericin B and flucytosine was most effective, according to measurements of cryptococcal clearance in the CSF (Brouwer 2004). It was even significantly better than triple therapy and also amphotericin B and fluconazole.

Nevertheless, in view of the toxicity of flucytosine (which is now only available for infusion, but not in tablet form), we prefer the combination of amphotericin B and fluconazole. In untreated patients, we almost always start HAART during the acute phase of treatment.

In addition to having significantly lower toxicity, liposomal amphotericin B is slightly more effective than conventional amphotericin B (Leenders 1997, Hamill 1999). However, even combinations with liposomal amphotericin B are very toxic. Daily monitoring of kidney and liver enzymes, blood count and electrolytes are recommended. Fluconazole should be administered as an infusion, particularly in confused patients.

In cases of isolated pulmonary involvement (CSF negative!) or other extracerebral manifestations, we treat without flucytosine and complete the acute therapy with amphotericin B and fluconazole within two instead of four weeks. If there is a positive cryptococcal antigen test without evidence of CNS, pulmonary or other infection, we treat with fluconazole alone.

Treatment success is monitored based on the clinical course and repeated lumbar punctures. CSF is negative in approximately 60 % of cases after two weeks (Saag 2000). When this is the case, maintenance therapy can be started, though not sooner

than after four weeks of acute therapy. If there is increased intracranial pressure, CSF drainage may become necessary. Steroids are ineffective (Saag 2000).

Prophylaxis

Primary prophylaxis against *Cryptococcus neoformans* is not recommended, as even in endemic areas, it has not been shown to provide a survival advantage (McKinsey 1999, Chariyalertsak 2002). Likewise, exposure can presumably not be avoided.

Fluconazole is given as secondary prophylaxis or maintenance therapy. It is significantly more effective than itraconazole – in a large randomized study, the relapse rate on fluconazole was only 4 % compared to 23 % on itraconazole, and the study was prematurely discontinued (Saag 1999). Fluconazole can probably be discontinued with sufficient immune reconstitution (above 200 CD4 cells/µl, undetectable viral load for three to six months), as demonstrated in several studies (Aberg 2002, Kirk 2002, Vibhagool 2003, Mussini 2004), and after at least six months of maintenance therapy. It is prudent to check for cryptococcal antigen before stopping (Mussini 2004). Positive results, especially with high titers associated with increased risk of relapse (Lortholary 2006), require continuation of treatment.

Treatment/prophylaxis of cryptococcosis (daily doses, unless specified otherwise), see also Drugs section for further details!

Acute therapy		Duration: always at least six weeks
Treatment of choice	Amphotericin B	Amphotericin B 0.5-0.75 mg/kg qd **or**
		liposomal amphotericin B 3 mg/kg qd (preparation by pharmacy)
		plus
	+ fluconazole	fluconazole 1 bottle à 200 mg i.v. bid **or**
		fluconazole 1 cap. à 200 mg bid
		plus
	+ flucytosine *	flucytosine 1 bottle à 250 ml (2.5 g) i.v. qid
		(= 100-150 mg/kg distributed in four separate doses)
Maintenance therapy		Discontinuation possible from > 200 CD4 cells/µl > 3-6 months
Treatment of choice	Fluconazole	Fluconazole 1-2 cap. à 200 mg qd
Alternative	Itraconazole	Itraconazole 2 cap. à 100 mg bid
Primary prophylaxis		Not recommended

***Note:** We usually omit flucytosine. Instead, we begin with HAART during the acute therapy phase in those patients, who are almost always HAART naïve.

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Salmonella septicemia

Infection with non-typhoid Salmonella, which typically only causes enteritis in healthy individuals, can lead to severe septicemia in immunocompromised patients (Jacobs 1985). Important reservoirs are in food, especially poultry. Recurrent non-typhoid Salmonella septicemia is AIDS defining. In Central Europe, Salmonella septicemia is rare in HIV infected patients, and accounts for less than 1 % of AIDS cases. In the Swiss cohort of over 9,000 patients, only 22 cases of recurring salmonellosis were documented over a period of nine years (Burkhardt 1999). In Southern Europe or Africa, salmonellosis is much more frequent. In some regions, salmonella is actually the most common proven pathogen in blood cultures from HIV infected patients. In addition to septicemia, atypical infections with osteomyelitis, empyema, pulmonary abscesses, pyelonephritis or meningitis have been described (Albrecht 1992, Nadelman 1985).

Signs and symptoms/diagnosis

Patients are often severely ill. Chills and high fever are usually present, but diarrhea may be absent. If treatment is delayed, there is a danger of septic shock.

Blood cultures mainly lead to isolation of enteritis-causing Salmonella strains such as *S. enteritidis* and *S. typhimurium*. The pathogens causing typhoid or paratyphoid fever, *S. typhi* and *S. paratyphi*, are rare.

Treatment

Ciprofloxacin is the treatment of choice (Jacobson 1989). Although oral bioavailability is good, we prefer intravenous dosing. Cephalosporins such as cefotaxime or ceftriaxone are also effective. In contrast, resistance to co-trimoxazole or ampicillin has increased. One week of treatment with ciprofloxacin or ceftriaxone is usually enough. Maintenance therapy should continue for 6-8 months and not be stopped too early (Hung 2001). However, lifelong secondary prophylaxis, which was propagated in the past (Nelson 1992), no longer seems necessary.

Prophylaxis

Drug prophylaxis is not recommended. However, HIV infected patients should generally be told to pay attention to food hygiene.

Treatment/prophylaxis of Salmonella sepsis (daily doses)

Acute therapy		7-14 days
Treatment of choice	Ciprofloxacin	Ciprofloxacin 1 bottle à 200 mg i.v. bid
Alternative	Ceftriaxone	Ceftriaxone 1 bottle à 2 g i.v. qd
Prophylaxis		
	For relapses	Ciprofloxacin 1 tbl. à 500 mg bid (6-8 months)

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Immune reconstitution inflammatory syndrome (IRIS)

For the first time, in mid-1997 and early 1998, atypical manifestations of CMV retinitis (Jacobsen 1997) and MAC disease with abscess formation (Race 1998) were described for the first time in HIV infected patients within a few weeks of initiation of HAART. Although the pathogens and localization were very different, all these illnesses had a distinct inflammatory component and were associated with significant immune reconstitution in these patients. It was therefore postulated that a syndrome during which a latent infection present at initiation of therapy is fought more effectively by the recovering immune system (Overview: Shelbourne 2006).

Meanwhile, manifestations of numerous diseases have been attributed to the "immune reconstitution inflammatory syndrome" (IRIS). These usually differ significantly from the courses of diseases seen during the pre-HAART era. One should not be surprised by "atypical" clinical or radiological findings. IRIS has 3 rules:

1. Anything is possible.
2. Nothing is as it was in the pre-HAART era.
3. IRIS does not mean that HAART has failed. The prognosis is usually good!

How frequently does IRIS occur? In our experience, a frequency of 5-10 % in patients with less than 200 CD4 cells/µl is realistic. A high viral load before initiation of therapy or a rapid drop on HAART seems to be an important predictive factor for IRIS (Hoffmann 1999, Shelbourne 2005). However, the overall prevalence rate of 25 % cited elsewhere seems slightly too high (French 2000). If only the patients, who for example were infected with mycobacteria or cryptococcus before HAART was started, are taken into account, rates of 30 % were reached (Shelbourne 2005).

Mycobacterial IRIS. For MAC, the number of published cases with fistular lymphadenitis, cutaneous or muscular abscesses, osteomyelitis, nephritis or meningitis is too large to be cited here. In a total of 83 patients starting HAART with a CD4-cell count of less than 200/µl, we have seen 6 mycobacterioses, among these 4 MAC infections, within the first weeks of beginning therapy (Hoffmann 1999). Lymph node abscesses usually occur during the first weeks on HAART. Not all cases are avium: IRIS cases with *Mycobacterium xenopi* or *Mycobacterium kansaii* have also recently been described (Chen 2004, Phillips 2005).

There are now also numerous reports on tuberculosis (John 1998, Chien 1998), which are reminiscent of the "paradox" reactions to TB treatment known since the 1950s. Common to all these patients is the fact that, clinically, they initially deteriorate drastically under sufficient tuberculostatic treatment and HAART-induced immune reconstitution. Meningitis, as well as marked lymphadenopathy with unspecific histology, can complicate the course of disease, but respond astonishingly rapidly and well to steroids. In one study, four out of five patients, who had clinically developed atypical mycobacterioses after HAART and significant improvements in CD4-cell levels, showed a significantly increased MAC-specific T-cell response in vitro – proving in all likelihood that this phenomenon is indeed caused by the unmasking of subclinical infections (Foudraine 1999).

CMV IRIS. In addition to mycobacteriosis, numerous cases of unusual CMV infections under HAART have been published. Inflammatory CMV retinitis with vitritis that may lead to visual impairment, papillitis and macular edema, is now a distinct syndrome, differing significantly from the course of CMV retinitis seen in the pre-HAART era (Jacobson 1997, Whitcup 2000). Neovascularization endangers vision even after resolution (Wright 2003). A prospective study was conducted in 30 patients with CMV retinitis that had reached levels of more than 60 CD4 cells/µl for at least 2 months on HAART. Of these, 19 patients (63 %!) developed symptomatic vitritis, in some cases with considerable loss of vision (Karavellas 1999). In one small prospective cohort, the proportion reached 12 out of 14 patients (Whitcup 1999). As with MAC disease, in vitro studies have shown that the CMV-specific immune response is improved most significantly in those patients developing vitritis (Mutimer 2002, Stone 2002). Inflammatory CMV manifestations are not limited to the retina and may involve other organs (Gilquin 1997).

PML IRIS. The course of inflammatory PML that occurs during an IRIS is different from the infaust prognosis seen during the pre-HAART era (Cinque 2001, Collazos 1999, Kotecha 1998, Miralles 2001). Clinical symptoms are often more fulminant initially, and on radiology there is a contrast enhancement, which is atypical for PML, that may resolve over time. Patients have a better prognosis, and PML seems to even resolve completely (Hoffmann 2003, Du Pasquier 2003). We are following several patients with inflammatory PML who have been asymptomatic for years, some of whom live without any residual symptoms. However, fatal cases of inflammatory PML have also been reported (Safdar 2002). In our experience, steroids are ineffective, although there have been accounts of positive results (Nuttall 2004).

Cryptococcal IRIS. Numerous cases with inflammatory courses of disease have been described (Manfredi 1999, Woods 1998, Cinti 2001, Breton 2002, Jenny-Avital 2002, King 2002, Boelaert 2004, Lortholary 2005, Shelbourne 2005, Skiest 2005). After MAC/TBC and CMV, cryptococci are probably the most important IRIS pathogens. In particular, severely immunocompromised patients who start with HAART after cryptococcal therapy should be watched closely for the first few weeks and months. Newer studies show that 10-30 % of patients with co-infections develop a cryptococcal IRIS (Lortholary 2005, Shelbourne 2005). The MRI usually shows choriomeningitis with significant enhancement in the choroid plexus. Cryptococcal antigen in the CSF is positive, although culture remains negative (Boelaert 2004). The intracranial pressure is often particularly high (Shelbourne 2005). As well as meningitis, lymphadenitis can also occur (Skiest 2005).

Other infections. There are now various case studies, including leishmaniasis (Jiménez-Expósito 1999), pneumocystoses (Barry 2002, Koval 2002), cerebral toxoplasmosis (Tsambiras 2001, Stout 2002, Ghosn 2003) and herpes infections (Fox 1999). Herpes zoster and hepatitis B or C episodes also seem to occur on HAART, particularly during the first weeks (Behrens 2000, Chung 2002, Manegold 2001, Martinez 1998, Domingo 2001). HHV-8-associated Kaposi's sarcoma can worsen significantly on HAART in the presence of an IRIS (Bower 2005, Leidner 2005). Increasing dermatological problems such as exacerbation of pre-existing folliculitis or skin disease have also been reported (Handa 2001, Lehloenyia 2006). There are even reports about parvovirus and leprosy (Nolan 2003, Couppie 2004).

Other diseases. For a long time, diseases other than opportunistic infections have been recognized to occur under IRIS, including autoimmune diseases such as Graves' disease, lupus, Sweet's and Reiter's syndromes, Guillain-Barré syndrome, acute porphyria and sarcoidosis, to name but a few (Bevilacqua 1999, Behrens 1998, Fox 1999, Gilquin 1998, Makela 2002, Mirmirani 1999, Neumann 2003, Piliero 2003). Two cases of Peyronie's disease, a fibrosis of the penis, were reported (Rogers 2004)! These reports do lead one to wonder whether all of these manifestations are truly induced by immune reconstitution or perhaps merely chance occurrences. While most publications initially offered little information on the etiology beyond purely hypothetical discussions, it has recently become apparent that changes in the cytokine profile are involved in the pathogenesis of IRIS, together with an activation of the cellular immune response. However, it seems that the mechanisms differ according to disease and genetic profile (Price 2001, Shelbourne 2005).

Consequences

Patients starting HAART with less than 200 CD4 cells/µl (and particularly those who have a high viral load) require close clinical monitoring during the first weeks. It is important to be alert especially in very immunocompromised patients who have previously declined antiretroviral treatment, but now feel physically "affected" (subfebrile?) and want to start HAART "after thinking about it for a long time". Latent infections are often present in such cases, and these will rapidly become apparent as immune reconstitution occurs. The poorer the immune status, and the longer its duration, the higher the danger of IRIS!

Chest radiography, abdominal ultrasound and fundoscopy should be included in routine investigations of such patients before starting treatment. Clinical examination, often overlooked today, is to be taken seriously! The suggestion by some authors to start MAC prophylaxis even before HAART in severely immunocompromised patients seems problematic. Prophylaxis cannot prevent MAC IRIS (Phillips 2002 + 2005). Prospective clinical studies have yet to prove whether administration of IL-2 or GM-CSF is worthwhile (Pires 2005).

Mycobacterioses in particular should be treated generously with steroids. One should always be prepared for atypical localizations, findings and disease courses of opportunistic infections. The prognosis of IRIR is generally good, and the mortality is no higher than that of patients without IRIS (Park 2006).

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Wasting syndrome

Classic wasting syndrome is defined as involuntary weight loss of at least 10 % of original body weight, accompanied by persistent diarrhea (at least two bowel movements daily for more than 30 days) or extreme fatigue and/or fever without apparent infectious etiology. Wasting syndrome is therefore a classical exclusion diagnosis and really an epidemiological instrument rather than a specific disease – with thorough and competent searching, a specific causative agent can usually be found. Although very frequent in the past, classic wasting syndrome has become rare in the HAART era. In a large study conducted in 2000, however, 14 % of patients still indicated having lost more than 10 % of their original body weight (Wanke 2000). Wasting rates are even higher in intravenous drug users (Campa 2005). Weight loss remains an independent risk factor for mortality, even in the HAART era, and every patient should be weighed regularly! In one large study, mortality risk in patients with a loss greater than 10 % of body weight was more than 4-6-fold above that of patients with stable body weight (Tang 2002). Patients with classic wasting syndrome are often extremely weak. The risk for opportunistic infections is significantly elevated (Dworkin 2003). There is also cognitive impairment in these patients (Dolan 2003).

Diagnosis

The causes of wasting syndrome are complex. First, it is necessary to exclude or treat opportunistic infections (TB, MAC, cryptosporidiosis and microsporidiosis). If there are none to be found, several reasons remain that may contribute, even in combination, to wasting syndrome. These include metabolic disorders, hypogonadism, poor nutrition and malabsorption syndromes (overview: Grinspoon 2003).

Therefore it is important to start with a history. Does the patient have a sensible diet? How are meals distributed throughout the day? Is the patient depressed? Which drugs, which HAART is being taken? Distinction from antiretroviral-induced lipoatrophy (d4T? ddI?) is often difficult. Significant weight loss also occurs frequently on interferon (Garcia-Benayas 2002), but rapidly resolves after finishing treatment. In addition, hypogonadism should be ruled out (measurement of testosterone). There are several simple tests for malabsorption syndromes. It is prudent to start with testing albumin, TSH and cholesterol levels.

Further tests such as D-xylose absorption or biopsies of the small intestine should only be initiated after consulting a gastroenterologist. Other tests to determine body composition (DEXA, densitrometry, bioelectrical impedance analysis) should only be conducted in centers experienced in wasting syndrome in AIDS patients.

Therapy

Wasting syndrome always requires competent diet counseling. Exercise, if possible, is also good. However, both have only limited success. Supportive parenteral nutrition only helps if there are problems with absorption (Kotler 1990, Melchior 1996). HAART is important, ideally without AZT, d4T and ddI, possibly even omitting nucleoside analogs completely (see chapter on Nuke sparing).

Beyond this, many kinds of drug treatment have been attempted. However, these have limited success and are often problematic.

Megestrol acetate, a synthetic gestagenic hormone, shows some benefit as an appetite stimulant in wasting syndrome (Von Roenn 1994, Mulligan 2006). Its main problems are typical steroidal side effects, including hypogonadism - which should really be avoided in cases of wasting syndrome and which is not necessarily improved by concurrent administration of testosterone (Mulligan 2006). We therefore do not currently recommend the use of this drug.

What about THC (dronabinol)? Dronabinol, the main active ingredient in marijuana, has been licensed in the US since 1985 as Marinol™, and may be prescribed for pharmacy formulation as drops or hard gel capsules. This drug is certainly attractive for many patients and is sometimes actively demanded. Prescription should be carefully considered, particularly in view of the cost (approx. 600 Euro per month for the usual dose of 5 mg tid!). Without a clear diagnosis of wasting syndrome, the health insurance may cause substantial problems (contact beforehand!). Some health insurances reject the request in general. The effect on wasting syndrome is moderate at best, if detectable at all (Beal 1995). It is probably even weaker than megestrol acetate (Timpone 1997). THC is produced in Germany by the THC Pharma. The reason for the high price lies in the complicated production process. As simply importing a kilo of hashish from the Netherlands is not possible, THC has to be extracted from legally correct fibrous hemp; further details under: http:/www.thc-pharma.de. In the last few years, we have only given out scattered prescriptions for individual THC.

Hypogonadism is a frequent problem in patients with wasting syndrome. It is therefore useful to determine testosterone levels (age-dependent!). If levels are low, testosterone substitution is useful, both for weight gain and quality of life (Grinspoon 1998). A dose of 250 mg testosterone is given i.m. every 3-4 weeks, and there is a variety of less expensive generics. The effect is sustained, even with long-term use (Grinspoon 1999). If testosterone levels are normal, substitution in cases of wasting syndrome is not indicated. In women, one should be cautious with administration of androgenic hormones. There are other anabolic steroids available in addition to testosterone, such as oxandrolone or nandrolone. They are possibly somewhat more effective than testosterone (Gold 2006), but are likely to be associated with more side effects, particularly related to the liver (Corcoran 1999). Positive effects have been demonstrated for the anabolic steroid oxymetholone (Hengge 2003). However, the extremely high elevation of transaminases, which sometimes occurs, prevents the broader use of this drug.

Side effects as well as the high cost also limit the use of growth hormones, for which long-term data is still not available (Mulligan 1993, Schambelan 1996). However, the results of a meta-analysis suggest that growth hormones are more effective than anabolic steroids or testosterone in wasting syndrome (Moyle 2004).

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Rare OIs

by Christian Hoffmann and Gerd Fätkenheuer

The following describes several opportunistic infections that rarely occur in central Europe, or have become very rare as a result of HAART. These infections affect HIV patients more frequently than immunocompetent individuals, have more serious courses of disease than in HIV-negative patients and recur more frequently. Despite this, only three, namely histoplasmosis, isosporiasis and coccidioidomycosis, are AIDS-defining according to the current CDC/WHO classification.

Aspergillosis

Although Aspergillosis occurs almost only in severely immunocompromised patients, it is not AIDS defining. In the largest series described worldwide to date with 342 cases of invasive aspergillosis in HIV, almost all patients had less than 50 CD4 cells/µl (Mylonakis 1998). The main manifestation is in the lung (pneumonia, tracheobronchitis), but extrapulmonary infections can occur. These usually involve the CNS, but can principally be localized everywhere (Mylonakis 2000).

Aspergillosis particularly occurs in HIV infected patients on long-term (too long) steroid treatment for another OI. Severe neutropenia (< 1,000 leucocytes) is another risk factor. *Aspergillus fumigatus* is by far the most frequent pathogen (>90 %) followed by *A. niger, A. terreus, A. flavus* and *A. nidulans*. The patients, who are usually severely ill, complain of fever, cough, dyspnea and chest pain. Hemoptysis frequently occurs. Other manifestations include sinusitis or abscesses (kidneys, liver) (Hunt 2000).

The only way to reach a reliable diagnosis is biopsy. A serum antigen test for Aspergillus galactomannan can support the suspected diagnosis. Even proof of Aspergillus in pulmonary secretions is an indication of infection, although often dependent on colonization. Chest x-ray is often unremarkable. On HR-CT, pulmonary collections with a halo or cavitating lesions are suspicious for Aspergillosis.

Antimycotic therapy should be started as soon as Aspergillosis is suspected. Every delay significantly worsens the already poor prognosis – do not wait for the microbiological proof from the biopsy! Voriconazole is currently the therapy of choice, as a randomized study showed higher response rates than for amphotericin B (Herbrecht 2002). Voriconazole is given as 2 x 4 mg i.v./kg/day (loading dose 2 x 6 mg/kg on day 1, changing to oral therapy with 2 x 200 mg/day on day 7). It has the advantage of effective penetration into the brain parenchyma (Schwartz 2005), but causes visual disturbances in 20 % and often (reversible) elevation of liver enzymes. Amphotericin B is the alternative to voriconazole, although its inferiority is doubted by some authors (Jorgensen 2006). In cases of intolerance, contraindications or therapeutic failure, liposomal amphotericin B, capsofungin, posaconazole or high dose itraconazole can be considered. Systemic steroid therapy should be discontinued.

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Bacillary angiomatosis

Bacillary angiomatosis (BA) was first described in the 1980s in HIV patients (Review: Maguina 2000). It is caused by the two rickettsial species *Bartonella henselae* and *Bartonella quintana* ("Rochalimaea" until the beginning of the 1990s). Cats are the main hosts for *Bartonella henselae*, and cat fleas are the vectors. Various pathogen reservoirs for *Bartonella quintana* have been discussed, as patients from poor social backgrounds, in particular the homeless, frequently become infected (Gasquet 1998).

BA occurs far more frequently in North and South America than in Europe. In one study of 382 febrile HIV infected patients in San Francisco, Bartonella was found to be the causative organism in 18 % (Koehler 2003). However, BA remains an important differential diagnosis especially in cases with skin lesions of unknown etiology.

The vascular skin proliferation may be solitary, but is usually multiple, and with the cherry red or purple-colored lumps it is often clinically (and histologically) mistaken for Kaposi's sarcoma or hemangioma. In approximately 25 %, the skeleton is involved, with painful osteolytic foci (AP elevation!). In a collection of 21 cases, 19 patients had skin, 5 bone and 4 liver involvement (Plettenberg 2000). Manifestations in lymph nodes, muscle, CNS, eye, gingiva and gastrointestinal tract have also been reported.

Diagnosis of BA is not easy. The gram-negative bacteria are only visible on biopsy samples stained with Warthin Starry silver stain. Those who do not stain with this method will not find bacillary angiomatosis! Pathologists should be informed of the suspected diagnosis, as this stain is not performed routinely. PCR is also possible. Reference laboratories should be contacted for further questions.

Treatment is with erythromycin (at least 4 weeks with 500 mg qid). Relapses are common, which is why some physicians favor therapy for at least three months. Even doxycyclin is supposed to be effective, and is the therapy of choice for CNS

involvement. Since transmission is mainly via cats, American guidelines recommend not having cats as pets. If there is no way around this, the cat should be healthy and older than one year. Scratches should be avoided.

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Histoplasmosis

Histoplasma capsulatum is a dimorphic mould, found mainly in moist soil and without a capsule despite its name. The South and Midwest of the USA are endemic areas, as are Central America and Africa. Inhalation of microconidia, the spores of *H. capsulatum*, can cause granulomatous disease in the lungs of immunocompetent individuals. In HIV infected patients with impaired immunity (85 % have less than 100 CD4 cells/µl), infection leads to an acute, life-threatening disease with dry cough, fever, dyspnea and malaise (Gutierrez 2005). Miliary TB and PCP are important differential diagnoses. Disseminated courses of disease may also occur, in which the fungus can be detected in bone marrow or by liver biopsy (Albrecht 1994). Skin (ulcerations) or CNS involvement may also occur (Scheinfeld 2003, Wheat 2005).

Histoplasmosis is AIDS-defining. The pathogen can be detected quite reliably in the blood with an antigen test, similarly to the detection of cryptococcal antigen. Laboratory evaluations often reveal significantly elevated LDH and alkaline phosphatase as well as transaminases.

In milder cases, itraconazole (200 mg bid or tid) is effective, and can also be used as a secondary prophylaxis. It is significantly more effective than fluconazole (Wheat 2002). In all other cases, initial treatment should be with amphotericin B. Liposomal amphotericin B (3 mg/kg daily for 14 days) is not only less toxic, but possibly also more effective than amphotericin (Johnson 2002). Once the patient is stable, after 7-10 days, therapy can be switched to itraconazole. The acute therapy lasts 12 weeks overall, after which half-dose itraconazole (200 mg daily) is continued as secondary prophylaxis. Attention should be paid to interactions, especially

with ritonavir (Crommentuyn 2004). As with other OIs, secondary prophylaxis for histoplasmosis can be discontinued if immune reconstitution occurs (Goldman 2004). Immune reconstitution syndrome is possible under HAART (Nacher 2006).

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Isosporiasis

Isospora belli is a ubiquitous intestinal parasite. While it is rare in Europe, it is an important problem in the tropics and subtropics in particular. Similar to cryptosporidiosis, this microbe may cause epidemic-type outbreaks in immunocompetent hosts. Patients suffer (at least with mild) enteritis-like complaints, but sometimes also very severe watery diarrhea, abdominal pain, cramps and nausea. In immunocompromised patients, chronic diarrhea and malnutrition may occur (review: Goodgame 1996). Chronic isosporiasis with diarrhea lasting for more than four weeks is AIDS-defining. Detection of the relatively large oocysts is possible via normal stool sampling for parasites, as well as in acid-fast stains. Blood tests usually reveal eosinophilia (Certad 2003). Treatment is co-trimoxazole (960 mg daily for one week). Ciprofloxacin is slightly less effective (Verdier 2000).

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Coccidioidomycosis

Infection with the mould *Coccidioides immitis* is endemic in the Southwestern USA (review: Galgiani 2005). It should be considered in patients who have been in such regions. Laboratory personnel should be informed even in suspected cases, as there is a high risk of infection.

After inhalation of spores, the primary manifestation is in the lung (Pappagianis 1993). Approximately 1-3 weeks after exposure, a pneumonia-like illness develops with fever, cough, chest pain and general malaise. The infection, although often symptomatic, usually resolves in immunocompetent patients without sequelae. Occasionally, there is residual cavitation. Disseminated coccidioidomycosis beyond the lung and hilar lymph nodes (for example chronic meningoencephalitis) occurs almost exclusively in significantly immunocompromised patients with CD4-cell counts of less than 250/µl (Ampel 2001). Coccidioidomycosis is AIDS-defining. Prognosis was poor in the pre-HAART era. In an analysis of 602 patients with disseminated disease, mortality after one year was 63 % (Jones 1995).

Amphotericin as well as azoles are effective (Hernandez 1997), and should be combined if necessary (Ampel 2005). Detailed recommendations for the different situations (meningeal or disseminated cases must be treated more intensively) can be found in the publication by Galgiani 2005 (see below). Fluconazole should be given as maintenance therapy at high doses (400 mg). In the past few years, it seems that the disease has become rarer as a result of HAART, and that maintenance therapy can be discontinued when CD4 cells are greater than 250/µl with only initial pulmonary involvement. However, lifelong treatment is still recommended for cases of meningeal involvement (Woods 2000, Ampel 2001, Galgiani 2005).

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Leishmaniasis (visceral)

Leishmaniasis is the general term for protozoal infections of the species Leishmania. The cutaneous and visceral forms (kala azar) of leishmaniasis are differentiated, and the manifestations depend on the species (*L. donovani, L. infantum, L. cagasi*). According to WHO data, there are 12 million people infected with this parasite - 350 million live in risk areas. Epidemics have been described in Bangla-

desh, Brazil, India and the Sudan; in Europe, it is mainly the Mediterranean regions that are affected (usually *L. infantum*).

HIV infected patients become infected more commonly with visceral leishmaniasis. In Spain, the majority of patients with visceral leishmaniasis are HIV-infected (Pintado 2001). Although there is much in favor of it, leishmaniasis is not an AIDS-defining illness.

An evaluation of 15 cases in Germany showed significant immunosuppression (usually less than 100 CD4 cells/µl) in all patients. A few patients had not been in endemic areas for several years (Albrecht 1998).

Bone marrow involvement is reflected by the almost obligatory pancytopenia, which may be particularly severe in HIV infected patients (Pintado 2001). Other symptoms include fever, hepatosplenomegaly and mucocutaneous lesions. The diagnosis is usually made from bone marrow aspirate.

Treatment of visceral leishmaniasis is difficult (review: Olliaro 2005). Pentavalent antimony preparations such as stibogluconate (Pentostam™) and megluminantimonate (Glucantime™) have been used for about 60 years. These preparations (dosage 20 mg/kg i.m. or – less painful - i.v. daily for 28 days) are cheap but very toxic. Myalgias, arthralgias, gastrointestinal complaints, pancreatitis and cardiotoxicity often lead to discontinuation of the drug (Laguna 1999).

The German Association for Tropical Medicine therefore recommends liposomal amphotericin B (Ambisome™) as the treatment of choice (2-5 mg/kg daily). A very promising alternative – due to its good tolerability and efficacy, and whilst it is the only orally bioavailable leishmaniasis drug - is miltefosine (Impavido™), an alkylphosphocholine analog that was licensed in Germany in December 2004. It is still unclear how miltefosine inhibits leishmania metabolism, but a Phase III study in India demonstrated it to be highly effective (Sundar 2002). However, a newer randomized study in Ethiopia showed a somewhat weaker effect in HIV infected patients than stibogluconate, although a better tolerability (Ritmeijer 2006). It is administered at a dose of 100 mg daily (monthly cost: almost 2,300 Euro!). We have successfully treated two patients with miltefosine to date.

Relapses occur in almost half of all cases. HAART seems to change this – another argument for inclusion of visceral leishmaniasis in the AIDS classification (de La Rosa 2002, Fernandez-Cotarelo 2003).

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Microsporidiosis

Microsporidiosis is an important cause of diarrhea in HIV infected patients. Microsporidia are obligate intracellular protozoa. At least four genera that are pathogenic in humans have been described. Of these, *Enterocytozoon bieneusi* is the most important. Microsporidia were previously among the most frequent diarrhea-causing microbes, and in the pre-HAART era, could be found in approximately one third of all patients and in some studies in up to two thirds of all HIV infected patients with chronic diarrhea (Sobottka 1998). The incidence of microsporidiosis has reduced significantly due to HAART, and is now only diagnosed occasionally. Microsporidiosis is not AIDS defining, although chronic microsporidiosis almost always occurs in severely immunocompromised patients with CD4-cell counts of less than 50 cells/µl.

Diarrhea may be very severe and is usually watery, though not bloody. It is accompanied by abdominal pain, nausea and vomiting. Fever is almost always absent. Rarely, myositis, keratoconjunctivitis and sinusitis have been described. Infections of the biliary ducts are more frequent.

Even more than in the case of cryptosporidia, it is essential that the laboratory is experienced. Microsporidia are very small, and those who are not explicitly asked to detect them will not find them! Culture has not generally been established. Detection is most successful with specialized staining methods. Special transport or preparation is not necessary.

Albendazole (1-2 tbl. à 400 mg bid for 4 weeks) is quite effective, but certainly not in every case. In particular, *E. bieneusi* is frequently resistant to albendazole. Positive reports from France of treatment with fumagillin have been published (watch for thrombocytopenia!), but the case numbers remain low (Molina 2002). Case reports (Bicart-See 2000) are also available for niazoxanide (see cryptosporidiosis). Thalidomide can be considered for symptomatic treatment. HAART-induced immune reconstitution, however, seems to have the greatest effect (Carr 1998+2002, Maggi 2000).

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Nocardia

Nocardia are aerobic bacteria or actinomycetes that occur worldwide. Several species exist, which mainly cause pneumonia as well as systemic disease. In 30 cases of HIV patients with nocardiosis, the lungs were affected in 21 cases (Uttamchandani 1994). Pulmonary nocardiosis is often confused with tuberculosis. Extrapulmonary manifestation may occur in the skin, brain, nerves, muscle and bone. The immune response to Nocardia is cellular, and the risk of developing the disease is therefore generally high in immunosuppressed patients. In HIV infected patients, however, infections with Nocardia are rather rare. Patients are usually significantly immunocompromised (Javaly 1992, Uttamchandani 1994). Nocardia respond well to sulfonamides such as sulfadiazine even in HIV infected patients (Pintado 2003). In cases of suspected nocardiosis, an experienced laboratory should be consulted.

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Penicillium marneffei

Most fungi belonging to the Penicillium species are not pathogenic. One exception is *Penicillium marneffei*, which is a problem mainly for HIV infected patients in Southeast Asia, China, Hong Kong and Taiwan (Cooper 2000). In these areas, it is the most frequent fungal infection in AIDS beside cryptococcosis, and is considered AIDS-defining by many clinicians (but is not included in the CDC classification). Lungs and skin are affected most frequently, although disseminated cases also occur (Ma 2005).

The symptoms consist of prolonged high fever, lymphadenopathy, weight loss, malaise, cough and hemoptysis. The cutaneous and mucocutaneous lesions are reminiscent of molluscum contagiosum. There is often hepatosplenomegaly.

Amphotericin B and itraconazole are effective treatments (Sirisanthana 1998). In order to prevent relapses, infected patients should receive long-term prophylaxis with itraconazole (Supparatpinyo 1998). Primary prophylaxis is not recommended

even with longer stays in endemic areas (Chariyalertsak 2002). The only patient we have seen had spent several months on vacation in Thailand (Sobottka 1996).

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Rhodococcus

Rhodococcus equi (previously *Corynebacterium equi*) is a sporeless, gram-positive intracellular pathogen, which is ubiquitous in air, water and soil. R. equi has been found on all continents, and was first identified as a pathogen in young horses. In 1986, the first case in an AIDS patient was described (Samies 1986). In a collection of 78 HIV patients, most of those affected had less than 50 CD4 cells/µl. Rhodococcus causes severe granulomatous or abscess forming pneumonia, and sometimes also disseminated infection. Rhodococcus is best detected in sputum and blood cultures (Torres-Tortosa 2003). The coryneform bacteria seen in sputum cultures are often confused with normal diphtheroid flora found in the mouth and therefore not diagnosed.

The main symptoms are fever, dyspnea and unproductive cough (Capdevila 1997). Cavitation, mainly in the upper lobes, is frequently seen radiologically (Marchiori 2005).

Erythromycin, ciprofloxacin, rifampin and vancomycin are effective, and some of these drugs can also be combined. However, treatment is difficult and complete recovery is rare (Plum 1997), so that surgical measures may also be necessary if there is extensive cavitation.

Prognosis is rather poor. The extent to which this will change as a result of HAART remains controversial (Sanz-Moreno 2002, Torres-Tortosa 2003).

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Trypanosoma cruzi

Trypanosoma cruzi is a protozoan that is transmitted via contaminated feces of triatomid bugs (assassin bugs), found almost exclusively on the American continent. It causes Chagas disease, one of the most frequent causes of cardiomyopathy in South America.

HIV infected patients are more frequently affected and have higher levels of parasitemia (Sartori 2002), probably due to the fact that the Trypanosoma-specific immune response is mainly cellular in nature. In addition, a more frequent occurrence in HIV-infected patients is meningoencephalitis, which is usually severe and radiologically not distinguishable from cerebral toxoplasmosis or primary cerebral lymphoma. In HIV infected patients from South America, Trypanosoma infection should therefore be considered in the differential diagnosis (Silva 1999). However, treatment (for example benznidazole) is rarely successful.

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13. Kaposi's Sarcoma

Helmut Schöfer and Dana L. Sachs

Kaposi's sarcoma (KS) is a malignant, multifocal systemic disease that originates from the vascular endothelium and has a variable clinical course. The most frequently involved site is the skin , but mucous membranes, the lymphatic system and viscera – in particular the lung and gastrointestinal tract – can be involved. Five clinical forms are described: classic KS, KS secondary to immunosuppression; endemic African KS; epidemic HIV-associated KS and IRIS*-associated KS.

(*In association with the immunologic and viral immune reconstitution (see special chapter: Immune reconstitution inflammatory syndrome, IRIS) an aggressive type of Kaposi`s sarcoma was reported recently (Bower 2005, Leidner 2005). IRIS-associated KS can occur spontaneously or progress from a mild or stable disease within the first three months of immune reconstitution. The initiation of effective HAART with increasing CD4-cell count and a reduced HIV viral load, is a precondition. Cutaneous, mucosal, lymphatic and pulmonary KS, which in most cases of efficient HAART have a tendency to stabilise or regress completely, show a paradoxical reaction and grow rapidlyPulmonary lesions can be especially threatening.. Early systemic chemotherapy is used to halt disease progression. It is not necessary to discontinue HAART while treating IRIS-associated KS.)

All types of KS are due to infection with human herpes virus-8 (HHV-8), which is transmitted sexually or via blood or saliva. In men having sex with men (MSM) the number of life-time sex partners is the highest risk factor for HHV-8 infection, however, KS is significantly linked to low CD4-cell counts (Martró 2007). Months before manifestation of the tumors, HHV-8 viremia leads to development of specific antibodies. A cutaneous eruption has been described in association with HHV-8 seroconversion (Andreoni 2002).

In HIV-infected patients, KS is an AIDS-defining illness. Aggressive courses of disease, with lethal outcomes, have been observed in HIV patients with severe and untreated immunodeficiency. In such cases, the average survival time following diagnosis is less than one year. Since the introduction of HAART in 1996, the frequency of KS in HIV-infected patients has decreased sharply (by as much as 90% in the Department of Dermatovenereology at Frankfurt University Hospital), and the clinical course of disease has improved significantly. In many cases, stabilization or complete remission of tumors is possible with immune reconstitution and reduction of the HIV viral load. Of the available therapies, HAART is first line treatment. It can be used in combination with local treatments such as cryotherapy, retinoids, and radiation. Therapy with interferon-alpha, paclitaxel or chemotherapy with liposomal anthracyclines is only necessary if there is visceral progression of the disease whilst on HAART. New developments in KS therapies are phase clinical trials with matrix metalloproteinases inhibitors (e.g. COL-3; Dezube 2006), chemotherapy with irinotecan (Vaccher 2005). inhibition of the c-kit and PDGF receptors with imatinib etc.).

Signs, symptoms and diagnosis

In contrast to the classical KS found in older men, in whom the tumors usually occur on the lower legs and feet, HIV-associated KS does not have a preferential pattern of localization. It can begin on any area of the skin, but may also appear on oral, genital, or ocular mucous membranes. Typical findings are initially solitary, or a few asymptomatic purple macules or nodules, which have a predilection for distribution along relaxed skin tension lines. Disease progression is variable: the macules or tumors can remain unchanged for months to years, or grow rapidly within a few weeks and disseminate. Rapid growth can lead to localized pain and a yellow-green discoloration of the area around the tumor as a result of hemorrhage. Further progression of the tumor can lead to central necrosis and ulceration. The tumors may bleed easily. Plaque-like and nodular KS lesions, often become confluent and can be accompanied by massive edema. In the oral cavity, the hard palate is frequently affected. Lesions begin with purplish erythema and progress to plaques and nodules that ulcerate easily. KS lesions may also involve the external genitalia including the foreskin and glans penis.

The **diagnosis of KS** in the skin and mucous membranes can usually be made based on the following clinical features:

1. Purple macules or nodules
2. Distribution along skin tension lines
3. Green-yellow discoloration around the tumors corresponding to hemorrhage
4. Surrounding edema
5. Dissemination of lesions, possibly with mucocutaneous involvement

This is particularly characteristic for patients in whom HIV infection or another form of immunodeficiency is known. If there is clinical doubt, the lesions should be biopsied to confirm the diagnosis histologically. The clinical presentation may pose a challenge, especially with the telangiectatic, ecchymotic, keloidal and hyperkeratotic variants.

The important features of KS on routine histology include:

1. Epidermis is usually intact.
2. Slit-like spaces formed by new, thin-walled and partly aberrant blood vessels running alongside normal dermal vessels and adnexal structures.
3. Extravasated erythrocytes around the new vessels.
4. Hemosiderin deposits.
5. Lymphocytic inflammatory infiltrate.
6. An infiltrate of oval- or spindle-shaped cells (spindle cell KS).

When KS resolves, either spontaneously or following therapy, it often leaves gray-brown to light brown hyperpigmentation for months to years (post-inflammatory hyperpigmentation), caused by hemosiderin deposits from extravasated erythrocytes. The accompanying lymphedema can also persist for a similar length of time, particularly on the lower legs.

HHV-8, which contributes to the development of the tumor, can be detected in tumor tissue by PCR. This can be a helpful diagnostic tool in cases where the histopathological diagnosis of Kaposi's sarcoma is uncertain. HHV-8 antibodies are often detected months before the clinical manifestation of the tumor. Neutralizing antibodies seem to control the HHV-8 infection and thus protect against the clinical manifestation of Kaposi's sarcoma (Kimball 2004). In patients with Kaposi's sarcoma the titres of neutralizing antibodies are low. In contrast,, high titres of antibodies against HHV-8 latent and lytic antigens are strongly associated with the risk of subsequent development of KS (Newton 2006). The HIV tat-protein is able to promote the HHV-8 transmission directly, which could be an explanation for the high rate of KS in patients coinfected with HHV-8 and HIV (Aoki 2004, Chandra 2003). Epidemiological studies have shown that a high regional incidence of KS (e.g. in Southern Italy, as well as in Central Africa) correlates with an increased regional HHV-8 seroprevalence. HHV-8 seems to mainly be transmitted sexually. The KS frequently seen in African children is presumably transmitted via saliva (Pauk et al. 2000). A saliva reservoir of HHV-8 was also found in adult HIV patients (Triantos 2004).

On initial diagnosis of KS, the following investigations help to stage the disease:

1. Complete cutaneous inspection of the patient (including oral and genital mucous membranes)
2. Lymph node ultrasound
3. Abdominal ultrasound
4. Upper GI endoscopy (optional, but always required with mucocutaneous tumors)
5. Lower GI endoscopy (optional, but always required with mucocutaneous tumors)
6. Chest radiography
7. Determination of CD4+ T-cell count and HIV viral load (is initiation or optimization of antiretroviral therapy necessary?)

Prognosis and staging

HIV-associated KS ranges from indolent skin lesions to aggressive, disseminated disease with lymph node and visceral involvement. Left untreated, rapid tumor growth can lead to death of the patient within weeks. Malignant clonal tumor growth has been shown to occur in pulmonary KS. Whole body (99m)Tc-MIBI scans seem to be an effective tool, to demonstrate cutaneous and lymphnote KS and to monitor therapy (Peer 2007). The introduction of HAART has significantly improved the prognosis for patients with KS. Patients with extensive visceral involvement often achieve complete remission.

Table 1. Staging of HIV-associated epidemic KS (from ACTG, Krown 1997)

Early stage	Late stage
If **all** the following criteria are met:	If **one** of the following applies:
1. Tumor (T): 0	1.Tumor (T): 1
KS limited to skin and/or lymph nodes; minimal oral disease (non-nodular KS confined to hard palate)	Pulmonary or gastrointestinal KS; extensive oral KS; tumor-associated edema or ulceration
2. Immune system* (I): 0	2. Immune system* (I): 1
CD4+ T-cells > 200/µl	CD4+ T-cells < 200/µl
3. Systemic illness (S): 0	3. Systemic illness (S): 1
No history of OI or thrush, no B symptoms* of HIV infection	History of opportunistic infections, thrush, malignant lymphoma or HIV-associated neurological disease, B** symptoms of HIV infection

*CD4 cell count is not of any prognostic relevance in KS patients on HAART (Nasti 2003)

** unexplained fever, night sweats or diarrhea persisting for more than two weeks, involuntary weight loss of >10%

The classification system for HIV-associated KS, published in 1993 and reviewed in 1997 by the AIDS Clinical Trials Group (ACTG, Krown 1997, table 1), was adapted by an Italian working group to address KS in the HAART era. However, the changes proposed by Nasti et al (2003) have not yet been validated and accepted on an international level. Of particular concern is the suggested omission of the CD4+ T-cell count as a prognostic factor, which results in the classification of KS patients into those with a good (T0S0, T1S0, T0S1) and those with a bad prognosis (T1S1).

Treatment

If KS is diagnosed in HIV-infected patients who have not yet been treated, or who are no longer being treated with antiretroviral drugs, it is essential to start HAART (see HAART chapter). If the HIV viral load can be reduced (ideally below the level of detection) and immune reconstitution is achieved with an increase in the CD4 T cell count, KS stabilizes or even resolves completely in many patients. Long-term remissions (<60 months) have been demonstrated in an Italian study (Cattelan 2005). One exception, however, is KS with severe pulmonary involvement which can progress rapidly during the first three months of HAART (see IRIS associated KS).

The clinical observation that KS may resolve with protease inhibitors, even in the absence of a significant improvement in the immunological status, has been confirmed with the discovery of the direct anti-proliferative effects of the PIs indinavir and saquinavir (Sgadari 2002). The PI ritonavir has also been shown to have a direct anti-tumor effect (Pati 2002) In addition, the following treatment methods are available depending on the clinical stage of KS (table 1):

- Early stage (ACTG): Local treatment (see below). With progression: primary treatment with interferon-α combined with HAART or with with liposomal anthracyclines.

- Late stage (ACTG): Primary treatment for stage T 0, I 0, S 1 with interferon-α in combination with HAART or with liposomal anthracyclines. Should these therapies fail, paclitaxel or combination chemotherapy (ABV regimen) can be used.

Immunosuppressed transplant recipients with KS may benefit from a change from calcineurin inhibitors to sirolimus (Stallone 2005, Lebbé 2006).

Local therapy

Local therapy has the advantages of being (1) provided in the ambulatory care setting, (2) well-tolerated, and (3) less costly than in-patient therapy. The following methods are used depending on the size and location of tumors: cryosurgery, vinca alkaloids, intralesional bleomycin or intralesional interferons, soft x-ray radiation, electron beam therapy, cobalt radiation (fractionated), retinoids: 9-cis-retinoic acid, alitretinoin (Bodsworth 2001, Duvic 2000), and cosmetic camouflage. In addition to intralesional vinblastine, tumors of the buccal mucosa can be injected with 3 % sodium tetradecyl sulphate (which has comparable efficacy rates) (Ramirez-Amador 2002).

As Kaposi's sarcoma is a multifocal systemic disease, surgical treatment is limited to excisional biopsies for diagnosis and palliative removal of small tumors in cosmetically disturbing areas. Since tumors often extend further into the surroundings than is clinically visible and local trauma can lead to new tumors (Koebner phenomenon), local and regional recurrences can be expected. These can be prevented by radiation therapy: in order to reach the tumor cells spreading along the vascular channels, the field of radiation should be extended 0.5-1.0 cm beyond the edges of the tumor. KS is a strikingly radiosensitive tumor. Superficial macular or plaque-like KS lesions respond well to daily doses of 4-5 Gy (total dose 20-30 Gy, fractionated 3x/week) of soft x-ray radiation. To palliate fast growing tumors, a single dose of 8 Gy is recommended (Harrison 1998). For the treatment of extensive KS with edematous swelling and/or lymph node involvement, soft x-ray radiation, originating from 50-kV beryllium-windowed units, as used in dermatology, is not sufficient. Such tumors should be treated with electron beam therapy with conventional fractionation (5x2 Gy per week) to a target volume total dose of 40 Gy. Patients with KS of the lower extremities, frequently associated with lymphedema, may benefit from compression therapy with elastic stockings (Brambilla 2006).

Local chemo- and immunotherapy have the advantage of less or no systemic side effects compared to systemic treatments. Within the tumor, high concentrations of drugs with direct antiproliferative efficacy can be reached.

Chemotherapy

Theoretically, aggressive chemotherapy harbors particular risks for HIV-infected patients. Bone marrow suppression, , can lead to deterioration of existing, HIV-associated cellular immunodeficiency and occurrence of acute, life-threatening opportunistic infections. To maintain a high quality of life HIV-associated KS should preferably be treated by chemotherapy in the presence of clinical symptoms (e.g. pain), rapid tumor progression and/or visceral involvement. In such cases, even patients with a good immune status should receive PCP and toxoplasmosis prophy-

laxis with cotrimoxazole (480 mg/day or 960 mg 3x/week). The myelotoxic effects of several chemotherapeutic drugs on a hematopoetic system that has already been impaired by HIV infection may require further treatment with erythropoetin or blood transfusions.

The chemotherapeutics that achieve the highest remission rates for KS are anthracyclines. Compared to aggressive chemotherapy regimens (like ABV) pegylated, liposomal anthracyclines have a mild profile of bone marrow toxicity and other side effects . Treatment with intravenous pegylated liposomal doxorubicin (PLD) at a dose of 20 mg/m^2 body surface area every 2-3 weeks leads to partial remission in up to 80 % of treated patients and is well tolerated in combination with HAART (Lichterfeld 2005). Treatment with intravenous liposomal daunorubicin 40 mg/m^2 body surface area every 2 weeks has slightly lower remission rates (Krown 2004, Rosenthal 2002, Osoba 2001, Cheung 1999).

In comparative studies, liposomal daunorubicin showed the same and doxorubicin a higher efficiency than the previous gold standard of KS treatment, which consisted of combination therapy with adriamycin, bleomycin and vincristine (ABV regimen). In a comparative study on patients with moderate to advanced KS, the combination of pegylated liposomal doxorubicin with HAART was substantially more effective than HAART alone (response rate 76 % versus 20 %) (Martin-Carbonero 2004). A German multicentre study demonstrated superiority of PLD treatment over recombinant interferon alfa-2a in 18 patients with classic KS, but the number of patients treated with interferon was low (n=6), and mean follow-up was only 6,3 months, so further comparative studies should be performed. Both therapies were well tolerated (Kreuter 2005).

Cooley et al. (2007) confirmed a clinical benefit of pegylated liposomal doxorubicin in 80% of all patients treated and a tumour response rate in 55%. The most important side effects of anthracyclines are neutropenia (30%), nausea, asthenia and anemia. This usually occurs after 8-10 cycles. The cardiotoxicity associated with anthracyclines should also be considered. However, usually it only occurs with long-term administration (cumulative doses of 450 mg doxorubicin and higher). Macular and painful erythema of the palms and soles (palmoplantar erythrodysesthesia) is another notable side effect which can limit treatment.

Paclitaxel is also a very effective drug for the treatment of KS (Tulpule 2002). The recommended dose is 100 mg/m^2 body surface area administered intravenously over 3-4 hours every 2 weeks. Partial remission is achieved in up to 60 % of all treated patients. Paclitaxel is myelotoxic and almost always leads to alopecia, often after just one dose. Whether paclitaxel has important interactions with HAART therapy such as increasing the toxicity of paclitaxel is still under investigation (Bundow 2004). For this reason, patients on HAART and paclitaxel need very careful monitoring. Paclitaxel acts by disrupting the structural reorganization of intracellular microtubuli. This leads to mitotic arrest and programmed cell death (apoptosis) (Blagosklonny 2002). Paclitaxel can also be used successfully in those patients with tumor progression under anthracycline therapy.

Docitaxel (taxotere) seems to be an interesting alternative from the taxane group. It is FDA approved for the treatment of breast cancer, but very recently a phase II clinical trial showed that taxotere is effective and safe for the treatment of KS (Lim

2005). Relapses (following anthracycline or paclitaxel therapy) may also be treated with low dose oral etoposide (Evans 2002).

Table 2: Treatment recommendations for systemic therapy of Kaposi's sarcoma (evaluation of individual drugs in text)

Therapeutic agent	Dose	Requirement	Remission rate	Side effects
IFN-α (2a,b)	1-3 mil. I.U. sc daily until remission, followed by 3 x weekly	>200 CD4+ T-cells/µl Endogenous IFN-α < 3 U/ml, HAART	Approx. 40%	Fever, myalgia, depression
Pegylated IFN-α 2b*	50 µg sc 1 x weekly	As for IFN-α (2a,b)	?	As for IFN-α (2a,b)
Pegylated liposomal Doxorubicin	20 mg/m^2 iv at biweekly intervals	KS stage T1, S0-1 (see Table 1, staging of KS)	Approx. 80%	Neutropenia, anemia Rarely: Flushing, dyspnea, back pain, palmo-plantar erythrodysesthesia
Liposomal Daunorubicin	40 mg/m^2 iv at biweekly intervals	T1, S0-1 (see Table 1, staging of KS)	Approx. 60%	Neutropenia, anemia Rarely: Flushing, dyspnea, back pain, palmo-plantar erythrodysesthesia
Paclitaxel	100 mg/m² iv at biweekly intervals	T1, S0-1 (see Table 1, staging of KS)	Approx. 60%	Neutropenia, thrombocytopenia, anemia, alopecia Rarely: Hypotension, ECG-changes

*Pegylated IFN-α 2b has only been licensed for treatment of chronic hepatitis C

Immunotherapy

Interferons (IFN-α 2a, IFN-α 2b, IFN-β) are used successfully for classic, as well as sporadic and HIV-associated, epidemic Kaposi's sarcoma. Remission rates of 45-70% can be achieved. In addition to their well-known immunomodulatory activity, interferons induce apoptosis in tumor cells and lead to reduced β-FGF expression by inhibiting angiogenesis and therefore proliferation.

There are currently no standardized treatment regimens.. Daily doses of 3-6 million IU sc are usually given. After remission (tumor growth stopped, tumors flattened, loss of purple color, change to brownish color), interferon dosing can be reduced to 3x/week. Complete remission can, at the earliest, be expected after 6-8 weeks of treatment, but can occur significantly later.. An initial study showed that interferon doses can be reduced even further when given with HAART, thereby decreasing interferon side effects (Krown 2002). Depression with suicidal tendencies does not seem to be a dose-related side effect of interferons.

There is almost no data on the use of the new, pegylated IFN-α 2b for KS. It is depegylated to IFN-α 2b, the active substance, following subcutaneous application. It has been used successfully for the treatment of classical Kaposi's sarcoma (Thoma-Greber 2002) in a dose of 50µg/week subcutaneously. Whether higher doses or

shorter treatment intervals are necessary for HIV-associated KS still remains to be investigated. Such studies have become more difficult to perform as a result of the significant decrease in both the incidence and prevalence of KS since the introduction of HAART. In principle, this new formulation should lead to a further improvement in the efficacy of interferon. We have personal experience in the treatment of minor KS with 100µg pegylated IFN-α 2b weekly in two patients, which led to a satisfying remission with residual hyperpigmentation in both cases (Schöfer, unpublished data).

The efficacy of interferon treatment is dependent on the cellular immune status of the patient. In patients with more than 400 CD4+ T-cells/µl, remission rates are > 45%; with less than 200 CD4+ T-cells/µl they stand at only 7 %. The endogenous interferon levels are important prognostic indicators and are significantly elevated in the advanced stages of HIV infection which leads to reduced responses to exogenous interferon. The criteria for treatment with interferon in epidemic KS therefore include an early stage of HIV disease (CD4+ T-cells > 200/µl) and endogenous interferon levels < 3 U/ml. In the late stage of HIV disease, interferons should only be given in combination with an efficient HAART regimen. IFN-γ leads to tumor progression and is contraindicated.

Monitoring and follow-up care

In cases with isolated cutaneous and slowly progressive KS, HIV disease and HAART usually determine the necessary intervals for monitoring. However, even with a functional cellular immunity (CD4+ T-cells > 400/µl) and low viral load, tumor progression may be rapid with organ involvement in individual cases. Clinical examination of the skin, mucous membranes and lymph nodes is recommended at three-month intervals. The lungs and gastrointestinal tract should be monitored at 6-12 month intervals with appropriate diagnostic testing if indicated. However, evidence-based data that tumor follow-up leads to improvement in the remission rates as a result of close monitoring is not yet available for Kaposi's sarcoma.

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14. Malignant Lymphomas

Christian Hoffmann

Malignant lymphomas are neoplastic diseases of the lymphatic system that grow rapidly and aggressively, and lead to death within a few weeks or months if left untreated. Hodgkin's disease (HD) is distinguished from the large group of non-Hodgkin's lymphomas (NHL). In comparison to the normal population, HIV patients are affected significantly more frequently by all types of lymphoma (see Table 1) – the greatest risk is aggressive NHL of B-cell origin. Since the introduction of HAART, the incidence has declined, although not as impressively as with Kaposi's sarcoma or the most OIs (Clarke 2001, Little 2001), so that the relative proportion of AIDS-associated illnesses that are lymphomas is increasing. The reduction is seen principally in the subtypes that mostly occur in the setting of severe immunodeficiency (Kirk 2001).

In some HIV cohorts, malignant lymphomas have already overtaken Kaposi's sarcoma as the most frequent malignancy. In the EuroSIDA study, the proportion of AIDS-defined illnesses that were malignant lymphomas increased from less than 4 % in 1994 to 16 % in 1998 (Mocroft 2000). In France, lymphomas accounted for 11 % of all deaths in HIV infected patients in 2000 (Bonnet 2004).

Table 1. Relative risk of different lymphomas in HIV patients in comparison to the normal population (adapted from Goedert 2000)

Malignant NHL total		165
High-grade malignancy NHL		348
	Immunoblastic NHL	652
	Burkitt's NHL	261
	Not classifiable	580
	Primary CNS lymphoma (PCNSL)	> 1,000
Low-grade malignancy NHL		14
	Plasmocytoma	5
Hodgkin's disease		8

Malignant lymphomas in HIV-infected patients are biologically very heterogenous. The frequency and extent of oncogenic mutations or cytokine dysregulation differ, as does the histogenetic origin of the malignant cells (Porcu 2000). Furthermore, the association with EBV and other oncogenic viruses such as HHV-8 or SV40 is very variable. The extent of immunodeficiency also varies. Whilst Burkitt's lymphoma and Hodgkin's disease frequently occur even when the immune status is good, immunoblastic and especially primary CNS lymphomas (PCNSL) are almost always associated with severe immunodeficiency.

However, HIV-associated lymphomas – both NHL and HD – have numerous common clinical features. Characteristics include the usually aggressive growth, diagnosis in the advanced stages with frequent extranodal manifestations, poorer response to treatment, high relapse rates and an overall poor prognosis (Levine 2000).

Even in the HAART era, the treatment of malignant lymphoma remains challenging. Although aggressive chemotherapy is possible in many patients with existing immunodeficiency, treatment is complicated and requires a close cooperation between HIV clinicians and physicians with experience in hematology/oncology.

The following discusses systemic NHL, PCNSL and Hodgkin's lymphoma separately. Multicentric Castleman's disease will also be mentioned as a distinct entity, although it is not considered a malignant lymphoma. Low-grade (indolent) NHLs are very rare in HIV patients, and will therefore not be discussed here - treatment of such cases in the HAART era should follow the recommendations for HIV-negative patients.

Systemic non-Hodgkin lymphomas (NHL)

A close association between systemic NHL and AIDS has been described for a long time – the first cases were published only about a year after the first description of AIDS and even before the discovery of HIV (Ziegler 1982). High-grade B-NHLs have been AIDS-defining since 1985.

So far, more than 90 % of HIV-associated NHLs are of B-cell origin. They are almost always of high-grade malignancy. Two main histological types dominate: according to the WHO classification these are Burkitt's lymphomas, which comprise 30-40 % of cases, and diffuse large-cell B cell lymphomas, comprising 40-60 %. However, a relatively large proportion of HIV-associated lymphomas (up to 30 %) cannot be classified even by reference pathologists. A small proportion of NHLs (1-3 %) are primary effusion or body cavity-based lymphomas, representing a distinct entity (see below).

The prognosis of patients with NHL was poor in the pre-HAART era, being between 6 and 9 months (Levine 2000). Since the advent of HAART, this has changed (see below). Whether the clinical and pathological spectrum of NHL is also changing, is still unclear.

Signs and symptoms

The main symptom is lymph node enlargement. Lymphomas are firm, immobile or barely mobile and painless. A large proportion of patients have advanced-stage lymphoma at the time of diagnosis. Ann Arbor stages III-IV are almost always the rule, and B symptoms with fever, night sweats and/or weight loss are found in the majority of cases (60-80 %). General asthenia, significant malaise and rapid physical deterioration are also frequently seen. Extranodal involvement is common, and may be to a grotesque extent. In our own cohort of 203 patients, 81 % had at least one extranodal focus (Hoffmann 2003). Whether the orbital cavity, testes, heart, breasts, bladder, kidneys, muscles, or bones – every conceivable region can be affected. The gastrointestinal tract, liver, and bone marrow are affected particularly frequently. Secondary CNS involvement can also occur. With extranodal disease, additional symptoms arise depending on the localization. These include, for example, abdominal pain from hepatosplenomegaly, hemorrhage or ileus symptoms due to intestinal involvement, bone pain with skeletal infiltration, or headache caused by brain involvement.

Diagnosis

Rapid histological diagnosis is important. If bone marrow biopsy has not secured the diagnosis already, a lymph node (e.g. cervical, axillary or inguinal) should be extirpated. Mere puncture biopsy of a lymph node is often insufficient to identify the subtype.

It is important to send the material to a specialized pathology laboratory with extensive experience in HIV lymph node morphology. The basic pathological diagnosis should include information about the subtype (Burkitt?), the proliferation rate and the expression profile (definitely: CD20, and desirably: CD10, CD138, MUM-1) as this may implicate have therapeutic consequences (see below). For the treating physician, it is important not just to accept a pathological diagnosis, but to discuss it with the pathologist, especially if there is any doubt in the clinical picture.

All patients with NHL should be "staged" according to the Ann-Arbor classification (Tables 2a, b).

Table 2a. Staging according to the updated Ann-Arbor classification

I	Involvement of a single lymph node region (I) or involvement of a single extralymphatic organ or site (IE)
II	Involvement of 2 or more lymph node regions on the same side of the diaphragm (II) or localized involvement of an extralymphatic organ or site plus its regional lymph nodes, with or without involvement of other lymph node regions on the same side of the diaphragm (IIE)
III	Involvement of lymph nodes regions on both sides of the diaphragm (III), can be accompanied by localized extralymphatic organ involvement (IIIE) or spleen involvement (IIIS) or both (IIIE+S)
IV	Diffuse or disseminated involvement of one or more extralymphatic organs with or without associated lymph node involvement; or isolated involvement of an extralymphatic organ with involvement of distal (non-regional) lymph nodes.

Basic diagnostic tests for staging include chest radiography, abdominal ultrasound, bone marrow biopsy (only aspiration is not enough!) and CT scans of the neck, thorax and abdomen. In addition to an updated immune status and viral load, the following should be determined: blood count, erythrocyte sedimentation rate, CRP, uric acid, LDH, liver and kidney parameters and electrolytes. ECG and echocardiography are also important beforehand. The possible cardiotoxicity of chemotherapy (anthracyclines!) during the course of treatment can only be evaluated if these tests have been performed at the start! Pulmonary function should be tested before treatment with regimens containing bleomycin is initiated.

Table 2b. Every stage is divided into categories A and B

A	Asymptomatic
B	General symptoms: a) unexplained weight loss of more than 10 % in the last six months, and/or b) unexplained persistent or recurring fever with temperatures above 38 °C, and/or c) drenching night sweats

After two cycles of chemotherapy, a restaging should evaluate the treatment success. The restaging should be oriented according to the original localization of lymphoma. After completion of the chemotherapy, a complete restaging with bone marrow biopsy (if there was initial involvement) and all CT scans is necessary. With a complete remission, restaging is recommended initially at three-monthly intervals. These intervals can be prolonged to six months after one year and to twelve months after two years. Relapses after more than three years are rare.

In advanced stages of the disease (Ann Arbor III-IV), and with ENT involvement, CSF puncture should be performed at the start of systemic chemotherapy to exclude meningeal involvement. At the same time, 15 mg of methotrexate can be administered intrathecally as prophylaxis. Whether and when this (widely accepted by oncologists) action actually has any benefit or not, has never been shown in controlled studies.

Therapy

Due to rapid generalization, even "early stages" are rarely limited. The real stage of the disease is often underestimated – every aggressive HIV-associated lymphoma should therefore be treated primarily with systemic chemotherapy with curative intent. Surgery or radiation therapy alone are not sufficient in most cases. Treatment must be started rapidly due to the aggressive nature of these lymphomas. In particular, time should not be wasted on staging procedures. The necessary tests should be completed within a week.

In Europe, diffuse large-cell NHLs have been treated for many years with CHOP-based regimens (usually 4-6 cycles, see table). CHOP is the abbreviation used for the combination chemotherapy with the cytostatics **c**yclophosphamide, adriamycin (**h**ydroxydoxorubicin), vincristine (**o**ncovin) and **p**rednisolone. To date, no other chemotherapy regimen has been shown to have better efficacy. CHOP can be administered in ambulatory care and is fairly well tolerated. At least 4 cycles should be administered, and – as far as possible – 2 cycles after reaching complete remission (CR).

The standard three-week CHOP regimen ("CHOP-21") is shown in Table 3. Following the success of "CHOP-14" in older HIV-negative patients (Pfreundschuh 2004), "CHOP-21" can also be condensed: in "CHOP-14" (one cycle every two weeks) the use of the growth hormone G-CSF (e.g. Filgastrim 30-48 million units or Neupogen™ 300/480 µg s.c. daily on days 4 to 13) reduces the duration of neutropenia. This approach not only decreases the phase of increased susceptibility to infections, but also increases the dose intensity of chemotherapy. However, there is no comparative data on this yet for HIV infected patients. So far, we have had fairly positive experiences with this approach – in most HIV infected patients, it is possible to shorten the interval.

We recommend the administration of co-trimoxazole as an adjuvant therapy, up until one month after completion of the chemotherapy (960 mg three times weekly), independent of the CD4 cell count. Oral mucous membranes should be treated with mouthwashes and topical antimycotics such as amphotericin. Good adherence is an important factor. During chemotherapy, at least twice weekly monitoring of the

patient's condition, blood count, liver and kidney parameters is necessary. Treatment is usually continued with the full dose according to protocol if leukocytes are above 3,000/µl again after nadir and platelets more than 80,000/µl on the planned day of treatment. Patients should be advised to carry out daily temperature monitoring and be told to present immediately in case of fever.

Table 3: CHOP regimen (4-6 cycles of 3 weeks each, repeat on Day 22) *

Cyclophosphamide	Endoxan™	750 mg/m^2 i.v. Day 1
Doxorubicin	Doxo-Cell™, Adriblastin™	50 mg/m^2 i.v. Day 1
Vincristine	Vincristin™	1.4 mg/m^2 (maximum 2 mg) i.v. Day 1
Prednisolone	Decortin H™	2 tbl. à 50 mg qd p.o., Day 1-5
Mesna	Uromitexan™	20 % of cyclophosphamide dose at hours 0, 4, 8 i.v. (given as a short infusion) or orally

* Standard CHOP regimen (CHOP 21). Repeated on Day 22. Alternatively, with CHOP 14, the cycles are tightened with the help of G-CSF (see text).

Rituximab in HIV infection?

The introduction of the monoclonal CD20-antibody rituximab (MabThera™ or Rituxan™) was one of the biggest advances in oncology in recent years. In numerous lymphomas, this antibody, which binds highly specifically to CD20-positive B-cells (CD20 is expressed on most lymphoma cells), has markedly improved the effectiveness and length of response of conventional chemotherapy. A combination of CHOP and rituximab ("R-CHOP") is now standard in many lymphomas. Rituximab is usually well tolerated, but often leads to a longer lasting B-cell depletion, and occasionally to severe neutropenia (Voog 2003).

It is not clear whether rituximab has a similarly large clinical benefit for HIV infected patients as it has for HIV-negative patients with B-cell lymphoma. The results from AMC 010, a multicenter prospective and randomized US study, have at least raised doubts (Kaplan 2005). In total, 143 patients with CD20-positive AIDS-NHL were randomized to CHOP or R-CHOP (rituximab in the usual dose of 375 mg/m² on day 1 with a monthly maintenance therapy for 3 months following chemotherapy). In addition to the chemotherapy, all patients also received G-CSF, a co-trimoxazole prophylaxis and an AZT-free HAART. Both groups had minimal differences at baseline. In the rituximab group, the CD4-cell counts were slightly, but not significantly lower (128 vs 158/µl). With regard to other parameters, such as histology, stage of disease, etc., there were no significant differences. Even the planned CHOP cycles were carried out at the same intensity in both groups, and in both groups only slight dose reductions were necessary.

The essential results: neither group differed significantly in the length of response, disease-free or total survival. However, neutropenia and incidence of (especially severe) infection were significantly higher in the rituximab group. Out of a total of 15 patients who died from an infection, 14 had received rituximab. The cause of death was usually septicemia from various bacteria – both gram-negative and gram-positive were identified. Death occurred in the majority (8/15) of the patients during the first two cycles, although 6 cases happened during the rituximab treatment at the

end of the chemotherapy. Fatalities occurred in all centers and were therefore not due to a possible lack of expertise in any one location. A further risk factor for death from infection was a low baseline CD4-cell count – 8/13 patients had less than 50 cells/µl. The cause of the high rate of severe infections is still unclear. Pathophysiologically, it is at least possible that in pre-existing T cell defects present in HIV infected patients, a long-lasting rituximab-induced B cell depletion or hypoglobulinemia has particularly negative effects (Miles 2005).

According to these data, rituximab seems at first glance to have no significant beneficial effect on HIV infected patients with aggressive lymphomas, and if indeed there is one, this is cancelled by the increased risk of infection. In a further study from Italy, in which rituximab was given with CDE (cyclophosphamide, doxorubicin, etoposide), fatal infectious complications occurred in 8 % of patients (Spina 2005). In contrast, in a French study the infection rate was not increased and the CR-rates were as high as 77 % (Boue 2006).

It is our opinion that in HIV lymphomas, rituximab should only be used within clinical trials or on patients with low immunosuppression. In addition, it is imperative that more data is obtained. For this reason, a multicentric cohort study has been set up for Germany starting in 2006, which should incorporate as many patients as possible. Contact the author, IPM study center, telephone + 49 40 4132420.

More intensive chemotherapy as standard CHOP

After earlier studies showed that intensive chemotherapy led to a disproportionately high risk of infection and toxic complications (Kaplan 1997), the tendency for a long time was to withhold HIV infected patients from therapy and often to treat them with reduced-dose regimens. This seems to be changing in the age of HAART. Prospective studies have shown that the tolerability of chemotherapy is improved through HAART (Powles 2002, Sparano 2004).

In the past few years, small pilot studies have been repeatedly published in which HIV infected patients have been treated with CHOP regimens. There are also studies in which doxorubicin has been given as liposomal Caelyx™ (Levine 2004) or where the dose of cyclophosphamide was increased (Costello 2004). In addition, CDE, a regimen which, when given for several days as infusions is supposed to overcome the potential chemotherapy resistance of lymphoma cells, is propagated again and again (Sparano 2004). The CR rates in these studies were between 50 and 75 %. Whether these new attempts, which always cause a stir, are really better than CHOP, remains speculative. In our view, they are not ready for use outside of clinical trials.

Even stem cell transplantations are now possible in HIV infected patients – a scenario that was unthinkable earlier. High doses of myeloablative chemotherapy in combination with HAART are well tolerated (Gabarre 2000 + 2004, Kang 2002, Re 2003, Krishnan 2005). In HIV infected patients with Burkitt's lymphoma, intensive protocols that were originally developed for HIV negative patients are also being successfully employed (see below).

Today, the decisive question regarding more intensive chemotherapy in HIV patients is, therefore, not whether it can be used, but who actually needs it or will profit from an increased dose.

HAART and classic risk factors

At first glance, the effect of HAART on the prognosis of HIV-associated NHL seems contradictory. At least four large cohort studies (Conti 2000, Levine 2000, Matthews 2000, Chow 2001) have shown sobering results. These data contradict numerous, mostly smaller, but more closely analyzed and prospective studies. These showed without exception that HAART significantly improved prognosis (Thiessard 2000, Antinori 2001, Besson 2001, Ratner 2001, Powles 2002, Vilchez 2002, Navarro 2003, Vaccher 2003, Sparano 2004). In addition to survival, some studies also showed improved disease-free survival, response rates and even improved tolerability of chemotherapy.

While the "classic" NHL risk factors for survival (including Ann Arbor stage, LDH, age, Karnofsky score) are already of lower significance in HIV infected patients than the HIV-relevant factors (CD4-cells, history of AIDS), then the latter presumably lose relevance too when the impact of HAART is also considered (Hoffmann 2003, Lim 2005). In our own multicenter cohort with over 200 patients, the immunologic-virological success of HAART was an important and independent factor for the prognosis (Hoffmann 2003). This was also true for patients who still had a relatively preserved immune status (> 200 CD4 cells/µl at the time of lymphoma). The only additional clinical risk factors were extranodal disease and a history of AIDS, but had relatively weak predictive relevance. However, in a histological analysis, a post germinal centre profile was also associated with a worsened prognosis (Hoffmann 2003).

In practical terms, this means: in a treatment-naïve patient, the chances of complete remission are not necessarily poor even with an otherwise poor starting condition (advanced lymphoma or HIV). Every patient should start HAART as rapidly as possible, even with only moderate immunodeficiency. Chemotherapy with curative intent should follow and, if possible, doses should not be reduced. In order to obtain more data, all patients in the German cohort studies should be included (see above for telephone/contact).

Which HAART when?

Already existing, adequate HAART should be continued during chemotherapy if possible. Depending on the resistence situation, replacement of AZT (myelotoxicity!) and d4T/ddI (polyneuropathy, especially in combination with vincristine!) should be considered. In treatment-naïve patients, the first one or two CHOP cycles can be completed before starting HAART. Some clinicians prefer to complete all six cycles out of concern for interactions and cumulative toxicities (Little 2003). In our opinion, this is not necessary. The choice of antiretroviral drugs is not easy, however. d4T, ddI and AZT should be avoided because of their toxicities. The abacavir hypersensitivity reaction (malaise, fever!) can cause problems with differential diagnoses during chemotherapy; the kidneys have to be very closely monitored on tenofovir. Little is known of the possible interactions between PIs and NNRTIs with cyclophosphamide and other cytostatic agents. The effect on doxorubicin seems to be limited (Toffoli 2004).

In treatment-naïve patients without signs of resistance and pre-existing renal disease, we favor a combination of tenofovir, 3TC/FTC and an NNRTI. This is well

tolerated in most cases, has a low number of pills and low risk of interactions. As long as a boosted PI regimen is being used, the plasma PI levels should be regularly controlled.

Special entities of lymphoma

Burkitt's or Burkitt-like lymphomas (BL/BLL): the particularly high proliferative capacity and aggressiveness of BL/BLL is a problem even in HIV-negative patients. In this case, CHOP is insufficient (Trümper 2001). Although it is still unclear whether this is also true for HIV infected patients, many clinicians have tended to treat such patients more intensively. A modified dose-adapted protocol of the German multicenter study group for adult acute lymphoblastic leukemia (GMALL) is usually used for the treatment of HIV-negative cases of Burkitt-NHL/B-ALL, and consists of four to six short, intensive 5-day polychemotherapy cycles, alternating A and B cycles. A cytoreductive pretreatment with cyclophosphamide and prednisone, each for 5 days, was given before the first cycle. During cycle A, fractionated doses of ifosphamide for 5 days, intermediate- or high-dose methotrexate 500-3,000 mg/m^2, VM26, cytarabine (ara-C), vincristine, and dexamethasone are given. During cycle B, ara-C, VM26 and ifosphamide are replaced by doxorubicin and cyclophosphamide (Hoelzer 1996).

The preliminary data show better responses than with CHOP (Hoffmann 2006) and rates comparative to those of HIV-negative patients (Oriol 2003). However, the GMALL protocol is a very intensive chemotherapy, which cannot be administered on an outpatient basis. Strict monitoring of patients in hospital for several weeks is essential. Centers without experience in this intensive protocol should not administer it to HIV-infected patients.

As well as the B-ALL-protocol, other intensive therapies have been reported (Cortes 2002, Wang 2003). A significant problem with most of the studies is that there is no control group. There is no randomized study. However, there is increasing evidence that conventionally treated patients with Burkitt's lymphoma also have a worse prognosis even in the era of HAART (Conti 2000, Lim 2005, Spina 2005). Although this has not been confirmed by all investigators (Bower 2005), intensive therapy should be considered for every patient with Burkitt's lymphoma. A poor immune status and even the existence of a concurrent opportunistic infection does not necessarily have to be an obstruction (Lehmann 2005).

Plasmablastic lymphomas: are a relatively "new" entity in HIV infected patients. These lymphomas probably belong to the diffuse large-cell NHLs, but have characteristic immunophenotype, which usually indicates a post-germinal center cell origine – markers for the B-cell antigen CD20 are negative, whereas the plasma-cell reactive antibodies VS38c and CD138 are positive (Brown 1998, Teruya-Feldstein 2004). The oral cavity is the site of involvement (Gaidano 2002), although extra-oral manifestations do occur (Chetty 2003). There is a close association with HHV-8 infection. Like Burkitt's lymphoma, plasmablastic lymphomas have a very high rate of proliferation and are extremely aggressive. More recent data shows that the earlier very poor prognosis is markedly improved by HAART (Teruya-Feldstein 2004, Lester 2004). In a study on 89 NHL, we were able to show that a post germinal center profile, as often occurs in plasmablastic lymphomas, is independently

associated with a worse prognosis (Hoffmann 2005). It is our opinion that in these patients, a more intensive treatment than CHOP should be considered.

Primary effusion lymphoma (PEL): a further therapeutic problem is the relatively rare entity of the so-called primary effusion lymphoma which is also termed body cavity lymphoma (Carbone 1997, 2000). These lymphomas are often very difficult to diagnose histologically. A visible tumor mass is usually absent, so that malignant cells can only be found in body cavities (e.g. pleural, pericardial, peritoneal). There are histological similarities to immunoblastic and anaplastic cells with a non-B-, non-T phenotype. Every pleural or pericardial effusion occurring in an HIV infected patient and containing malignant cells, is suspicious of PEL. The involved pathologist should always be informed about this suspicion.

There is a characteristic close association with the herpes virus HHV-8, which can be detected in the malignant cells, and which provides a relatively typical gene expression profile (Simonelli 2005, Fan 2005). Recently, a solitary variant has been reported, which is neither morphologically nor immunophenotypically distinguishable from the classical PEL types (Chadburn 2004). The response to CHOP is usually poor and poorer than that of centroblastic NHL (Simonelli 2003). Case studies with complete remission on HAART alone have been described (Boulanger 2001, Hocqueloux 2001). We have, however, seen two PEL patients who have also died of progression despite CHOP and HAART after only a few months.

Recently, a combined chemotherapy with high dose methotrexate has been reported, with which, in at least 3/7 patients, a lasting complete remission could be achieved – a notable achievement in view of the otherwise poor prognosis, and an approach that should be followed up (Boulanger 2003). On the other hand, there are reports in which even intensive treatment regimens were unsuccessful (Waddington 2004).

Relapse therapy, stem cell transplantation

At the moment, no general recommendations for treatment of recurrent NHL can be given. The prognosis of recurrent NHL is poor overall. A team from the USA reported their positive experiences using the ESHAP protocol (etoposide, methylprednisolone, ara-C and cisplatin) – the frequently used DHAP regimen appears to have no effect in this case (Bi 2001). Salvage monotherapies with mitoguazon or liposomal daunorubicin are well tolerated, but purely palliative (Levine 1997, Tulpule 2001).

It should therefore always be checked whether a patient with recurrent lymphoma qualifies in principle for an autologous stem cell transplant (ASCT). In ASCT, the intensity of the chemotherapy can be markedly increased by the preceding gain of stem cells (own cells: autologous; foreign cells: allogenic). Following the myeloablative chemotherapy, the patients are re-infused with the stem cells.

Over 70 cases have been described so far worldwide (Gabarre 2000 + 2004, Re 2003, Krishnan 2005, Serrano 2005, Hoffmann 2006), including even a few allogenic SCT (Kang 2002). The critical problem in many hematological centers is above all a logistical one, namely the complicated storage of stem cells, which has to conform to strict safety regulations. The storage of potentially infectious HIV

material together with stem cells from non-infected patients in the normal cooling tanks is not allowed – an extra (expensive) tank is required.

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Primary CNS lymphoma

Primary CNS lymphomas (PCNSL) are a late complication of HIV infection and used to occur in up to 10 % of AIDS patients. The incidence of PCNSL has decreased significantly in the last years in comparison to systemic lymphomas.

PCNSL are EBV-associated in almost 100 % of cases (Camilleri-Broet 1997), and histologically are mainly diffuse, large-cell non-Hodgkin's lymphomas. The CD4 cells are almost always below 50/µl at the time of diagnosis. In the pre-HAART era, PCNSL had the poorest prognosis of all the AIDS-defining illnesses, with a median survival of less than three months (Fine and Maher 1993). In the last years, this bleak picture, often characterized by therapeutic nihilism, has changed significantly. In the HAART-era, survival may be several years and even complete remissions have become possible (Hoffmann 2001).

Signs and symptoms

Different neurological deficits occur depending on the localization and the size. Epileptic seizures may be the first manifestation of disease. Personality changes, changes in vigilance, headache and focal deficits such as paresis are also frequent. Fever is usually absent. However, as patients are almost always severely immunocompromised, constitutional symptoms may mask the actual problem.

Diagnosis

Cranial CT or (better) MRT scan should be performed rapidly. The usually single masses absorb contrast medium, show a small to moderate edema, and often take up very little room. The most important differential diagnosis is cerebral toxoplasmosis. A solitary mass with a small edema is usually more indicative of PCNSL. How-

ever, 2-4 lesions may be present, which are usually fairly large (more than 2 cm in diameter). More than four lesions of a PCNSL are rarely found.

In addition to an updated toxoplasmosis serology, which – if negative – makes toxoplasmosis rather unlikely, a recent CD4 cell count should be available. The better the immune status, the less likely the diagnosis of PCNSL. In our own cohort, less than 20 % of patients had more than 50 CD4 cells/µl at the time of diagnosis. At over 100 cells/µl, however, cerebral toxoplasmosis is also less likely.

In addition to the physical examination, a minimal diagnostic program (chest radiography, abdominal ultrasound) should clarify whether the CNS involvement is secondary to systemic lymphoma. This should always include fundoscopy to exclude ocular involvement (up to 20 %).

Besides cerebral toxoplasmosis, differential diagnoses include abscesses, glioblastoma and cerebral metastasis of solid tumors. In the absence of increased intracranial pressure, lumbar puncture is advised in order to detect malignant cells. With a positive EBV-PCR of CSF, the suspicion of PCNSL becomes more likely. In such cases, cerebral lymphomatous granulomatosis has to be considered, which shows a very complex picture on MRT (Wyen 2006, Patsalides 2006).

In most cases, a treatment attempt for toxoplasmosis can be made initially, without steroids wherever possible. If this is unsuccessful, PCNSL is more likely. In such cases, stereotactic brain biopsy is essential to secure the diagnosis. This, however, only makes sense if steroids have not been given previously – even low doses of steroids make histopathological diagnosis impossible.

Treatment

For many years, cranial radiation therapy has been the only option for patients with PCNSL, independent of the HIV status. In HIV-negative patients, using the combination of radiation therapy and steroids, a remission of 12-18 months duration is usually achieved. In HIV patients in the pre-HAART era, radiation only improved survival from 0.9 to 3.0 months (Fine 1993). Survival of more than one year was rare.

The prognosis for HIV-negative patients has improved in the last years due to the combination of methotrexate-based (MTX) chemotherapies and radiation. Smaller studies have indicated that monotherapy with high doses of MTX is effective, thereby reserving radiation therapy for relapses (De Angelis 2001). Whether this is also applicable in HIV infected patients is not clear. In addition, the incidence of HIV-associated PCNSL is now diminishing to such an extent that no prospective studies are expected in the forseeable future. A clear recommendation for treatment can therefore not be made.

Some clinicians still favor cranial radiation therapy alone in HIV infected patients (fractionated, 40 Gy total dose). In our experience, a treatment attempt with intravenous MTX is justified (3 g/m^2 every 14 days with leucovorin rescue) – in order to avoid possible neurological damage from radiation. A small study in HIV infected patients has shown that this approach is practical (Jacomet 1997).

However, the decisive factor always – independent of the specific therapy chosen – is the best possible immune reconstitution. Under HAART, survival of several years has become realistic. Complete remissions have even been described after

treatment with HAART alone (McGowan 1998, Corales 2000). In our own cohort of 29 patients with histologically diagnosed PCNSL, all four patients who experienced an increase in CD4 T cells survived longer than 18 months. Three out of four patients reached complete remission. One patient has now lived for over six years without evidence of relapse (Hoffmann 2001). In a multivariate analysis, HAART was shown to be the only factor associated with a prolonged survival in addition to cranial radiation therapy. Two of these patients, however, died after about three years of a progressive neurological syndrome, which was probably a long-term sequela of radiation therapy in both cases. In view of the better prognosis for patients today, radiation toxicity should therefore be considered more than in the past. Three further studies from France, the USA and Australia have since shown a survival of several years due to HAART (Rigolet 2001, Skiest 2003, Newell 2004).

All patients with PCNSL should therefore be treated intensively with HAART, to achieve the best possible immune reconstitution. If only a moderate immune reconstitution is possible, additional immunomodulatory or antiviral therapies should be evaluated. The partially positive reports about ganciclovir and interleukin-2 (Raez 1999, Aboulafia 2002) or hydroxyurea (Slobod 2000) should, however, be interpreted with care. “Between the lines” of these publications, in which either individual or hardly more than 2-4 patients were described, HAART was almost always a factor.

With signs of raised intracranial pressure, rapid administration of steroids (e.g. dexamethasone 8 mg tid, decreasing the dose rapidly after resolution of edema) is indicated, even if diagnostic testing is more difficult as a result.

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Hodgkin's disease (HD)

The incidence of HD is elevated in HIV infected patients by a factor of 5-10 compared to the HIV-negative population. For particular subtypes of HD, such as lymphocyte-depleted and mixed-cellularity HD, the relative risk is presumably much higher (Frisch 2001). Despite this and the growing realization that these subtypes at least are clearly associated with immunodeficiency, HIV-HD is not considered as an AIDS-defining illness.

HAART does not appear to reduce the incidence of HD. On the contrary: it seems to be increasing (Biggar 2006, Engels 2006). In our experience, the patients that develop HD frequently have a well-suppressed viral load and good immune status. The reasons for it are still unclear.

An advanced stage of disease at diagnosis is typical for HIV-HD, as is frequent extranodal involvement and a trend towards prognostically poorer subtypes (Tirelli 1995, Rapezzi 2001, Thompson 2004). Mediastinal disease is less frequent than in HIV-negative patients. A further difference to HD in seronegative patients is the predominance of cases with Reed-Sternberg cells, as well as the clear association with EBV infection, which is 80-100 %, and is an important etiologic factor for development of HIV-HD.

In comparison to HIV negative HD, which is one of the most highly treatable tumors overall, the prognosis of HIV-HD in the pre-HAART era was poor with a median survival of only 15-20 months (Andrieu 1993, Errante 1999, Levine 2000, Tirelli 1995). The response to chemotherapy was also moderate. Complete remission rates were between 40-80 %, and hematological and infectious complications were frequent.

Even if there is much evidence to support that this is changing in the era of HAART, as with NHL, there is little data so far. In our own cohort of 56 patients, the median survival was 40 months. In patients with adequate HAART, the two-year survival rate was 84 %, which is encouraging (Hoffmann 2004). Other groups have also reported better prognoses with HAART (Ribera 2002, Gérard 2003).

Signs and symptoms

B symptoms occur in the majority of cases. Extranodal and advanced stages are also frequent. Lymphomas are firm, immobile or hardly mobile and painless, and clinical distinction from HIV lymphadenopathy or tuberculous lymphadenitis is not possible.

Diagnosis

Staging is necessary as for non-Hodgkin lymphoma (see NHL section). Diagnostic lymph node extirpation is even more important here than with NHL, as puncture only rarely allows diagnosis of Hodgkin's disease. Single accurate diagnostics are better than half-heartedly bothering the patient with repeated punctures and losing time unnecessarily! Extirpation is usually possible as an outpatient. As with NHL, specimens should be sent to reference laboratories if possible. Since bleomycin will be administered, a lung function test should always precede the first chemotherapy.

Treatment

As for HIV-negative HD, treatment should depend on the Ann-Arbor staging and possible risk factors such as extranodal involvement, more than three affected lymph nodes or a large mediastinal tumor. Thus the distinction can be made between limited (I-II without risk factors), intermediary (I-II with risk factors), and advanced (III-IV) stages.

The classical ABVD regimen (four double cycles) with follow-up radiotherapy is recommended for limited or intermediary stages. ABVD is the abbreviation for the combination chemotherapy with the cytostatics adriamycin, bleomycin, vinblastine and DTIC (dacarbazine). Ambulatory treatment is possible.

Table 4: ABVD regimen (4 double cycles, repeat on Day 29)*

Adriamycin (= doxorubicin)	Doxo-Cell™, Adriblastin™	25 mg/m^2 i.v. Day 1 + 15
Bleomycin	Bleomycin™, Bleo-Cell™	10 mg/m^2 i.v. Day 1 + 15
Vinblastine	Velbe™, Vinblastin Hexal™	6 mg/m^2 i.v. Day 1 + 15
Dacarbazine (DTIC)	Detimedac™	375 mg/m^2 i.v. Day 1 + 15

*ABVD regimen. Due to strong emetogenicity of dacarbazine, 5HT3-receptor blocker anti-emetics should always be administered, e.g. granisetron (Kevatril™), or ondansetron (Zofran™).

In HIV negative patients with advanced stages (as is often the case for HIV-HD) the escalating BEACOPP regimen of the German Hodgkin Study Group has been used in the last years. This has proven to be significantly more effective, both with regard to response rates and long-term survival. But, the BEACOPP regimen is more toxic, and whether these positive results can be seen in HIV-HD is still not clear. However, based on initial reports and our experience, BEACOPP seems to be possible (Hartmann 2003). There is also growing experience to date with the Stanford V protocol, for which there have recently been promising reports (Spina 2002).

Patients are preferably treated within a prospective study. A stage-adapted protocol has been developed for Germany (Study leader: Dr. M. Hentrich, Munich; information via hiv.net).

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Multicentric Castleman's Disease (MCD)

Although rare, multicentric Castleman's disease (MCD) is a highly problematic illness for those affected – not only due to the (in HIV infection) rather poor prognosis, but also because many clinicians and pathologists are not very familiar with this entity. It is not rare for the usually severely ill patients, who experience the disease in impulses, to be subjected to long diagnostic procedures. In comparison to the benign, localized hyperplasia of lymphatic tissue, first described by the American pathologist Benjamin Castleman in 1956, HIV-associated MCD, although nei-

ther a lymphoma nor AIDS-defining illness, is a malignant lymphoproliferative disease. In the pre-HAART era, the median survival time was just 14 months (Oksenhendler 1996).

The pathogenesis of MCD is not well understood. There is an almost obligatory association to HHV-8, and approximately half of the patients have Kaposi's sarcoma. Cytokine dysregulation, possibly due to viral interleukins, seems to be crucial. In particular IL-6 and IL-10 are elevated with close association to the HHV-8 viral load (Oksenhendler 2000). The extent of CD4 cell depletion varies significantly - we have seen patients with a normal immune status and low HIV plasma viremia. "Progression" to malignant lymphoma (often HHV-8-associated subtypes such as primary effusion lymphoma) is frequent. Out of 60 MCD cases, 14 patients developed malignant lymphoma after a median observation period of 20 months (Oksenhendler 2002).

Signs and symptoms

The main signs are the often impressive lymph node enlargements, which can be soft (as in tuberculosis) to rock hard (as in lymphoma) on palpation. These are almost always combined with considerable B symptoms including fever, night sweats and weight loss. Almost all patients complain of weakness and significant malaise. There is always massive splenomegaly. Hepatomegaly (70 %), respiratory symptoms (65 %) and edema with hypoalbuminemia (55 %) are also seen in the majority of cases. The illness typically proceeds in impulses, which can last for a few days to weeks and during which patients have a high fever and are very ill. These impulses are interrupted by long phases, sometimes lasting for several months, in which the patients feel relatively well. Without any intervention, the lymph nodes can return to normal. With prolonged duration of the illness, the acute phases become more frequent.

Diagnosis

Ultrasound reveals hepatosplenomegaly. Laboratory tests show elevated CRP, hypergammaglobulinemia and hypoalbuminemia. There is often significant anemia (may be hemolytic, often reflecting pancytopenia).

The diagnosis is made histologically from an extirpated lymph node – providing that the pathologist knows what HIV-associated multicentric Castleman's disease looks like. The germinal centers of the lymph nodes are layered like an onion and have vessels running through them. Hyaline-vascular and plasma cell types of Castleman's disease can be distinguished. Clinicians should explicitly indicate their suspicion. It is possible that many cases are never correctly diagnosed. In the presence of an impulsive course of disease with B symptoms, splenomegaly, high CRP, and fluctuating lymph node swellings, the pathological diagnosis of HIV-associated lymphadenopathy should not be simply accepted. HIV infection alone never causes illness as severe as MCD!

Treatment

At present, there is no clear recommendation for a specific treatment for MCD. HAART should be given whenever possible, although it doesn't always help (Du-

pin 1997, Lanzafame 2000, Aaron 2002, de Jong 2003, Sprinz 2004). Some cases have even been described to occur or worsen after starting HAART, leading to the suspicion that the inflammatory component of MCD may be increased by immune reconstitution (Zietz 1999). Apart from HAART, there are many diverse forms of therapy, which unfortunately means that so far none of them is particularly convincing. The problem lies also within the countless case reports, where a probable positive "publication bias" has to be taken into account. On the other hand, something has to be done quickly in HIV infected patients with MCD: the course of disease can be fulminant. In our experience, CRP is a useful parameter aside from symptoms and signs, for measuring the course of disease and observing the success of MCD treatment.

Virostatics – because of the association with HHV-8, several antiviral substances have been tried, including ganciclovir, which was successful on at least one patient (Caspar 2004). We have observed improvement in two patients on valganciclovir. In contrast, the use of foscarnet or cidofovir had no benefit (Coty 2003, Senanayake 2003, Berezne 2004).

Chemotherapies – well-tolerated drugs such as vincristine (2 mg i.v. as a bolus at 14-day intervals), vinblastin, or oral etoposide (50 mg daily) have proven effective according to several reports as well as our own experience (Scott 2001, Kotb 2006). Even CHOP chemotherapy can help, but does not seem to significantly prolong survival.

Rituximab: this monoclonal antibody against CD20-expressing cells, which is also used in B cell lymphomas (see above), has been successfully tried in several patients (Corbellino 2001, Marcelin 2003, Casquero 2006). In a French study, 16 to 24 patients achieved a complete remission after one year and four courses of rituximab (Gèrard 2006). The overall survival after one year was approximately 92 %; for disease free survival, the rate was 74 %. The mode of action is not clear, but is probably due to the fact that HHV-8 primarily infects the B cells coating the lymph node. These B cells are eliminated by rituximab. It should be noted that an accompanying Kaposi's sarcoma can progress on rituximab.

Other immunotherapies: positive as well as negative cases exist for interferon (Coty 2003, Nord 2003). From Japan, there are data on seven HIV-negative patients, who were treated successfully with IL-6 receptor antibody (Nishimoto 2000). Thalidomide is a new approach, which suppresses cytokine dysregulation or the inflammatory component, and for which case studies are available (Lee 2003, Jung 2004). In contrast, steroids have no effect on MCD.

Splenectomy – may be appropriate in severe cases. In 40 patients, the median survival following splenectomy was 28 versus 12 months (Oksenhendler 2002). According to a US team, the symptoms were improved in 10/10 patients following splenectomy (Coty 2003). It is speculated that IL-6 production is reduced and that a large reservoir of HHV-8 is removed through the splenectomy.

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Part 5

Special Chapters

15. The New HIV Patient

Sven Philip Aries and Bernhard Schaaf

The initial interview

Can and should be spread over several appointments at short intervals.

What the patient should know afterwards

- In general terms, how the virus causes illness.
- The difference between being HIV-infected and suffering from AIDS.
- The importance of CD4 cells and virus burden.
- How third parties can become infected and how this can be avoided with a great degree of certainty.
- That additional venereal diseases should be avoided, as these can worsen the course of HIV infection; and that it is, at least in theory, possible to become infected with another more pathogenic or resistant strain of HIV.
- Where HIV therapy comes in and how good it can be.
- A healthy balanced diet and regular physical exercise can help improve the prognosis.
- Smoking increases the risk of a number of complications.
- Where to find further information.
- The self-help groups and facilities available in the area for the support of HIV-infected patients.
- What further tests are planned and their usefulness for future treatment.

What the doctor should know afterwards

Infection and risk

- When, where and why was the positive HIV test performed? Was there a negative test prior to this? What risks has the patient taken in the meantime? The question regarding risks can help in the assessment of potential dangers for the patient in further treatment. In the case of a patient without recognizable risk, the test result may be held in doubt until confirmation is given (see also “Laboratory”).
- Where has the patient been recently? This is important because certain germs, which are dangerous for the immunodeficient patient, occur in specific regions. For example, someone who has lived in Hollywood for a lengthy period has a relevant risk of histoplasmosis (which is very rare in Europe).
- What drugs are consumed? Large amounts of alcohol are not only toxic to the liver, but also make adherence more difficult due to loss of control. For smok-

ers, the cardiovascular complications of lipodystrophy during therapy are more threatening.

- Family history of diabetes.
- Tuberculosis among contacts of the patient.

Concomitant illnesses

- What previous illnesses, what concomitant illnesses?
- Former treated or untreated infections and STDs, including syphilis and Hepatitis B/C?
- What medications are taken regularly/occasionally?

Social

- What is the social background of the patient? What does he do professionally? What duties does he have to fulfill? What are his priorities? Who knows about his infection? Who will help him when he becomes ill? Who does he talk to about his problems? Does he have any friends who are also infected? Is he interested in getting in touch with social workers or self-help groups?

The Laboratory

- The HIV test is checked in a cooperating laboratory. Cross-reactive antibodies, for example in the case of collagenosis, lymphoma or recent vaccination can lead to false-positive test results. Western blot is only positive if gp41+120/160 or p24+120/160 react.
- The HIV-viral load is mandatory. A HIV resistance test should be done if available.
- Complete blood count: 30-40 % of all HIV patients suffer from anemia, neutropenia or thrombopenia. Check-up at least every 3-6 months, asymptomatic patients included.
- CD4 cell count at the beginning and every 3-4 months thereafter. Allow for variations (dependent on time of day, particularly low at midday, particularly high in the evening; percentage with less fluctuation).
- Electrolytes, creatinine, GOT, GPT, γGT, AP, LDH, lipase.
- Blood sugar determination in order to assess the probability of metabolic side-effects when undergoing antiretroviral therapy.
- Lipid profile, as a baseline determination to check the course of metabolic side-effects when undergoing antiretroviral therapy.
- Urine status (proteinuria is often a sign of HIV-associated nephropathy).
- Hepatitis serology: A and B, in order to identify vaccination candidates; Hepatitis C, in order to possibly administer HCV therapy prior to ART.
- TPHA test.
- Toxoplasmosis serology IgG. If negative: important for differential diagnosis, if CD4 cells <150/µl – prevention of infection (no raw meat). If positive: medical prophylaxis if necessary.

- CMV serology (IgG). For the identification of CMV-negative patients. If negative: important for differential diagnosis, then information about prevention (safe sex). In cases of severe anemia, transfusion of CMV-negative blood only. If positive: prophylaxis if necessary.
- Varicella serology (IgG). If negative: in principle, active vaccination with attenuated pathogens is contraindicated, but at > 400 CD4 cells/µl it is probably safe and perhaps useful.

The examination

- Physical diagnosis, including an exploratory neurological examination (incl. vibration sensitivity and mini-mental test).
- Tuberculin skin test according to Mendel Mantoux with 10IE. Positive if greater than 5 mm: give prophylaxis; if negative: repeat examination annually. The role of the new Interferon-gamma Release Assays is under investigation.
- Chest X-ray. Contradictory recommendations, probably only makes sense in case of positive tuberculin skin test, in smokers and in patients with suspected disease of the thoracic organs.
- Sonographic scan of the abdomen and lymphnodes. A harmless, informative examination as a baseline finding, but not mentioned in the standard guidelines.
- ECG and pulmonary function test. Simple tests to rule out any cardiovascular and pulmonary disease.
- For women, a PAP smear upon initial diagnosis, after 6 months and then, if negative, once a year. Important because of the approx. 1.7-fold increase in the risk of cervical carcinoma.
- For homosexually active males, an anal PAP smear is recommended every 3 years (due to approx. 80-fold increase in risk of anal carcinoma).
- Especially at low CD4 cell counts (e.g. <200/µl) funduscopy (ophthalmological consultancy!) in order to rule out active CMV retinitis or scars. Advisable in cases of good immune status also (photographic documentation as a baseline).
- Nutritional advice and/or treatment of malnutrition.
- Verifying vaccinations (see chapter on vaccinations).
- Checking the necessity of OI prophylaxis.
- Checking the indication for an antiretroviral therapy.

16. Vaccinations and HIV

Dirk Albrecht and Thomas Weitzel

The increased morbidity and mortality of infectious diseases are key features of HIV infection; vaccination and immunoprophylaxis can make an important contribution to their prevention. However, adverse effects and vaccination failure are also increased in HIV patients. Indications and timing of vaccination should therefore be individually tailored.

As vaccination responses decline with decreasing immune status, indications for vaccination should be considered early after HIV diagnosis (see chapter *The New HIV Patient*). In patients with poor immune status, vaccinations generate little response or are even contraindicated. In these cases, the immunization status of close contact persons should be checked for completeness, routes of exposure to infectious agents should be discussed with the patient and minimized, in some situations passive immunizations should be considered. After a rise in CD4-cells under ART, indications should be reconsidered, some vaccinatinations repeated.

Vaccination recommendations should always take into account the national guidelines, which reflect the strategies for preventing infectious diseases that might differ from country to country. Also, the availability of vaccines may vary. This chapter is, to a certain extent, based on the German standards and the vaccines marketed in Germany.

Assessing the protective effect of a vaccination

- Poor immune status at the time of vaccination decreases the likelihood of developing a protective response. As a general rule, CD4+ T-cell counts < 300/µl may result in a reduced response to immunization; at < 100/µl, significant immunization effects are improbable (Rousseau 1999). ART-mediated immune reconstitution effects require a dynamic approach to vaccination strategies. Consequently, vaccinations should be reconsidered if CD4+ T-cells rise to > 200/µl in patients on ART. Nevertheless, even after immune reconstitution, the CD4+ T-cell nadir might influence the effectiveness of vaccination (Lederman 2003).
- In addition, history taking should include individual risk and current status of protection: Sexual behavior? Contacts to people carrying a particular infection? Travel? Frequent contacts with children? Is a prior infection documented or likely? Are prior vaccinations documented? Depending on their immune status, a poorer response to previous vaccines and an accelerated decline of protective immunity over time must be expected in HIV patients. Antibody titer controls should be considered more frequently than in healthy individuals.

Assessing the risk of a vaccination

Following a vaccination, a rise in viral load is often observed (e.g for tetanus, pneumococcus, influenza, HBV). This effect reflects the stimulation of cellular immunity; viral replication peaks one to three weeks later. Thus, a routine viral load

should not be performed within four weeks of vaccination. Numerous studies demonstrated that these viral load elevations are immunologically and clinically irrelevant. However, one study of influenza vaccinees showed 2 out of 34 patients whose HIV strains developed new RT- or protease-gene mutations (Kolber 2002). This risk should be considered in patients with limited therapeutic options. Furthermore, elevations of viral load might lead to an increased risk of materno-fetal transmission during pregnancy.

Apart from that, adverse effects of inactivated vaccines are not increased in HIV patients. With live vaccines, however, life-threatening and fatal complications have been reported for smallpox, tuberculosis, measles, and yellow fever. Indications for live vaccines in HIV patients should be carefully examined.

Vaccination of contacts

Whenever HIV patients are susceptible to vaccine-preventable infections, particular care should be taken to vaccinate close contacts, who, after gaining protective immunity, will not transmit the disease. However, if contacts are vaccinated with certain live vaccines (e.g. oral polio vaccine), the HIV patient is at risk of acquiring vaccine-associated illness. Thus, oral polio vaccination of contact persons is contraindicated and the inactivated vaccine should be used. Secondary transmission of MMR or varicella following vaccination is very unlikely; only if contacts develop vaccine-associated varicella, the HIV patient should receive acyclovir prophylaxis.

Vaccinations in HIV-infected children

HIV-infected children should be vaccinated according to national children vaccination schedules, with the following exceptions for live vaccines:

(1) In children with severe immunodeficiency, as defined by CD4+ T-cell counts < 750/µl (0-12 months old), < 500/µl (1-5 years old), and < 200/µl (> 5 years old), or by relative CD4 counts < 15 %, MMR vaccination is contraindicated.

(2) In immunodeficient children, varicella vaccination is contraindicated; in this case, guidelines vary to the extent of immunosuppression: while German guidelines still set the threshold for contraindication at relative CD4+ T-cells < 25 % (STIKO 2005), the US recently adopted a strategy in analogy to MMR supporting the vaccination of children with >15% CD4+ T-cells (Kroger 2006).

A possible strategy to avoid unnecessary live vaccines is to predict their probability of success by measuring the response to inactivated vaccines: if there is no measurable response to diphtheria/tetanus booster, a benefit from live vaccines such as MMR or varicella is unlikely, even if CD4+ T-cell counts are higher than the above mentioned limits (Tim Niehues, pers. comm.). In these cases, immunoglobulin prophylaxis might be useful.

HIV-infected children should receive a series of the 7-valent pneumococcal conjugate vaccine, starting in the third month of life, and supplemented by the 23-valent-polysaccharide vaccine after the second year of life (Mofenson 2005).

Postexposure prophylaxis

In susceptible individuals, the risk of infection and/or disease severity can be reduced by postexposure prophylactic measures. These include active and passive immunizations as well as chemoprophylaxes. Usually, the time between exposure and beginning prophylactic measures is crucial and should be minimized. Table 2 provides an overview of reasonable postexposure prophylaxis regimens in HIV patients.

Practical approach to vaccinations

Informed consent: HIV patients should be circumstantially informed regarding the benefits and risks of vaccines, with particular attention to HIV-related vaccine problems. Some countries might require written information material and/or a written informed consent. Vaccine information statements in different languages are available via the Internet (e.g. www.immunize.org).

Timing of a vaccination: Vaccination should be postponed in the presence of a moderate to severe acute infection; a mild infection might be ignored. Live vaccines such as MMR, varicella or yellow fever have to be given either simultaneously or at least four weeks apart from one another. Live vaccines should not be administered within three months after a dose of immunoglobulin. When viral load measurements are crucial for decisions on ART, vaccinations should be postponed.

Primary vaccination series or booster: In general, a primary vaccination schedule is only necessary when no prior vaccination is reported or documented; an incomplete primary series should be completed, but not repeated (consider titer controls).

Route of application: Vaccination routes are recommended by the manufacturer of each vaccine. High immunogenicity and few complications make intramuscular injections the preferable route of application for the majority of vaccines. The most recommended site is the deltoid muscle, in infants the anterolateral thigh. Many water-soluble vaccines can also be administered subcutaneously. In hemophiliacs, subcutaneous vaccination followed by thorough compression of the injection site for > 2 minutes usually allows vaccination without the coadministration of clotting factors. Only a few vaccines require subcutaneous injection, including meningococcal polysaccharide, Japanese encephalitis, yellow fever, and varicella vaccines. Intradermal rabies vaccination, which is licensed in some countries, should not be performed in HIV patients due to reduced immunogenicity (Tantawichien 2001).

Details on individual vaccines

Tetanus/Diphtheria/Pertussis: Following a primary series during childhood, lifelong protection should be maintained by boostering at regular intervals. According to a Danish study (Kurtzhals 1992) and our own experiences in Germany, adult HIV patients frequently have insufficient protection against diphtheria. Depending on their CD4+ T-cell count, HIV patients have a reduced booster response and an accelerated antibody waning (Moss 2003). Whenever possible, tetanus-diphtheria combination vaccines should be used, which, in Germany, are also available in combination with polio and/or pertussis. In the context of a rising incidence of pertussis in adolescents and adults, boostering with acellular pertussis vaccine in ado-

lescents has recently been recommended, and is under discussion for adults (Halperin 2005). Since the adult pertussis booster vaccines are exclusively available in the above-mentioned combinations in Germany as well as in other countries, their use should be considered when tetanus/diphtheria vaccines are given.

Pneumococcal: Even under ART, HIV patients have an increased risk of invasive pneumococcal infections (Barry 2006), which can be reduced by a vaccination (Breiman 2000, Grau 2005). However, in patients with CD4+ T-cell counts < 500/µl, the response to pneumococcal polysaccharide vaccine was decreased (Weiss 1995), and a double-dose booster did not induce a better response (Rodriguez-Barradas 1996). Similar observations were made with the conjugate vaccine in HIV-infected adults and children (Ahmed 1996, Mahdi 2005).

According to current recommendations, HIV patients with CD4+ T-cells > 200/µl should receive pneumococcal vaccination as early as possible after their HIV diagnosis (Benson 2004, Kroger 2006, DH 2006). In patients with CD4+ T-cell counts < 200/µl, the effectivity of the vaccine is uncertain, but vaccination should be considered; after a stable rise to > 200/µl under ART, pneumococcal vaccination should be repeated. Infants from 3 months to 2 years of age should be vaccinated with the 7-valent conjugate vaccine, supplemented by the 23-valent polysaccharide vaccine at age > 2 years.

Confusing data arose from a prospective randomized study on 1,392 HIV patients in Uganda, which reported an increased incidence of pneumococcal infections in the vaccine group (French 2000). Long-term follow-up of the initial patient collective, on the other hand, showed reduced mortality in the vaccine group; thus, the effects of pneumococcal vaccination in an African setting on patients without ART is currently unclear (Watera 2004).

Influenza: Among HIV patients, an increased incidence of influenza has not been found, but complications and severe courses are more common and increased mortality has been observed (Lin 2001). The vaccine is safe and effective in HIV patients (Yamanaka 2005), should be given annually and is recommended from the 6th month of life (Smith 2006). In children under ten years of age, the first vaccination should include two doses at a 4-week interval. When CD4+ T-cells are < 100/µl, a response is rarely measurable, and it is unclear whether the benefit outweighs the cost (Rose 1993). The intranasal live vaccine is not licenced for HIV patients.

Hepatitis B: All HIV patients seronegative to HBV should be vaccinated; as the combination vaccine with hepatitis A is advantageous with regard to price and possibly immunogenicity (Van der Wielen 2006), indication for hepatitis A vaccination should be considered in this context. The vaccination response rate and durability, being generally reduced in HIV patients, correlate with CD4+ T-cell counts; thus, vaccination should be performed early after HIV diagnosis (Laurence 2005). Immuno reconstitution under ART increases vaccination response (Wonk 1996) as does viral load suppression (Overton 2005).

The immune response should be monitored by anti-HBs levels 4-8 weeks after the last dose: anti-HBs levels > 100 IE/l indicate protective immunity; a booster should

be performed after ten years. With levels < 100 IE/l, the response is inadequate and an immediate booster should be performed followed by another antibody control.

Immune response can be increased through repeated immunization, increased vaccine doses and adjuvants (Cooper 2005, Brook 2006). The increased-dose vaccines recommended e.g. for dialysis patients have lower failure rates in HIV patients (Fonseca 2005), and should be considered in non-responders.

In patients with isolated anti-HBc, a constellation occasionally observed in HIV patients, an HBV vaccine should be given (Gandhi 2005); if after the first vaccine dose anti-HBs is detectable, a prior hepatitis B infection should be assumed and the vaccination cycle does not need to be completed.

Hepatitis A: This infection is common among HIV patients (Fonquernie 2001). The vaccine is indicated in patients with chronic liver disease or increased risk of exposure, in some countries it recently even became part of the general child vaccination schedule. Routine pre-vaccination serology (HAV IgG) is not generally recommended, but can be considered in patients with possible prior exposure (e.g. Germans born before 1950). A combination with HBV is available and reduces costs.

Measles: As measles can cause severe disease in HIV patients (Kaplan 1992), susceptible patients should be vaccinated whenever possible. The status of protection should be checked prior to trips in endemic areas (see chapter on Travel). Unless two vaccinations are documented, a serological test should be performed. In the US, persons born before 1957 are considered immune. The vaccine is contraindicated in symptomatic HIV infection and/or with CD4+ T-cell counts < 200/µl or < 14 % (in children: age-specific thresholds, see above). In Germany, usually MMR is used. For susceptible patients, immunoglobulin is indicated post- and in certain high-risk situations even prior to exposure.

Yellow fever: Information on the effectivity and safety of yellow fever vaccine in HIV patients is only available from < 50 patients, all with CD4+ T-cell counts > 200/µl (Goujon 1995, Receveur 2000, Tattevin 2004). These limited data indicate good tolerability, but reduced rates of seroconversion. One case report describes fatal encephalitis in a patient with a very low CD4+ T-cell count, who was asymptomatic at the time of vaccination (Kengsakul 2002).

International recommendations state that vaccination is possible when HIV patients are asymptomatic, have a good immune status, and exposure can not be avoided (Cetron 2002); in daily practice, CD4+ T-cell counts > 200/µl are often used as cutoff (Schuhwerk 2006). Due to reduced response rates, titer controls might be useful. We recommend the documentation of seroconversion in a paired serum sample (before, and 2-3 weeks after vaccination). If vaccination is contraindicated, a medical waiver should be issued to patients traveling to countries where yellow fever vaccination is mandatory. For the population in endemic areas, the WHO recommends vaccine use even in areas with high HIV prevalence (Moss 2003).

Human Papillomavirus (HPV): Recently, an inactivated HPV vaccine was introduced for young women (ACIP 2006). Due to the increased risk for HPV-

associated tumors, this vaccine could be relevant for HIV patients; however, so far there are insufficient data.

Rotavirus: Since 2006, two live vaccines for infants are available, but not yet generally recommended. In infants with immunodeficiency, severe and chronic rotavirus infections are described; thus, according to US recommendations vaccination can be considered (Parashar 2006). Further studies on the safety in HIV-infected children should be awaited.

The following **Tables** give an overview over current vaccines and recommendations. In **Table 1**, HIV-specific recommendations can be distinguished as follows:

- A: in HIV patients generally recommmended
- B: in HIV patients applicable independent of immune status
- C: in HIV patients applicaple depending on immune status
- D: in HIV patients contraindicated

Table 2 lists postexposure vaccinations and prophylaxes.

Table 1: Vaccines and their indications in HIV patients

Vaccine[1]	Vaccine type[2]	Indication[3]	Recommendation in HIV Comments
Cholera	I. inactivated + toxoid II. live	travelers with high risk of exposure[4]	**I. B** **II. D** I: also limited protection against some forms of travelers' diarrhea
Diphtheria	toxoid	generally recommended	**B** reduced dose after 6th tyear of life
Hemophilus influenzae b (HiB)	polysaccharide	generally recommended in childhood; asplenia	**B** consider in unvaccinated HIV patients (Kroger 2006)
Hepatitis A	inactivated	chronic liver disease increased risk of exposure	**B**
Hepatitis B	recombinant antigen	generally recommended in childhood	**A**
Influenza	I: inactivated/ fractionated antigen II: live (intranasal)	chronic disease, age > 60 years, high transmission risk	**I. B** **II. D** year-specific antigen combination according to WHO
Japanese encephalitis	inactivated	travelers with high risk of exposure[4]	**B**

Table 1: Vaccines and their indications in HIV patients

Vaccine[1]	Vaccine type[2]	Indication[3]	Recommendation in HIV Comments
Measles	live attenuated	generally recommended in childhood susceptible travelers[5] to endemic areas	**C** susceptible HIV-patients[5]
Meningococcal (groups A, C, W135, Y)	I. 2-/4-valent polysaccharide II.2-/ 4-valent conjugate	generally recommended in childhood immunodeficiency (e.g. complement deficiencies, asplenia); travelers with high risk of exposure[5]	**I + II: B** no protection against serotype B (high prevalence in Europe and Brazil) mandatory for pilgrims to Saudi-Arabia
Mumps	live attenuated	generally recommended in childhood susceptible persons[5] with frequent contact to children	**C**
Pertussis	purified acellular antigens	generally recommended in childhood in some countries lifelong booster (every 10y)	**B** booster available only in combination vaccines
Pneumococcal	I. 23-valent polysaccharide II. 7-valent conjugate	general recommendation for chronic disease, immunodeficiency, age >60 years	**I + II: A** I: 2 years and older II: 2 months to 5 years protection only against subset of the naturally occurring strains
Poliomyelitis	I. inactivated (IPV) II. live (OPV)	children: generally recommended adults: increased risk of exposure (e.g. health care, travel to endemic areas): boost after 10 y	**I. B** **II. D**
Rabies	inactivated	occupational risk of animal contact travelers with high risk of exposure[4]	**B** often poor response, serological testing recommended, no intradermal vaccination
Rubella	live attenuated	generally recommended in childhood susceptible persons[5] with frequent children contact, susceptible women[5] of child-bearing age	**C**
Smallpox	live attenuated	controversial	**D** (for prophylaxis) HIV patients should avoid contact with vaccinees for 2 weeks (risk of transmission of

Table 1: Vaccines and their indications in HIV patients

Vaccine[1]	Vaccine type[2]	Indication[3]	Recommendation in HIV Comments
			vaccine strain)
Tetanus	toxoid	generally recommended	**B**
Tick-borne encephalitis (TBE/FSME)	inactivated	inhabitants of and travelers to endemic regions with risk of tick exposure occupational exposure	**B** consider regional distribution profile European TBE vaccine is probably protective against RSSE (Hayasaka 2001)
Tuberculosis	live BCG-strain	varying strategies	**D**
Typhoid fever	I. polysaccharide II. live	travelers with high risk of exposure[4]	**I. B** **II. D**
Varicella	live attenuated	generally recommended in childhood/adolescence susceptible persons[5] with frequent contact to children or immunosuppressed patients susceptible women[5] of child-bearing age	**C**
Yellow fever	live attenuated	travelers to endemic areas travel requirements in some countries!	**C** vaccination only in authorized institutions

1. Combination vaccines should be used whenever possible
2. Not all vaccines are licenced or available in all countries
3. Also observe national vaccination guidelines and manufacturer's recommendations
4. If in doubt, seek travel medicine advice
5. *Susceptible*: No documented history of the disease, no prior vaccination, no specific antibodies in serological test

Table 2: Postexposure vaccines and chemoprophylaxes for HIV patients

Disease	Type of prophylaxis	Indication[1]	Comments
Diphtheria	I. active immunization II. chemoproph.	close / face-to-face contact with a case patient I. if last vaccination > 5 y II. independent of immunization status	II: e.g. erythromycin 4x 500 mg/d x 7-10 d
Hemophilus influenzae b	chemoproph.	patients with immunosuppression or persons from their close environment after close contact with a case patient	rifampicin 1x 600 mg/d x 4 d
Hepatitis A	I. active immunization II. simultaneous immunoglobulin	I: every exposure of a susceptible person[2] II: additionally in patients at risk of severe course (e.g. HBV- or HCV-infection)	
Hepatitis B	I. active immunization/booster II. simultaneous immunoglobulin[5]	protection status after percutaneous exposure[3]: insufficient: I+II partial: I complete: not needed	
Influenza	I. active immunization II. chemoproph.	I: community outbreak with strain covered by vaccine II: direct exposure of any unvaccinated HIV patient; in patients with severe immunodepression independent of their immunization status	II: Influenza A or B: oseltamivir: 1x 75 mg/d x 10d (alternative: zanamivir: 1 x 10 mg/kg/d x 10d; not ubiquitously licenced for prophylactic use)
Measles	I. active immunization/booster II. (simultaneous) immunoglobulin	I: exposure of a susceptible person[2] II: exposure of a susceptible person[2] with more than mild immunosuppression, when response to active immunization is unlikely or immunization is contraindicated	active immunization within 72 hours of exposure consider contraindications for vaccination!
Meningococcal	I. active immunization II. chemoproph.	following an index case: I: according to health authorities II: all household members; persons in contact with oropharyngeal secretions; close contacts in child-care centers, dormitories	II: aim <24h after exposure; consider within 14d; (index case was infectious 7d prior to symptoms!) rifampicin 2x 600 mg/d x 2 d or ciprofloxacin 1x 500 mg or ceftriaxone 1x 250 mg i.m.
Mumps	active immunization	exposure of a susceptible person[2]	active immunization within 3 (-5) days of exposure

Table 2: Postexposure vaccines and chemoprophylaxes for HIV patients

Disease	Type of prophylaxis	Indication[1]	Comments
			consider contraindications or vaccination!
Pertussis	I. active immunization II. chemoproph.	I: exposure with incomplete immunization II: close contacts, e.g. household contacts	II: within 7 days of exposure macrolides, e.g clarithromycin, 2 x 500mg/d x 7 d
Polio	I. active immunization	any exposure independent of immunization status	avoid delays!
Rabies	I. active immunization/booster II. simultaneous immunoglobulin[5]	according to national or local recommendations	HIV: consider double dose of active vaccine on day 0, consider immunoglobulin more liberally in immunosuppressed patients
Rubella	active immunization	exposure of a susceptible person[2]	within 5 days of exposure consider contraindications for vaccination!
Tetanus	I. active immunization/booster II. simultaneous immunoglobulin[5]	I: vaccine status unknown, incomplete primary series or last booster > 5 years ago II: unknown, 0 or 1 dose of primary series or 2 doses of primary series and > 24 hours between injury and booster	after minor, clean wounds: booster only if last is > 10 years ago; simultaneous immunoglobulin not needed
Tuberculosis	chemoproph.	HIV patient after contact with open TB case	treat in analogy to latent TB (see TB chapter)
Varicella	I: active immunization II: simultaneous immunoglobulin[5] III: chemoproph.	I: exposure[4] of a susceptible patient[1]; II/III: exposure[4] of a susceptible patient[1] with more than mild immunosuppression	I: up to 5 days after exposure or 3 days after beginning of exanthema; consider contraindications; not in combination with II/III! II/III: consider < 96h post exposure III: consider >96h post exposure (e.g. acyclovir 4 x 800 mg x 5 d)

1. always also observe national guidelines and licensure status
2. *susceptible:* No documented history of the disease, no prior vaccination, no specific antibodies on serological testing.
3. *h*epatitis b protection status: (if available within 48 hrs, test anti-HBs titer)
   complete: good responder and last dose < 5 years ago; or anti-HBs > 100 IE/ml within the last 12 months
   partial: good responder and last dose > 5, but < 10 years ago; or current anti-HBs documented > 10 (but < 100) IE/ml
   insufficient: anything less than partial or complete protection
   good responder: anti-HBs documented > 100 IE/ml after primary series
4. *chickenpox exposure*: face-to-face contact, household contact, > 1 hour in the same room; *zoster exposure*: direct contact with skin lesions or their secretions. The indication for immunoprophylaxis following zoster exposure is unclear due to insufficient data; stated is the personal opinion of the authors.
5. specific hyperimmunoglobulin available in some countries

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Links

- Advisory Committee on Immunization Practices (ACIP): http://www.cdc.gov/nip/publications/acip-list.htm
- Department of Health (United Kingdom). Immunisation Against Infectious Disease - "The Green Book":

  http://www.dh.gov.uk/PolicyAndGuidance/HealthAndSocialCareTopics/GreenBook/fs/en
- World Health Organization vaccines page: http://www.who.int/vaccines

17. Traveling with HIV

Thomas Weitzel

HIV patients are fond of traveling. In Europe and the USA, annually 10-15 % of HIV patients travel abroad, often to tropical regions and also to developing countries (Kemper 1995, Simons 1999). In the future, with increasing expectancy and quality of life, travel activities of HIV patients will further rise.

Travel preparations

HIV patients bear an increased risk of travel-associated infections, particularly if when CD4+ T-cell counts are below 200/µl. Furthermore, the effectiveness of vaccinations is reduced. Therefore, travel activities should be well prepared. An overview of travel recommendations can be accessed through different Internet sites. Especially before traveling to tropical or subtropical countries, it is recommended to obtain additional advice from travel medicine specialists. Long-term travelers should get informed on the medical infrastructure at their destination. A first-aid kit for HIV-infected travelers should contain, besides local antihistaminics, disinfectants, sun protection, analgesics, antipyretics, antiemetics, and antidiarrheals, an antibiotic for the empirical treatment of acute diarrhea (see below).

Antiretroviral therapy (ART)

Before traveling, ART should be proven to be effective and well tolerated for at least three months. Depending on the destination, planned activities, and possible compliance problems, which occur quite frequently during travel (Salit 2005), an interruption of therapy can be considered. If ART is being continued during traveling, the following aspects should be considered:

- A stockpile of antiretroviral drugs should be packed, preferably in the hand luggage, in case the suitcases get lost.
- The availability of the ART at destination should be checked beforehand. If necessary, prescriptions and a medical letter in English should be taken along.
- Because of some countries´ entry regulations (see below) it may be useful to pack antiretroviral drugs in neutral packages.
- Storage requirements for the drugs (refrigeration, etc.) must be kept in mind.
- Unplanned therapy interruption during travel should be discussed beforehand in detail.

General precautions

The higher risk of gastrointestinal infections in HIV patients demands adherence to the principles of food and water hygiene (Hayes 2003). The following food and drink are to be avoided:

- Raw fruit or vegetables that are not peeled
- Raw or undercooked meat or fish dishes
- Tap water
- Ice cubes made from tap water
- Unpasteurized milk or milk products
- Food prepared or distributed under insecure hygienic circumstances (e.g. by street vendors)

Even brushing teeth or swimming carries the risk of swallowing small amounts of potentially contaminated water. In the lack of hygienic beverages, tap water should be boiled. In areas up to 2,000 meters above sea level, a boiling time of one minute kills all potential pathogens; at higher altitudes, the boiling time should be prolonged to three minutes. Chemical or filtration methods of water treatment are less reliable.

Also protective measures against vector-transmitted infections are of special importance (see links). Those include:

- Outdoors, long and bright clothes should be worn
- Repellents (e.g. DEET based) should be applied to uncovered skin areas (sun protection has to be applied beforehand
- Outdoor stays during dawn or night ought to be avoided
- Sleeping areas should be mosquito safe (a mosquito net is the best repellent!)
- Impregnation of clothes and mosquito nets with permethrine provides additional safety

Since condoms and lubricants abroad are not always of reliable quality, a sufficient amount of these products should be brought, to guarantee safe sex during the holiday.

Because of possible *Strongyloides stercoralis* infection (see below), direct skin contact to fecally contaminated soil should be avoided. It is wise to wear closed shoes and place a towel underneath when lying or sitting on the ground.

Precautions against zoonotic infections such as salmonellosis or cryptosporidiosis include proper hand washing following animal contact.

Vaccinations

A travel medicine consultation is an opportunity to check and complete routinely recommended immunizations such as tetanus/diphtheria, pneumococcal, influenza, and hepatitis B vaccinations. It has to be kept in mind that the southern hemisphere influenza season is from April to September, while in the tropics influenza can occur all year long. Additional immunizations have to be considered according to travel style, duration, and destination. Open immunization questions usually require

the consultation of a specialized institution (see links for institutions in Germany). Further details on this issues are available in the chapter on vaccinations in this book.

Malaria prophylaxis

Interactions between antiretroviral drugs and drugs for malaria prophylaxis, such as chloroquine, mefloquine, doxycycline, and Malarone™ (atovaquone/proguanil), are inadequately evaluated (Khoo 2005).

In healthy volunteers taking mefloquine (Lariam™) together with ritonavir, a 30 % reduction of the steady-state plasma level of ritonavir was reported; however, mefloquine did not change the ritonavir level after a single dose of ritonavir (Khaliq 2001). The explanation is probably a reduced bile production caused by mefloquine. No relevant interactions seem to occur if mefloquine is coadministered with nelfinavir or indinavir (Schippers 2000).

Chloroquine is metabolized by CYP2D6, but is also excreted by the kidneys; explicit data on interactions of chloroquine with HIV drugs are lacking. In vitro, chloroquine inhibits HIV replication and shows synergistic effects together with protease inhibitors (Savarino 2004). On the other hand, PIs display an inhibitory effect on plasmodia in vitro and in animals. Whether these observations could have an impact on the clinical management of HIV infection or malaria is still uncertain. (Parikh 2005, Andrews 2006).

Clinical data on the interactions of Malarone™ with HIV drugs are missing. In vitro data indicate that ritonavir and lopinavir reduce levels of atovaquone and that ritonavir increases the level of proguanil. Atovaquone decreases the indinavir level by 20 % and increases the AZT level by 30 %.

Doxycycline is not metabolized by the cytochrome p450 system. Thus, relevant interactions with HIV drugs are not anticipated.

Available data and clinical experience indicate that mefloquine as well as doxycycline and chloroquine can be safely and effectively used in patients taking antiretroviral therapy. Although clinical studies are lacking, the same applies for Malarone™. Thus, recommendations for malaria prophylaxis are not limited by concomitant HIV medication. Mefloquine, however, should not be used in HIV patients with neurological disturbances.

Common drugs for malaria stand-by treatment are chloroquine, mefloquine, Malarone™, and Riamet™ (artemether/lumefantrine). Both components of Riamet™ are substrates of CPY3A4; due to incalculable increases in drug exposure, Riamet™ is contraindicated together with protease inhibitors (see Riamet™ product information).

Entry regulations and travel insurance

Although contentious as a measure of health policy and not recommended by the WHO, more than 150 countries, including the USA, refuse entry to HIV infected individuals. This particularly affects long-term stays in connection with work or study. To avoid problems, information on entry regulations should be obtained beforehand. Peter Wiessner and Karl Lemmen's brochure "Schnellfinder" provides an

excellent and comprehensive overview on entry policies. In cooperation with David Haerry of the Swiss Aids Info Docu, a regularly updated version of this databank is available online (see links).
The American foreign ministry also publishes a list of countries with HIV-specific entry restrictions (see links). Under certain circumstances, e.g. visits to conferences, family members, or business travel, journeys to the USA are possible for HIV patients if they apply for a "visa waiver". However, the procedure is time consuming and the passport endorsement can complicate further travel to the USA or other countries.

Travel insurances usually exclude existing illnesses and often refuse HIV patients explicitly. Only in some countries, e.g. the UK and the USA, special HIV travel insurances are available.

Special risks

Enteric infections

Reduced immunological defense and diminished gastric acid production increase the risk of gastrointestinal infections in HIV patients. Furthermore, bacterial enteric infections such as salmonellosis, shigellosis, and *Campylobacter* infections bear a high risk of bacteremia and relapse. Infections caused by *Cryptosporidium sp*., *Isospora belli* and microsporidia are dangerous due to their chronicity.

Prophylactic use of antibiotics, although reducing the prevalence of travel-associated diarrhea, is not generally recommended in HIV patients. In certain situations though, e.g. HIV patients with advanced immunodeficiency traveling under poor hygienic conditions, prophylaxis with ciprofloxacin (500 mg per day) should be considered. In Southeast Asia, an increasing rate of quinolone resistance makes azithromycin a useful alternative. Because of widespread bacterial resistance, cotrimoxazole and doxycycline are insufficient.

HIV patients should be advised to empirically self-treat travel-associated diarrhea for five to seven days with ciprofloxacin (500 mg per day) or alternatively azithromycin (400 mg per day).

Malaria

Synergistic interactions between HIV and malaria are subject to recent and ongoing research (Kublin 2006, Brentlinger 2006). Proinflammatory cytokines, released during plasmodial infection, increase HIV replication. On the other hand, HIV patients suffer malaria episodes with increased frequency and severity which has fatal consequences especially in African (Korenromp 2005, Kamya 2006).

The efficacy of antimalarial therapy is not influenced by HIV. Accordingly, recommendations for malaria therapy generally apply to HIV patients. As described above though, drug interactions of antimalarial and HIV drugs are not well-established. The treatment of complicated malaria is problematic since the indicated drugs, quinine, quinidine, or artemisinin derivates, are all metabolized by CYP3A4. The coadministration of these drugs with CYP3A4 inhibitors as protease inhibitors,

efavirenz, or delavirdine, requires intensive care monitoring and, if possible, drug level monitoring.

Measles

On a global scale, measles are a common infection. For 2005, the WHO reported more than 20 million measles cases with about 345,000 deaths worldwide. In HIV-infected patients, measles occur more frequently and more severely, and viral shedding is prolonged (Moss 2002). American studies showed a high mortality rate, mostly due to giant-cell pneumonitis (Kaplan 1996). Non-immune HIV patients should therefore consider active or passive immunization before traveling to areas with a high prevalence of measles (see chapter "Vaccinations and HIV").

Leishmaniasis

Visceral leishmaniasis (kala azar) is a life-threatening infection complicated by limited therapeutic options. German data revealed that most imported cases were acquired in Mediterranean countries, that long-term travelers were affected more frequently, and that HIV patients had a higher infection risk than healthy travelers (Harms 2003, Weitzel 2005). Most frequently, HIV patients with CD4+ T-cell counts below 200/µl are affected (Kaplan 1996). Due to the infection's potentially extended latency period, symptoms can occur long after exposure. Diagnosis is challenging, mostly requiring cooperation with a specialized center. Cutaneous leishmaniasis does not seem to occur more frequently in HIV patients.

Severely immunocompromised HIV patients must be informed of the risk of leishmaniasis even when traveling to Mediterranean countries. Preventive measures against mosquito bites should be followed to avoid leishmanial infections; because of the vector's small size, the use of an impregnated mosquito net of small mesh size is advisable.

Tuberculosis

Globally, tuberculosis is the most prevalent HIV-associated opportunistic infection. Many tropical and subtropical regions bear an increased tuberculosis risk compared to European and North American countries. Therefore, a tuberculin skin test should be performed before and after long-term travel to countries of high tuberculosis endemicity. Patients with a positive tuberculin skin reaction or with a known high risk exposure should receive a course of treatment for latent tuberculosis (see chapter "Tuberculosis"). HIV-infected individuals should avoid risk areas such as hospitals, prisons or homeless-shelters, or wear adequate facemasks.

Endemic mycoses

Endemic mycoses are rare infections. Nevertheless, they are able to cause life-threatening opportunistic infections in HIV patients even years after stays in endemic areas. Most agents of endemic mycoses are thought to enter the pulmonary tract after inhalation of infective spores. In areas endemic for *Penicillium marneffei* (South East Asia, Southern China) and *Coccidioides immitis* (south-west parts of the USA, parts of Central and South America), increased exposure to dust or soil should be avoided (e.g. construction sites, agriculture, garden work, excavations).

Histoplasma capsulatum is prevalent worldwide in soil contaminated with bird and bat droppings. Exposure might happen during eco or adventure tourism and should be avoided by HIV-infected persons. In individual cases, e.g. severely immunocompromised HIV patients with a foreseeable contact to agents of endemic mycoses, primary prophylaxis can be considered. Depending on the expected pathogen, either fluconazole or itraconazole should be prescribed.

Another fungus causing severe infections in HIV patients is *Sporothrix schenkii.* This pathogen, which occurs worldwide, enters the body through cutaneous lesions. Wearing gloves while working with plants, hay, or peat moss can reduce the sporotrichosis risk.

Sexually transmitted diseases

In travelers, the risk of sexually transmitted diseases is markedly increased (Richens 2006). It is estimated that 5 to 10 % of the HIV infections of German patients were acquired during holidays. HIV-positive travelers should be aware of the special risks that sexually transmitted diseases including HIV reinfection present to them.

Other parasites

The following parasitic pathogens are relevant for traveling HIV patients:

- *Strongyloides stercoralis* is prevalent in most tropical and subtropical areas. The parasite is transmitted by cutaneous larval invasion after skin contact with fecally contaminated soil. In HIV patients, there is the risk of a "hyperinfection syndrome" with a high fatality rate (Gompels 1991). Besides HIV infection, corticosteroid use is an important risk factor, as these drugs seem able to increase larval maturation triggering a cycle of massive autoinfection.
- *Trypanosoma cruzi* is endemic in large parts of Latin America. This protozoan causes Chagas disease and is transmitted by triatomine bugs. Chagas disease, which often persists asymptomatically for many years, can reactivate in severely immunocompromised HIV patients. In these cases, lesions radiologically resembling cerebral toxoplasmosis are often found in the central nervous system (Rocha 1994).
- *Babesia sp.*, tick-borne protozoa with a worldwide distribution, are able to cause infections in a broad spectrum of vertebrates. Severe infections, clinically resembling malaria, occur more frequently in severely immunocompromised HIV patients (Falagas et Klempner 1996).
- Free-living ameba (*Acanthamoeba sp.* and *Balamuthia mandrillaris*) are ubiquitous, living in soil and water. In HIV-infected, these organisms can cause severe infections of the central nervous system (granulomatous encephalitis), as well as local infections of the skin and cornea (Sison 1995).

Medical problems after traveling

Because of the infections mentioned in this chapter, travel-associated diseases in HIV patients have to be diagnosed and treated in a timely manner. In temperate countries, where most tropical diseases are rare, diagnosis is often delayed. An analysis of imported visceral leishmaniasis revealed a median time span of 85 days

until the diagnosis was established (Weitzel 2005). Furthermore, tropical diseases often manifest atypically in HIV patients (Karp et Neva 1999). The differential diagnosis of febrile syndromes in HIV-infected individuals is already very broad; after traveling the clinical situation can become even more complex needing close cooperation of HIV and Tropical Medicine specialists.

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Links

- Travel Medicine
  http://www.cdc.gov/travel/
  http://www.who.int/ith/
  http://www.crm.de/
- Tropical Medicine institutions in Germany
  http://dtg.org/institut.html
- German recommendations for malaria prophylaxis and therapy
  http://dtg.org/malaria.html
  http://www.uni-duesseldorf.de/WWW/AWMF/ll/042-001.htm
- Entry regulations and HIV-associated restrictions
  http://www.aidsnet.ch/linkto/immigration/
  http://travel.state.gov/travel/HIVtestingreqs.html
- Drinking water & mosquito protection
  http://www.cdc.gov/travel/foodwater.htm
  http://www.cdc.gov/travel/mosquito_tick_protection.htm

18. HIV and HBV/HCV Coinfections

Jan-Christian Wasmuth and Juergen Rockstroh

HIV and HCV Coinfection

Epidemiology and transmission

Coinfection with HIV and HCV occurs frequently, due to the fact that both are transmitted via the same pathways (parenteral, sexual, vertical). 240,000 people (30 % of HIV-infected individuals) are estimated to be infected with both viruses in the USA.

Several European countries have even higher rates of coinfection. In Spain, at least 50 % of the 130,000 HIV-infected patients are also HCV-positive as a result of the high incidence of i.v. drug users. More than 90 % of coinfected individuals are positive for HCV RNA, i.e. have chronic hepatitis C.

As HCV is ten times more infectious than HIV on blood-to-blood contact, intravenous drug users and recipients of blood products are particularly susceptible to coinfection. The probability of transmission from needlestick injuries after exposure to HCV-contaminated blood is 2–8 %, compared to only 0.3 % after exposure to HIV-contaminated blood.

In contrast, sexual transmission of HCV occurs significantly less frequently than HBV or HIV. As a result, HCV is rare in homosexual men and coinfection is more seldom in this group. However, there have been reported clusters of cases of acute hepatitis C among homosexual HIV-positive men, clearly indicating that HCV can be sexually transmitted. The risk of transmission probably depends on the number of sexual partners and the performance of sexual practices that are prone to injuries (Vogel 2005). In total, about 4–8 % of all HIV-infected homosexuals are also infected with HCV.

Perinatal transmission of hepatitis C is rare in immunocompetent individuals (<1 %). The transmission rate rises with increasing immunosuppression in HIV-positive mothers, and is estimated to be as high as 20 %. On the other hand, HIV-positive mothers treated effectively with HAART do not appear to have an increased risk for materno-fetal transmission of the hepatitis C virus (< 3 % in combination with cesarean section; Pembreya 2005).

Clinical course and pathogenesis

Course of hepatitis C in HIV/HCV-coinfected patients

The clinical course of hepatitis C coinfection is determined by the HIV-associated immunosuppression. Progression of immunosuppression accelerates the course of hepatitis C. The latent period until liver failure or hepatocellular carcinoma is extimated to be 10-20 years, whereas it is 30-40 years in HCV-monoinfection.

The improved treatment options for HIV infection have increased the likelihood of patients actually living to experience the development of liver failure. The associ-

ated decrease in mortality with HIV infection has resulted in a relative increase in hepatitis-associated mortality. In many centers, liver failure is now the most frequent cause of death in HIV-infected patients.

Conversely there is no significant influence of hepatitis C on the course of HIV-infection, whose progression is not altered (Rockstroh 2005).

The unfavorable course of hepatitis C in HIV infection can be improved by treatment of HIV infection with HAART. In addition, the development of liver failure can be delayed by the improved immune function under HAART. This is particularly true for patients who achieve a good immune recovery.

On the other hand, hepatitis C infection can aggravate the potential hepatotoxicity of several HAART regimens. Up to 10 % of patients have to discontinue HAART due to severe hepatotoxicity. This risk is associated especially with the so-called "d-nucleosides" (ddI, ddC, d4T). These substances should be avoided in coinfected patients. Nevirapine and tipranavir should be used with caution.

In some coinfected patients, a temporary increase in transaminases is observed after initiation of HAART. This most likely corresponds to an increased inflammatory activity of hepatitis C as a result of the improved immune status. Nevertheless, long-term follow-up has shown that HAART improves the course of hepatitis C. Indications for HAART, according to current treatment guidelines, should be carefully checked in all coinfected patients.

Diagnosis

The diagnostic tests used in coinfected patients are the same used in patients with HCV monoinfection (table 1). Detection of HCV antibodies (anti-HCV) proves exposure to HCV, but does not distinguish between resolved and chronic hepatitis C. Chronic hepatitis C is diagnosed by the detection of HCV viremia (i.e. HCV RNA). It should be noted that HCV antibodies might be lost during the course of HIV infection as a result of the underlying immunosuppression, although nowadays this phenomenon has become rare, probably due to improved test kits. It may therefore be useful to determine HCV RNA levels, even if the anti-HCV test is negative, if there is clinical suspicion or advanced immunodeficiency. Similarly, determination of HCV RNA levels is indicated in cases of suspected acute (primary) HCV infection, as HCV antibodies usually only become detectable one to five months after infection.

Patients with HIV/HCV coinfection have significantly higher levels of HCV viremia than patients with HCV monoinfection (about 1 log). However, the level of viremia does not have a prognostic value for the course of hepatitis C. Accordingly, regular testing of HCV-RNA as a routine clinical procedure is not necessary. However, some patients might loose HCV-RNA in parallel to progression of immune deficiency, but experience a flare up of hepatitis C together with clinical symptoms following immune reconstitution under HAART (Kim 2006). Therefore, regular testing around the initiation of HAART seems to be prudent. Otherwise we consider routine measurement of HCV RNA once a year sufficient. It is possible to predict a response to treatment from the level of the HCV viremia: if the concentration of HCV RNA is below 800,000 IU /ml, the probability of treatment success is signifi-

cantly higher than at levels above 800,000 IU /ml (800,000 IU/ml equals about 2 million copies/ml dependent on the test used).

Response rates are influenced by HCV genotype. Six genotypes with numerous subtypes are known, and are seen to have different regional distributions: genotypes 1 and 3 are predominantly found in Europe, whereas genotypes 4 and 5 are found in Africa, and genotype 6 in Asia. Genotypes 2 and 3 in particular are associated with significantly better responses to interferon therapy. Coinfection with several genotypes is possible. Before initiating treatment genotyping should be performed.

Grading of liver fibrosis is essential in order to estimate the extent of liver damage. Among non-invasive procedures the Fibroscan system is of special interest. This technique (transelastography) allos to determine liver stiffness that correlates with the extent of liver fibrosis. Due to the development of such non-invasive procedures the role liver biopsy before starting HCV-therapy has to be newly defined. Similarly, follow-up by liver biopsy if no treatment is commenced most likely will not be necessary any more. If a liver biopsy is not available, current consensus recommendations suggest treatment of hepatitis in case of genotypes 2+3, or genotype 1 and low HCV viremia. If a liver biopsy has been performed that shows no significant fibrosis, immediate treatment is usually not required regardless of the underlying genotype.

There are several histological classifications used. In Europe the METAVIR-Score is used most often. It distinguishes five stages of fibrosis (0 = no fibrosis, 1 = portal fibrosis without septa, 2 = few septa, 3 = significant septa without cirrhosis, 4 = cirrhosis). Hepatitis activity is graded according to the intensity of necroinflammatory lesions (A0 = no, A1 = mild, A2 = moderate, A3 = severe). Treatment is recommended for grades F2-F4; it may be deferred for grades F0+F1.

If there is clinical suspicion requiring the detection or exclusion of extrahepatic manifestations (vasculitis, glomerulonephritis, systemic cryoglobulinemia), appropriate investigations may be necessary (skin biopsy, urine tests, kidney biopsy, detection of serum cryoglobulins).

The recommendations for autoantibody testing to exclude autoimmune disease vary and test results are difficult to interpret: up to 60 % of all patients with hepatitis C have autoantibodies such as ANA, RF, anticardiolipin, SMA, and LKM1 antibodies as an accompanying autoimmune phenomenon without any clinical relevance. If the titers of these autoantibodies increase or appear for the first time during interferon therapy, treatment does not usually have to be discontinued, and so the need for routine testing of autoantibodies is arguable. In order to exclude autoimmune hepatitis, however, ANA, SMA, ANCA, and LKM1 antibodies should be determined before interferon therapy is initiated. Patients with positive results should be monitored closely for deterioration of liver function on interferon therapy as a sign of active autoimmune hepatitis. If liver function worsens, interferon should be discontinued. The need for immunosuppressive therapy can only be decided on a case-by-case basis.

Before treatment with interferon, TSH levels should always be determined to exclude thyroid disease. With normal thyroid function, it is sufficient to monitor TSH at 12-weekly intervals. In cases of hypothyroidism, substitution with levothyroxine is recommended, and thyreostatic treatment is similarly recommended for hyperthyroidism before initiation of interferon therapy. After adequate treatment, interferon

therapy can usually be administered under close monitoring of TSH (every 4 weeks). Approximately 5 % of patients develop thyroid dysfunction on interferon therapy. This generally manifests within the first 3 months of treatment. If hypothyroidism is induced, interferon therapy can usually be continued in combination with substituted levothyroxine. The first manifestation of hyperthyroidism is enough cause for most authors to discontinue treatment, although even here it may be possible to continue interferon therapy in certain cases. In the majority of patients, thyroid dysfunction resolves after discontinuation of interferon. However, it may also persist, and therefore cases need to be considered individually.

Up to 12 % of patients with hepatitis C have thyroid autoantibodies before treatment with interferon (antibodies against thyroid peroxidase = anti-TPO, antithyroglobulin antibodies and TSH receptor antibodies). In these patients, the risk of a deterioration in thyroid function on interferon is significantly higher than in patients without these antibodies. If possible, autoantibodies should be determined in all patients before beginning treatment, but at the very least in those patients with abnormal TSH levels, in order to have a baseline value to allow subsequent monitoring.

If no treatment is initiated alpha-Fetoprotein (AFP) and sonography of the liver should be performed every 6-12 months to early detect a hepatocellular carcinoma (HCC). This is particularly relevant for patients with F3/F4-fibrosis. As the course of hepatitis C is accelerated in HIV-coinfection and 10-30 % of the patients will develop HCC without preceding cirrhosis, regular screening should be considered for all patients. Some experts recommend even shorter intervals that are not yet feasible in most circumstances.

Table 1: Diagnostic procedures for hepatitis C in HIV-coinfection

Diagnosis of hepatitis C
HCV-Ab (positive 1-5 months after infection, may be lost with immunosuppression)
HCV-RNA (not prognostic for progression, but response to treatment)
Status of liver damage
Grading of fibrosis (e. g. Fibroscan, liver biopsy)
Parameter of synthesis (e. g. coagulation, protein, albumin, CHE)
Ultrasound and AFP every half a year
Before treatment
HCV genotype
Autoantibodies (ANA, SMA, ANCA and LKM1)
TSH, thyroid autoantibodies if applicable
Monitoring of treatment
Differential blodd count and liver enzymes every 2-4 weeks
HCV-RNA every 12 weeks (and at week 4 to evaluate early virologic response)
CD4-count every 12 weeks
TSH every 12 weeks

Therapy

Most important reasons to treat hepatitis C are the unfavourable course in HIV-coinfection, increased life expectancy due to successful HAART, increased liver-related mortality, and an increased risk of hepatotoxicity of HAART. In addition, ist has been shown that successful treatment of hepatitis C improves survival.

The goal of hepatitis C treatment is to achieve permanently negative HCV RNA levels. This is generally referred to as a sustained response. It is defined as a negative HCV RNA six months after completion of treatment.

Negative HCV RNA at the end of the treatment period is described as an end of treatment response. If transaminases have normalized, this is referred to as a biochemical response. However, the latter does not correlate with the further clinical course of hepatitis C and is therefore no longer used today. Failure to respond to treatment is referred to as a non-response.

In the following text, response rates always refer to sustained responses. This is because only sustained responses have been clearly associated with the resolution of liver fibrosis and extrahepatic manifestations, as well as with the prevention of further transmission.

When HCV RNA becomes detectable again after having been negative, it is referred to as a relapse. The probability of a relapse is highest within the first months following completion of treatment and decreases steadily afterwards. Therefore, the success of therapy is usually determined and evaluated six months after the end of treatment. In individual cases, relapses may occur at later time points, sometimes after years. Therefore, regular monitoring is advisable even following successful treatment (monitoring of transaminases; HCV RNA if there is reason to suspect a relapse).

The combination of pegylated interferon with ribavirin is regarded as standard therapy in coinfected patients. Response rates around 50 % can be achieved (Torriani 2004, Nuñez 2006). In patients with genotypes 2 and 3 response rates are significantly higher (about 80 %) than in patients with genotypes 1 and 4 (about 40 %). Duration of treament is tailored acoording to individual factors such as genotype and initial treatment response. In general, duration is 48 weeks. However, patients with genotypes 1 and 4 might benefit from an extended treatment period (Nuñez 2006). On the other hand, in selected patients with genotypes 2 and 3 who respond very quick to the treatment (HCV-RNA negative at week 4) a shorter duration seems to be possible.

Liver transplantation may be an option for patients who have cirrhosis and can not be treated with interferon.

Concerns that interferon treatment could have a negative effect on HIV infection have not been confirmed in any study. In fact, there is further suppression of detectable HIV viremia in the majority of patients as a result of the antiviral effect of interferon. Absolute CD4+ T-cell counts may drop slightly due to temporary leukopenia, but percentage values usually rise. No treatment study to date has shown a significant deterioration of HIV infection (Soriano 2004).

The treatment options remain inadequate for patients with a non-response or relapse. In patients treated earlier with interferon monotherapy, an attempt can be

made using a combination of PEG-interferon and ribavirin. There are currently no standard recommendations for treatment of patients after failed PEG-interferon therapy. Some patients will respond to re-treatment, especially in case of bad adherence or suboptimal management of adverse events during the initial treatment. In single patients, a triple combination of PEG-interferon, ribavirin and amantidine (2 x 100 mg/day) has been used successfully, although reliable data are not available. HCV-specific protease inhibitors and polymerase inhibitors, as well as other new substances, will add new options in the next years.

Practical tips for management of treatment

The following treatment recommendations have been compiled for HIV coinfection:

Indications and contraindications

As HIV coinfection accelerates the course of hepatitis C and increases the risk of hepatotoxicity after initiation of HAART, the indication for treatment should be determined in **every** patient with diagnosed HIV/HCV coinfection.

In particular, treatment should be discussed for cases with a bioptically confirmed fibrosis of grade F2-F4. Extra-hepatic manifestations of hepatitis C are also an indication for treatment (vasculitis, glomerulonephritis, systemic cryoglobulinemia). The following factors are associated with a more favorable response to treatment:

- HCV RNA < 800,000 IU/ml (+ genotype 1)
- HCV genotype 2+3
- Age < 50 years
- Low grade of fibrosis (either histologically, or by non-invasive technique)
- Normal γ-GT
- Stable HIV infection

In addition, contraindications should be evaluated. The most important are:

- Decompensated liver cirrhosis or history of decompensation (but not compensated cirrhosis, i.e. CHILD A cirrhosis!)
- Leukopenia (<1,500/µl)
- Thrombocytopenia (< 50,000/µl)
- Anemia (< 10 g/dl)
- Severe, as yet untreated thyroid dysfunction
- CD4+ T-cell count < 200/µl (relative contraindication, see below)
- Severe psychiatric illnesses
- Symptomatic cardiac disease
- Active opportunistic infections
- Active drug or alcohol abuse
- HIV treatment with ddI (AZT and d4T should be avoided too)

Methadone or polamidone substitution is **not** a contraindication if good monitoring can be ensured during the treatment phase. However, patients with active drug or alcohol abuse should first be introduced to the appropriate programs.

When to treat

If a decision to treat hepatitis C is made, the immune status of the patient and current antiretroviral therapy must be considered.The following scheme is suggested:

Patients without HAART

If possible, HCV should be treated before HIV. Reasons for this include the increased hepatotoxicity of HAART with concurrent hepatitis C; possibly impaired immune reconstitution resulting from hepatitis C; better compliance; and finally, prevention of drug interactions.

If the CD4+ T-cell count is above 350/µl, treatment of hepatitis C can be started. It is unclear whether a high viral load (> 50,000/ml) requires initiation of HAART.

If the CD4+ T-cell count is between 200 and 350/µl, the patient might benefit from treatment of hepatitis C if HIV RNA is below 5,000 copies/ml. If it is higher, initiation of HAART should be considered.

A CD4+ T-cell count below 200/µl is a relative contraindication. HAART should be initiated first. When there is an adequate increase in the CD4 count, interferon therapy can be reconsidered.

Patients on HAART

If CD4+ T-cells are above 350/µl under stable HAART and the viral load is below the level of detection, treatment can be started.

If CD4+ T-cells are between 200 and 350/µl and the viral load is stable below the limit of detection, the decision should be dependent on the overall situation (with consideration of severity of hepatitis, HCV genotype and status of HIV infection).

A CD4+ T-cell count below 200/µl is a relative contraindication. It is a judgement call to decide whether to take the risk of a treatment attempt with interferon (with the likelihood of a poor response and the danger of a further decline in the CD4+ T-cell count as a result of interferon treatment).

If necessary, antiretroviral treatment should ideally be modified several weeks before HCV therapy is initiated. ddI is contraindicated with concurrent HCV therapy (as it can lead to pancreatitis, mitochondrial toxicity, and more cases of liver decompensation). AZT and d4T should also be avoided if possible, in order to prevent additive toxicities (zidovudine: anemia and leukopenia; stavudine: mitochondrial toxicity). Before modifying HAART, it should be insured that the treatment success of HIV therapy is not going to be compromised. In such cases, HCV treatment should only be started if the overall clinical situation is stable, i.e. good viral suppression has been achieved and side effects have been evaluated or treated.

Treatment practice

The combination of PEG-interferon with ribavirin over a period of 48 weeks is recommended as the standard therapy (Rockstroh 2004, Alberti 2005). However, this standard duration has to be adapted according to genotype and speed of viral response (Soriano 2007).

Two interferons are currently available as PEG-interferons: PEG-Intron™ and Pegasys™. PEG-Intron™ is administered subcutaneously and the dose is based on body weight at 1.5 µg/kg. Pegasys™ is injected subcutaneously at a fixed dose of 180 µg. Both substances are administered once a week, and must be kept refrigerated.

The dosage of ribavirin should be adapted to body weight: patients below 75 kg should receive 1,000 mg daily, patients above 75 kg 1,200 mg daily regardless of genotype. The capsules can be taken once daily, or spread over the day.

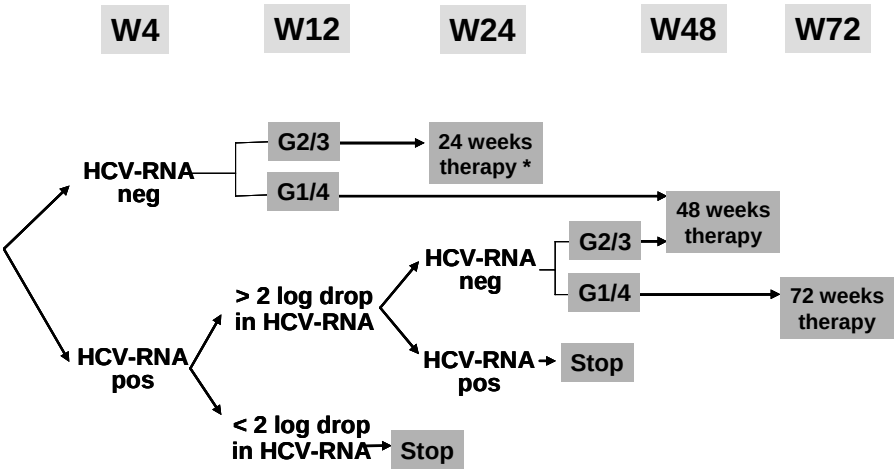
Patients must be made aware of the fact that both interferon and ribavirin are potentially teratogenic. A reliable method of contraception for at least six months after treatment is therefore important.

All patients require regular clinical monitoring. This should initially take place every 2 weeks; later at least every 4 weeks. Laboratory monitoring should include (see table 1):

- A complete blood count and transaminases every 2-4 weeks
- Thyroid function tests every 12 weeks (more frequently with pre-existing dysfunction)
- Immune status every 12 weeks
- Lactate levels every four weeks in patients on stavudine comedication

HCV RNA is the most important parameter for measuring the treatment response and is determined after 4, 12, and 24 weeks to decide on the duration of treatment.

The duration of treatment depends on the individual treatment response (see figure 1). If a very early response can be achieved (HCV-RNA negative at week 4), a shorter duration of treatment may be possible in genotypes 2 and 3 (in patients with low viral load at baseline and only minimal fibrosis). If in all other cases the viral load has not dropped by at least 2 logs after 12 weeks, treatment should be discontinued, as there will be no response (“2 log stopping rule”).



** In patients with low viral load at baseline and minimal fibrosis*

Figure 1: Hepatitis C treatment algorithm; modified after Soriano 2007

Management of adverse events

The management of possible side effects is often the decisive factor for the success of treatment (s. table 2). A high discontinuation rate of up to 30 % in numerous (older) clinical studies is likely also to have been due to a lack of experience with combination therapy. Proper management of side effects probably results in significantly better treatment success rates. It is often helpful to indicate to patients that side effects are reversible after stopping therapy.

Patients should be counseled extensively on the expected side effects before beginning treatment. Following main aspects should be explicitly addressed:

Almost all patients experience influenza-like symptoms or malaise when beginning treatment. As the severity of symptoms cannot be predicted beforehand, treatment should be initiated at a time when there are no important private or professional events pending (e.g. before a weekend). The administering physician should be readily available during the first days of treatment. In addition, paracetamol should be prescribed (dosage has to be adjusted individually; single dose = 1,000 mg). Symptoms usually improve within the first two to four weeks. Most patients tolerate treatment quite well and can continue their daily activities normally. However, it is possible that particularly in the initial stages of treatment, they may be unable to work for several days. In rare cases, the side effects may be so grave that patients are unable to work for the entire duration of treatment. This also needs to be discussed with the patient in advance.

Ribavirin causes hemolytic anemia in up to 20 % of patients. This can be treated with epoetin alfa. Dose recommendations differ: usually approximately 100 IE/kg body weight are injected subcutaneously three times a week. 40,000 IE once a week also significantly improve ribavirin-induced anemia (Sulkowski 2005). Alternatively, halving the dose (hemoglobin below 10 g/dl) or discontinuing ribavirin alto-

gether (hemoglobin below 8.5 g/dl) are possible options. However, dose reductions, frequently used in the past, should only be made if epoetin does not help. Studies have shown that the correct dosing of ribavirin is associated with a better treatment response. A daily 5 mg dose of folic acid is recommended to reduce hematoxicity.

Treatment with granulocyte colony stimulation factor (GCSF) may ameliorate an interferon-induced leukopenia. Clinical experience is very limited so far. However, so that the required dose of interferon can be maintained in case of severe leukopenia (neutrophil count below 500/µl), this recommendation seems to be justified. Doses have to be adjusted individually. In most instances low doses are adequate, as hematopoiesis itself is not impaired (e.g. Filgrastim 30 Mio IE once a week).

The evaluation of psychological side effects is made at every clinic visit. Observations made by others, such as family members, may also be very helpful. Mild depression whilst on interferon can be treated with well-tolerated antidepressants (e.g. paroxetin 20 mg daily). In case of relevant history prophylactic use of paroxetin can be discussed. Therapy should be stopped immediately in cases of severe depression or on development of suicidal thoughts.

The frequent occurrence of weight loss can be lessened with dietary counseling. It is important to ensure a regular diet that is tailored to the patient's wishes (e.g. inpatients with drug addiction). It is possible that the weight loss is a form of lipoatrophy, and therefore nucleoside analogs with a lower risk for development of lipodystrophy should be used if possible.

Thyroid dysfunction may develop during treatment with interferon (see above), but does not always require discontinuation of interferon. In the majority of cases hyperthyroidism develops at first, that may progress to hypothyroidism in the further course. Manifestation of hyperthyroidism is enough cause for most authors to discontinue treatment. If discontinued timely, prognosis is excellent. If interferon treatment is continued, irreversible hypothyroidism requiring lifelong hormone replacement may develop. In case of preexisting hypothyroidism interferon treatment usually can be continued with ongoing substitution of levothyroxine.

Table 2: Most important adverse events with PEG-interferon/Ribavirin

Adverse event	Management
Interferon-associated	
Influenza-like symptoms	Paracetamol
Leukopenia, Thrombopenia	Dose reduction of IFN, G-CSF
Psychiatric Symptoms	Antidepressants, Discontinuation of IFN
Weight loss	Well balanced nutrition
Autoimmune Phenomena	Discontinuation IFN
Ribavirin-associated	
Hemolysis	Folic acid, Erythropoetin, Dose reduction of Ribavirin

Recommendations for treatment of hepatitis C are constantly evolving. Therefore an experienced treatment center should always be contacted if clarifications are needed.

Due to the complexities of HIV/HCV coinfection, patients should be treated within clinical studies wherever possible.

Acute Hepatitis C

During recent years a constantly growing number of cases of acute hepatitis C has been observed in homosexual men. These mainly had had contacts with high risk of infection (e.g. use of sex toys, fisting). As HCV-antibodies are produced only long time after infection, diagnosis of acute hepatitis C is made according to history, elevated transaminases (ideally normal before) and positive HCV-RNA.

The optimal management of acute hepatitis C remains unclear. Data available so far show an improved response rate of about 60 % (up to 80 % in genotype 2/3) if treatment is initiated early (Vogel 2005). These data support early treatment even in the presence of HIV coinfection. On the other hand spontaneous clearance after acute infection might be better than previously expected. The following aopproach might be feasible:

In case of symptomatic acute hepatitis C (especially jaundice), patients are followed for 12 weeks in order to await possible spontaneous clearance. Patients with asymptomatic acute hepatitis C can be treated immediately. We treat for a period of 24 weeks with peg-interferon alone for genotypes 2+3, and peg-interferon plus ribavirin for genotypes 1+4. However, the optimal strategy is unclear at the moment. If possible, patients should be treated within prospective clinical studies.

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HIV and HBV coinfection

Introduction

The hepatitis B virus is one of the most common human pathogens worldwide. Up to 95 % of all HIV-infected patients have been infected with hepatitis B, and approximately 10-15 % have chronic hepatitis B, with considerable variation among geographical regions and risk groups. It is estimated that around 100,000 HIV-infected patients in the USA suffer from chronic hepatitis B. Sexual transmission is the most frequent route of contraction. Transmission via the bloodstream is more probable than for HIV: following a needlestick injury contaminated with HBV-infected blood, the risk of infection is around 30% (HCV approx. 2-8 %; HIV approx. 0.3 %). Primary HBV infection leads to chronic hepatitis in 2-5 % of immunocompetent adults, whereas HIV-infected patients experience chronification about five times more often. A possible reason for this is the HIV-associated immunosuppression, whereas virus-specific factors such as the extent of HBV viremia and genotype seem to be not so relevant. Hepatitis B and HIV share several common features, although hepatitis B is a double-stranded DNA virus. After entering the hepatocyte, viral DNA is integrated into the host genome. Viral RNA is translated by HBV reverse polymerase into new viral DNA and transcribed into viral proteins. Reverse transcription may be inhibited by nucleos(t)ides reverse transcriptase inhibitors. Integration of the virus into the host genome of hepatocytes and CD4+ T-cells prevents its eradication. The diagnosis of HBV is established as in patients without HIV infection. Table 1 summarizes the interpretation of serological test results. Screening HIV-infected patients for HBV starts with HBsAg, anti-HBs, and anti-HBc. If a positive HBsAg is found, testing for HBeAg, anti-HBe, and HBV DNA should follow. There is debate about a so-called occult infection due to immune escape. This means patients lack HBsAg, but are positive for HBV DNA. Recent studies have not found evidence of such occult infection and the prevalence and impact in coinfection remains unclear.

Table 1: Interpretation of serological test results for HBV

Interpretation	HBsAg	anti-HBs	anti-HBc	HBeAg	anti-HBe	HBV-DNA
No prior contact with HBV	–	–	–	–	–	–
Acute infection	+	–	+ (IgM)	+	–	+
Past infection with immunity	–	+	+ (IgG)	–	+	–
Chronic hepatitis B	+	–	+ (IgG)	+	–	+
Occult infection[1]	–	–	+ (IgG)	–	–	+
Pre-core mutant	+	–	+ (IgG)	–	+	+
Inactive carrier state	+	–	+ (IgG)	–	+	–
Immunity after vaccination	–	+	–	–	–	–

[1] Controversial. See text above.

In general, patients with chronic hepatitis B should be screened for hepatocellular carcinoma (HCC) every 6 to 12 months. Serum alpha fetoprotein and an ultrasound

of the liver should be performed. This recommendation is independent of apparent cirrhosis, as 10 to 30 % of patients who develop HCC do not have pre-existing cirrhosis.

Course of hepatitis B with concurrent HIV infection

In HIV-infected patients, chronic hepatitis B has an unfavorable course compared with monoinfected patients, and the risk of liver-associated mortality is significantly increased (about 15 times). Following the decrease in HIV mortality, an increase of liver-associated mortality has been observed (Thio 2002, Konopnicki 2005). In addition to increasing mortality, HIV coinfection accelerates the progression of hepatitis B and increases the risk of cirrhosis. Despite the worsening described, initially the clinical course is usually more benign in HIV-positive patients, although viral replication is increased. This seems contradictory at first, but can be explained by the impairment of cellular immunity, which may lead to an increase in viral replication, but at the same time also reduces hepatocyte damage. Therefore, transaminases in HBV/HIV-coinfected patients are frequently only mildly increased. In contrast, HBV DNA, as a marker for viral replication, is higher than in immunocompetent patients. Accordingly, despite less inflammatory activity, liver fibrosis and cirrhosis are more common. This phenomenon has also been described in other immunocompromised patient populations (e.g. organ transplant recipients).

There is a direct correlation between the extent of immunosuppression and the control of viral replication of HBV: Even in cases with apparently resolved hepatitis B (anti-HBe positive, HBV DNA negative), increasing deterioration of the immune system may result in reactivation of the HBV infection. Notably, some cases of reactivation of hepatitis B have been described following immune reconstitution after initiation of HAART.

In contrast to the unfavorable course of hepatitis B, the course of HIV-infection is not altered significantly by coinfection. However, HAART-related hepatotoxicity develops about three times more frequently in patients with chronic hepatitis B. Whether or not the prognosis of HBV/HIV-infected patients is changed by HAART and HBV-effective therapies, remains to be seen. HBV-associated mortality seems to decrease, if HBV can be controlled effectively (e.g. French GERMIVIC-cohort).

Prevention

All patients infected with HIV but with negative hepatitis B serology should be vaccinated! The vaccine may, however, be less effective due to immunosuppression. Approximately 30 % of HIV-infected patients have a primary non-response (only 2.5 % in immunocompetent individuals). This is particularly true for patients with CD4+ T-cell counts less than 500/µl whose response rate is only 33 %. Therefore, a conventional dose is administered to patients with CD4+ T-cell counts greater than 500/µl (20 µg at months 0, 1, and 12), whereas an intensive schedule is recommended for patients with CD4+ T-cell counts less than 500/µl (20 µg at months 0, 1, 2, and the last dose between month 6 and 12). In case of non-response (checked 12 weeks after each cycle), vaccination is repeated at double the dose in four steps (40 µg at months 0, 1, 2, and 6-12). Patients with CD4+ T-cell counts

less than 200/µl, who are not on HAART, should receive HAART first and HBV immunization thereafter.

Loss of protective immunity is seen in up to 30 % during each year following seroconversion. Therefore, anti-HBs should be monitored once a year and consideration should be given to booster doses if anti-HBs-antibody levels are less than 100 IU/l. HIV patients, who are not adequately immunized against HBV, should be screened yearly to look for newly acquired infection.

HIV/HBV-coinfected patients who are seronegative for hepatitis A should be vaccinated against hepatitis A (months 0, and 6), as there is an increased rate of severe or fulminant hepatitis in case of acute hepatitis A. Patients who are susceptible to both hepatitis A and B can be vaccinated with a bivalent vaccine (months 0, 1, and 6).

Following immunization, patients should be counseled about common measures to prevent further transmission and transmission of other viruses such as hepatitis C (safer-sex practices, avoidance of needle-sharing and others). They should be educated about strategies to prevent progression of liver disease such as avoidance of alcohol consumption, tobacco use (controversial), or herbal supplements, many of which are hepatotoxic. The application of hepatotoxic drugs (e.g. anti-tuberculous agents) should be carried out cautiously.

Newborns of mothers with chronic hepatitis B should receive hepatitis B-immunoglobulin and active immunization.

Treatment

Treatment of chronic hepatitis B is problematic in coinfected patients because of the impaired immune function. As HBV persists in infected cells even after successful treatment, eradication of HBV seems not possible with current treatment strategies. Similar, development of protective anti-HBs-antibodies with subsequent loss of HBsAg is difficult to achieve. Current treatment goals are seroconversion from HBeAg to anti-HBe, a complete suppression of HBV DNA, normalization of transaminases, improvement of liver histology, and prevention of hepatocellular carcinoma. Other benefits of HBV therapy include the reduction in the risk of transmission and possibly in the risk of HAART-induced hepatotoxicity.

Drugs with HBV activity

HBV can be treated with nucleoside analogues, nucleotide analogues, and interferon (see table 2). Some nucleos(t)ides are effective against HIV also. Therefore, HBV-medication will be part of the HIV combination therapy in most circumstances, unless there is no need for HAART. 3TC, FTC, tenofovir and probably entecavir are effective against both HIV and HBV. Adefovir and telbivudin are effective against HBV only. Interferon is almost irrelevant in the setting of HBV/HIV coinfection in contrast to HBV monoinfection where it is regarded standard treatment.

Antiviral potency can be graded as follows (measured as reduction in HBV-replication after one year): entecavir > telbivudin > tenofovir > 3TC > adefovir > FTC. Entecavir allows a 7 log reduction in HBV replication, tenofovir about 6 log, 3TC 5 log, and FTC 3 log. At the moment treatment recommendations do not take

into account these possible differences in potency. It is not clear yet, whether these differences are of clinical relevance.

Development of resistance is a matter of concern. Monotherapy with 3TC selects a mutation in the YMDD-motif of the polymerase gene in about 20% of patients per year (production of HBeAg may stop in case of such mutation similar to a pre-core-mutant). There might be cross resistance between 3TC, FTC, entecavir and telbivudin, that can be overcome partly by increase of dosing (e.g. entecavir dose will be higher, if the patient has been treated with 3TC in the past). Adefovir and tenofovir are nucleotide analogues with different mechanisms of resistance, and therefore will be effective after failure of nucleoside analogues in most instances. Tenofovir seems to be active even after failure of adefovir.

In the light of the lesson learned from HIV and the high resistance rate of HBV on lamivudine therapy, combination of at least two drugs seems prudent in order to avoid development of resistance. Small series found no resistance development, if a nucleoside and nucleotide analogue were combined. However, there is no proof for better efficacy for this approach. At present, combination therapy with one nucleoside and one nucleotide analog should be preferred to monotherapy if feasible.

Optimal treatment duration is not clear. As eradication is not realistic, a lifelong suppression of HBV is the more realistic scenario similar to HIV treatment. HIV/HBV coinfection will require continuous treatment of HIV anyway, so drugs effective against HBV will be integrated into the HAART.

A clinical picture of acute hepatitis may develop if HBV treatment is discontinued. This may result even in fatal liver failure. Any interruption of treatment must be thoroughly balanced in HBV/HIV-coinfected patients. In case of loss of effectiveness the treatment may be discontinued without any precautions. No clinical deterioration has to be expected.

In case of renal insufficiency all nucleos(t)ide analogues have to be dose adjusted.

Interferon might be the treatment of choice in a certain subgroup of patients. These have no need for HAART and positive predictive factors for response to interferon: high CD4-count, HBeAg positive, elevated ALT, low HBV-DNA. Treatment with interferon is limited due to its toxicity (see section on hepatitis C, and section on drugs). Inteferon is contraindicated in patients with decompensated liver disease. In case of advanced liver disease it should be used only with great caution.

Finally, liver transplantation may be an option for selected patients who have cirrhosis and/or develop hepatocellular carcinoma.

Table 2: Current therapeutic options for chronic hepatis B in HIV/HBV-coinfected patients

Drug	Dose	Duration
Adefovir	10 mg QD	Minimum of 12 months, possibly life-long
FTC, Emtricitabin	200 mg QD	Undefined
Entecavir	0,5 mg (if 3TC naive) 1 mg (if 3TC experienced)	Undefined
3TC, Lamivudin	300 mg QD[1]	Minimum of 12 months in HBeAg+ patients and 6 months after HBeAg seroconversion Indefinite in HBeAg- patients
Telbivudin[2]	600 mg QD	Undefined
Tenofovir	300 mg QD	Undefined
Interferon-α	5 MU per day or 10 MU 3 x / week	4-6 months in HBeAg+ patients 12 months in HBeAg- patients
Pegylated Interferon	Pegasys® 180 µg 1 x / week PEG-Intron® 1,5 µg/kg 1 x / week	Only Pegasys is licensed of hepatitis B in monoinfected patients. Here legth of therapy is 12 months

[1]Zeffix, the lower dose, should not be used in HIV-coinfection.[2]Telbivudin has been licensed in the States in October 2006. Licensing in Europe is still pending.

Treatment guidelines

In principle, due to accelerated progression and increased mortality in coinfection, treatment possibilities should be examined for every patient. Treatment is recommended if (Alberti 2005, Soriano 2005, Brook 2005):

- ALT is consistently > 2-fold above the norm (high pre-treatment ALT values correlate with better treatment responses to interferon and lamivudine);
- HBeAg is positive;
- HBV DNA > 20,000 IU/mL, if HbeAg+
  > 2,000 IU/mL, if HbeAg-
  (the optimal threshold is unknown; 20,000 IU correspond to approximately 105 copies/ml depending on the assay used)
- Significant inflammation or liver fibrosis has been detected bioptically.

Currently, the indication for HBV therapy is based on serological markers alone. To determine the extent of liver fibrosis several non-invasive methods are available now. Of special interest is the Fibroscan™ system that measures liver stiffness as a correlate of liver fibrosis. Grading of fibrosis probably will gain more importance in the near future. The impact of liver biopsy will decrease. Liver biopsy is recommended particularly for patients with the inactive carrier state (positive for HBsAg, but no other marker of replication). There are several histological classifications used. In Europe the METAVIR-Score is used most often. It distinguishes five stages of fibrosis (0 = no fibrosis, 1 = portal fibrosis without septa, 2 = few septa, 3 = numerous septa without cirrhosis, 4 = cirrhosis). Hepatitis activity is graded according to the intensity of necroinflammatory lesions (A0 = no activity, A1 = mild activity, A2 = moderate activity, A3 = severe activity). The following non-binding treatment recommendations may be suggested, but need to be confirmed in further

studies (figures 1 and 2). An effective treatment of HIV infection must not be put at risk. Accordingly, 3TC, FTC, tenofovir and entecavir (see below), which are effective against both HIV and HBV, have to be combined with other substances effective against HIV in order to ensure an adequate HAART. On the other hand, adefovir and telbivudin are not effective for treatment of HIV and must not be considered as part of the HAART regimen.

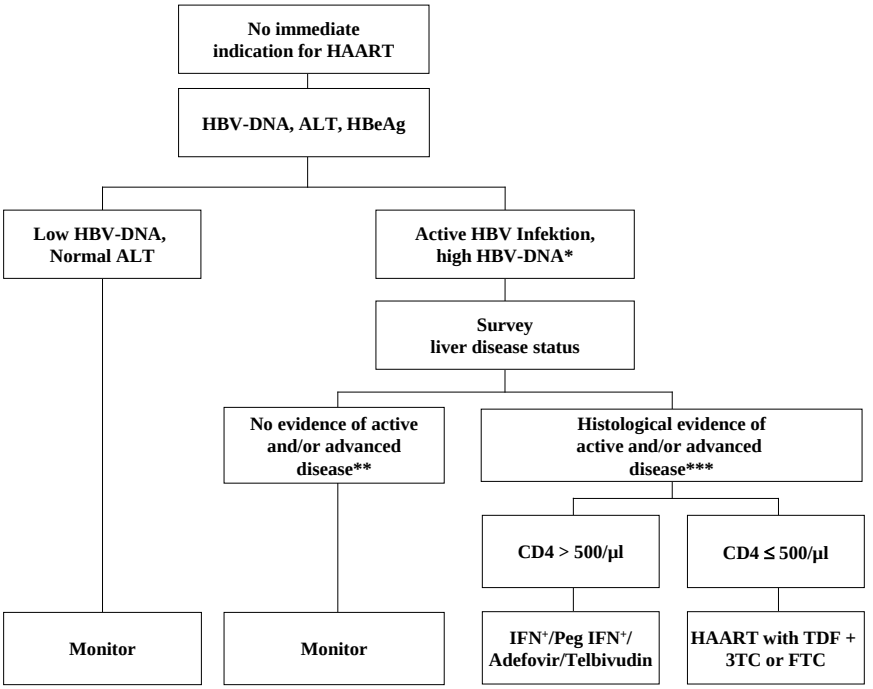

Figure 1: Treatment recommendations for HIV-HBV coinfected patients without indication for HAART (modified after Alberti 2005)
* HBV-DNA > 20,000 IU/ml in HBeAg+ patients; > 2,000 IU/ml in HBeAg- patients
** Metavir < A2 and/or < F2; ***Metavir ≥ A2 and/or F2 (for Metavir-Score refer to text)
+IFN and PEG-IFN are preferred in HBeAg positive patients
Monitoring means: transaminases every 3 months, INR/HBV-DNA every 6 months

The main consideration is the need for HAART:

- If there is no need for HAART, the use of drugs without HIV activity seems the best choice (i.e. adefovir, telbivudin or IFN-α; see figure 1). Lamivudine, emtricitabine, and tenofovir should be avoided. Surprisingly, most recently entecavir has been described to be at least partially effective against HIV. This may even lead to selsection of resistance mutations (M184V) (McMahon 2007). Therefore, entecavir should be avoided in HIV-infected patients without indication for HAART.
- If the patient is under HAART or needs HAART due to low CD4+ T-cell counts, drugs with both HIV- and HBV-activity should be included in the HAART regimen (see figure 2). In treatment naïve patients who start therapy, the combination of FTC (or 3TC) and tenofovir is preferred as nuke backbone.

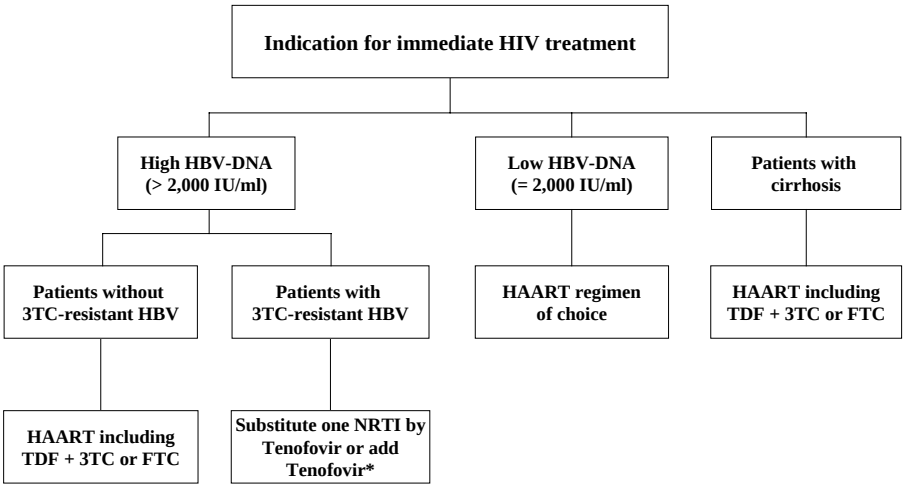

Figure 2: Treatment recommendations for HIV-HBV coinfected patients with indication for HAART (modified after Alberti 2005)
* If compatible with treatment of HIV infection. As an alternative, a substance without HIV-activity may be added (preferably entecavir).

A transient elevation of transaminases – which is usually moderate and soon resolves – may be observed after initiation of HBV therapy. It is caused by immunoreconstitution and subsequent increased inflammatory activity. In case of marked and/or ongoing elevation of transaminases, alternative explanations have to be considered (e.g. increasing HBV replication, resistance of HBV, lactic acidosis, hepatotoxicity of antiretroviral drugs, superinfection with hepatitis viruses other than hepatitis B).

Initial normalization of ALT and significant reduction of HBV DNA will be achieved in most cases by any anti-HBV agent. ALT levels do not correlate well with inflammatory activity and are influenced by many other factors such as hepatotoxicity of HAART or other drugs, alcohol consumption, and immune reconstitution. Therefore, their value for monitoring treatment is limited. HBeAg seroconver-

sion will occur in as many as 25 % of patients. The most desirable endpoint of HBsAg loss is observed in only 5-10 % of patients within one year of the start of treatment with IFN-α, but occurs less frequently with nucleos(t)ide analogs.

As most cases of acute hepatitis B even in HIV-infected patients resolve spontaneously, only supportive treatment is recommended. In addition, data on this situation are sparse (e.g. danger of resistance in case of early therapy with no more options afterwards).

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19. GBV-C infection

Matthias Stoll

Almost one century ago, in 1917, the Austrian neurologist Julius Wagner von Jauregg was able to obtain improvement in patients with late stage symptomatic neurosyphilis, by infecting them with the malaria parasite. This approach might appear strange to physicians in the contemporary era of antimicrobial treatment. However, at that time it was by far the most effective option and it earned its discoverer the Nobel Prize for Medicine in 1927. Thus, even an infection with obligatory pathogens may result in harm reduction under certain conditions.

GB virus C is a flavivirus that is closely related to hepatitis C virus. The name GB virus stems from early experiments on the transmission of acute hepatitis from humans to marmoset monkeys. One of the first source patients had the initials "G.B." and was a 34-year old colleague of the author of the experiment (Deinhardt 1967). Later on, two hepatotropic viruses, GB virus A (GBV-A) and GB virus B (GBV-B), were isolated from these monkeys. Two independent research groups simultaneously discovered the related GB virus C (GBV-C) in humans with hepatitis in the middle of the 1990s. Subsequently, the GB virus C has promoted the discussion as to whether the natural course of HIV infection might be modulated in a favorable way by this particular coinfection. In addition, because GBV-C was first found in humans with hepatitis, and due to its close relationship to the hepatitic GBV-A and GBV-B viruses, GBV-C was also called "hepatitis G virus (HGV)" by one research group. This name should no longer be used, because it has since been shown that GBV-C neither causes hepatitis nor worsens preexisting hepatitis (Berenguer 1996, Tillmann 1998, Rambusch 1998, Stark 1999). In fact, GBV-C is not a hepatotropic but a lymphotropic virus. Despite intensive research, GBV-C has not been shown to cause any other known disease.

The virus can be found in six different genotypes (Muerhoff 2006) and it is frequently and worldwide found in humans: approximately 10 to 40 % of blood donors have specific antibodies against GBV-C and up to 5 % of them show GBV-C virus replication. Assuming that the virus is apathogenic, affected individuals are not excluded from the donation of blood and consequently, serological diagnostics on GBV-C are not routinely performed. Two serological markers for GBV-C infection exist: GBV-C viremia is determined using a PCR method; and antibodies to the envelope region E2 (anti-E2) are detected by ELISA. As they are mutually exclusive, either GBV-C viremia or the presence of anti-E2 is detectable in GBV-C infected individuals. In most cases, GBV-C viremia is transient and ends with seroconversion to anti-E2, resulting in immunity to new infections. However, this does not seem to be a lifelong immunity (Table 1). Transmission of GBV-C occurs parenterally and mucosally, thus similar to HIV, HBV and HCV infections.

GBV-C: Harmless or rather a friendly virus?

The first report of decreased HIV disease progression and mortality in GBV-C coinfected patients was from a German monocentric study, published in 1998. Initially, these results did not draw much attention, although they were confirmed by other

working groups (Toyoda 1998, Heringlake 1998). Later on, longer follow-ups revealed again a favorable prognosis for HIV-infected individuals with GBV-C viremia (Tillmann 2001, Xiang 2001). These results encountered considerable resonance in the international press – and articles in some newspapers reported in a vociferous manner a "miracle virus, which stops AIDS". As a consequence, some patients requested sources of supply for GB virus C from their physicians and wanted to infect themselves with it. In summary, the GBV-C story became involuntarily discredited by a couple of simplified and unscientific reports in the secondary literature. Concomitantly, a controversial discussion of the data started within the scientific community. In recent years, however, several studies have focused on the influence of GBV-C status on surrogate markers and clinical progression in HIV infection.

Table 1: Serological markers and stages of GBV-C infection

	Marker:	**GBV-C-Viremia (RNA)**	**Anti-E2-Antibodies**
	Method:	PCR / b-DNA	ELISA
GBV-C negative		negative	negative
Replicative GBV-C Infection		positive	negative
Past GBV-C Infection		negative	positive

The heterogeneity of the HIV/GBV-C coinfected cohorts is a major methodical problem in an attempt to compare the results from the different studies published recently. Some studies did not follow up the status of the GBV-C viremia longitudinally. The serological status of GBV-C, however, can change over time, and the distinction between the three possible stages of GBV-C serostatus is crucial for the interpretation of the studies (see table 1). Overall, it is agreed that there is no difference between the clinical course of HIV-infected individuals without contact to the GB virus C (GBV-C negative) and those with cleared GBV-C infection (anti-E2-positive). But GBV-C viremia (GBV-C RNA positive) is prolonged in HIV infection. Persistence of GBV-C RNA in HIV-positive patients was associated with less rapid progression of clinical disease, lower death rates, smaller reduction in CD4 T cells, reduced increase in HIV plasma viremia, and improved quality of life – in comparison with HIV-infected individuals without GBV-C viremia in a meta-analysis (Zhang HIV Med 2006). These effects were more pronounced in studies with longer follow-up periods. Confirmatory results came up from additional data published later on (Handelsman 2006, Mosam 2007, Yirell 2007, Souza 2006, Li 2006) Prospective cohort studies are on the way, but still may need longer follow-up periods (Sheng 2007).

However, some studies – partially with considerable follow-up time – could not confirm a beneficial effect of GBV-C viremia on HIV infection (Sabin 1998, Birk 2002, Bjorkman 2004, Kaye 2005, Williams 2005, van der Bij 2005, Ryt-Hansen 2006). These conflicting results might be explained by gender-specific effects, different GBV-C genotypes, overreporting of chronic GBV-C viremia due to missing follow-up of GBV-C viremia in the studies or by unknown reasons.

Several studies have described more pronounced antiretroviral and immunological effects of antiretroviral therapy in HAART-treated GBV-C RNA positive patients (Bjorkman 2007). However, other studies did not find these differences (Tillmann

2005). But no study to date describes a negative influence of GBV-C viremia on the effect of HAART.

Therefore, to summarize the various cohort studies it could be cautiously concluded that a favorable clinical long-term course of HIV infection in GBV-C RNA positive individuals may be restricted to patients with ongoing GBV-C replication. However, most studies were retrospective and performed in only a few centers. Therefore, at present, it cannot be completely excluded that the association between GBV-C viremia and ameliorated HIV infection is at least in part biased by other factors.

The fundamental chicken-egg dilemma still remains unsolved: whether GBV-C viremia is an epiphenomenon or a cause for the different outcomes of HIV infection is not yet clear. But increasing evidence came up from various in vitro studies, that GBV-C interacts with HIV in a complex pattern.

Proposed pathomechanisms: One question and multiple answers.

A couple of immunomodulatory or antiviral mechanisms can be induced by GBV-C and may play an interacting role with HIV coinfection: in GBV-C-infected peripheral blood cells decreased expression of chemokine receptors (CCR5 and CXCR4) has been found on the surface of CD4+ and CD8+ T-cells. A potential pathomechanism for this down-regulation of chemokine receptors is the E2-protein-induced release of RANTES from T lymphocytes by its binding to the CD81 receptor (Tillmann 2002, Xiang 2004), independent to CD81-binding (Kaufmann 2007), or by other pathways (Jung 2007). Chemokine receptors are targets for HIV. Therefore, a result of decreased chemokine receptor expression is a decrease in HIV replication. Surprisingly, anti-E2 antibodies were also able to inhibit HIV replication in vitro (Xiang 2006b), which is in contrast to the observation that anti-E2 seroconversion accelerates the clinical HIV progression. Another study showed that a peptide consisting of a 85-amino acid subunit from NS5A (which is a viral protein from GBV-C) was able to induce RANTES in vitro and therefore down-regulates HIV replication (Xiang 2006a). Complex disturbances of the cytokine profile have been described in HIV-infected individuals in vivo, but are less prevalent in individuals with GBV-C/HIV coinfection (Nunnari 2003). Focusing on the innate immunity, normalized levels of CD69 (Fas-ligand) could be demonstrated on NK cells and were less pronounced on lymphocytes in GBV-C viremic HIV-infected individuals, resulting in down-regulation of apoptosis (Mönkemeyer 2006). Plasmacytoid dendritic cells, which play a major role in the T-cell mediated immune response against viral pathogens, have been found to be elevated in GBV-C+/HIV+ coinfected individuals (Bhatnagar 2007). In addition, further direct and indirect mechanisms of GBV-C or its components on HIV replication have been described. Contradictory extents of some effects of GBV-C on HIV in different cohorts could be due to different levels of lymphotropism of different GBV-C genotypes or to host-related factors (Jung 2007).

How to deal with GBV-C-viremia in HIV-infection?

The microbial zoo of pathogens of infectious diseases is crawling with lots of horrifying micro monsters, which can cause dreadful illnesses. In this frightening environment, the description of the little viral Tamagochi named GBV-C, which does not hurt its host and perhaps is able to protect him and to reduce harm caused by another infection, would be a nice fable. But beyond the tales of a potentially healthy infection at least three questions are still open:

1. GBV-C seems to play a complex causal role rather than its replication is only a secondary epiphenomenon, which is particularly frequent when HIV infection has a favorable clinical course for other reasons. But on which pathophysiological mechanisms is this based?

2. If we were able to define the pathways of GBV-C-associated modulation of HIV disease more in detail, how could we translate them into new therapeutic approaches?

And last, but not least whilst this issue remains unsolved:

3. If persisting GBV-C viremia slows down the progression of an HIV coinfection, will it be of advantage to maintain a durable replication of GBV-C in these patients?

Some authors favor the explanation that GBV-C viremia is an epiphenomenon of higher CD4+ T-cell counts. GBV-C replicates predominantly in CD4 T-lymphocytes and therefore it could be expected that the level of GBV-C viremia decreases if the helper T-cell counts drop (van der Bij 2005). This hypothesis, however, does not explain why HIV-infected patients should not be able to induce the CD4+ T-cell dependent specific humoral immune response against the E2 envelope protein of GBV-C with high CD4+ T-cell levels and how they are later able to do so with an impaired immunity. Initial evidence for a causal role of GBV-C came from in vitro experiments on GBV-C and HIV coinfected cell cultures (Xiang 2001). HIV replication in the cultured cells was decreased when the cells had been infected with GBV-C prior to HIV, but HIV replication remained on the same level when the cells were infected with GBV-C afterwards.

Until now, little has been known about the factors relevant for maintenance or termination of GBV-C replication. The question had been risen, whether interferon treatment of hepatitis C – which is able to terminate GBV-C replication as well – could be harmful in GBV-C viremic HIV-/HCV-coinfected individuals. One study found no disadvantage in immunological and clinical surrogate-markers after interferon therapy but the results indicate differential effects of distinct GBV-C genotypes (Schwarze-Zander 2006). Two studies in HIV-2 infected individuals did not show an association between GBV-C viremia and disease progression, indicating as well a role of the genotype of HIV(Descamps 2006). GBV-C viremic HIV-positive individuals had a higher endogenous Interferon production, which might explain in part the beneficial effects on HIV progression (Capobianchi 2006). Further studies will be necessary to understand whether the clearance of GBV-C viremia induced by interferon therapy will have any impact on the course of HIV infection. Until then this issue is of potential impact for counseling in HIV, HCV, and GBV-C coinfection. But routine tests to determine the GBV-C status are still not available, and sensitivity and specifity of recent tests vary considerably (Souza 2006). Therefore,

there is at least a need for screening for GBV-C serostatus, prospective follow-up, and individual counseling during interferon therapy and in controlled studies.

The history of GBV-C, as well at that of HIV, is still young. Increasing insight into effects and mechanisms of HIV and GBV-C interaction and into the role of individual-specific host factors give the opportunity to elucidate clinically relevant regulation pathways of HIV. This could help us in the development of new therapeutic concepts prior to, or in addition to, HAART. Presumably, these concepts could be promising with respect to their clinical and therapeutic impact, because, in several studies, a benefit of GBV-C replication remained evident under HAART.

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20. HIV and Renal Function

Ansgar Rieke

A quarter of the cardiac output is consigned to the perfusion of the kidneys – even though the kidneys amount to just 0.5 % of the total body weight. Approximately every 20 minutes, i.e. 70 times a day, the entire blood plasma is filtered by the kidneys. Therefore, kidney glomeruli are target organs for every hematogenous infection. Viral infection can cause primary glomerulonephritis, whereas an immune reaction can lead to secondary glomerulonephritis. HIV infection, hepatitis B and C as well as bacterial infections are all typical causes of renal disease. Nephrotoxic agents precipitate renal diseases that affect the interstitium and the tubular apparatus in particular, and we will have to deal with this increasingly in the era of HAART.

Nephroprotection

In view of the prolonged use of antiretroviral medication, long-term renal side effects are to be expected. Similar to experiences with diabetes mellitus and diabetic nephropathy, the principles of therapy should be particularly emphasized: adjustment of blood pressure values to < 130/80 mm Hg and no smoking. However, they have not yet been scientifically investigated in relation to HIV infection. The consequent adjustment of diabetes mellitus or change of therapy to avoid a metabolic syndrome are in principle advantageous and will probably have a long-lasting positive side effect on renal function.

On the basis of current data, the viral changes of the glomeruli and the renal tubules due to HIV infection should be reason enough to start/maintain an antiretroviral therapy in a symptomatic patient, rather than to worry too much about potential nephrotoxic side effects.

Clinical manifestation/diagnosis of nephropathy

The major symptoms of glomerulonephritis are proteinuria and "***nephritic sediment***". Clinically, a difference is made between nephrotic syndrome (loss of protein), acute nephritic syndrome (acantocytes as a sign of GN), rapid-progressive GN (loss of renal function in only a few days), asymptomatic proteinuria or hematuria and chronic GN.These entities are all treated differently and require the collaboration of a nephrologist. HIV-associated nephropathy (HIV-AN) is a form of glomerulonephritis and is diagnosed in cases of nephrotic syndrome with edema, hypoalbuminemia, hyperlipidemia and proteinuria of more than 3.5 g/day. However, even a mild proteinuria is possible. The occurrence of proteinuria and erythrocyturia is pathognomonic for glomerulonephritis (GN) and, together with a nephritic sediment, usually confirms the diagnosis. Under a polarizing microscope, a trained eye can easily identify the renal (glomerular) origin of the erythrocytes, on the basis of glomerularly deformed acanthocytes. More than 5 acanthocytes per field of vision is a significant sign for GN. Extensive erythrocyturia (bleeding) below the re-

nal pelvis (tumor of the urinary tract collection system?) can be excluded by sonography and, if necessary, by cystoscopy.

The clinical symptoms are determined by the ***extent of proteinuria*** with loss of protein and imbalance, as well as loss of renal function. The severity of edema, tiredness, reduced performance, susceptibility to infections, hyperlipidemia, anemia, metabolic acidosis, problems with the calcium-phosphate metabolism, as well as venous thrombi and newly diagnosed arterial hypertension is limited by the length and intensity of the renal insufficiency. An ***increase in serum creatinine*** is not to be expected until the glomerular filtration rate (GFR) is below 50 %, and should be identified early by clearance measurements. As a urine collection over two 24-hour periods is difficult to organize, three methods are generally used for estimating the clearance. 1. Formula according to Cockroft and Gault: 140-age x kg body weight) divided by (serum creatinine mg/dl x 72). For women, the result is multiplied by 0.85.

2. MDRD formula: this is more precise and only requires laboratory data (creatinine, urea, age and gender). The formula is as follows:

creatinine clearance (MDRD) = 170 x Krea $[mg/dl]^{-0.999}$ x age $^{-0.176}$ x (urea [mg/dl] x $0.46]^{-0.170}$ x albumin $[g/dl]^{-0.318}$ (for women: x 0.762)

3. Cystatin C clearance: cystatin C is a low molecular weight protein which is constantly generated by the organism, is filtered freely and regardless of gender, muscle mass, age with a minor intraindividual variability (< 5%) can serve as a marker for the creatinine value "blind range". However, determination is by no means inexpensive. The formula is: GFR (ml/min//1.73m^2) = 78 x 1/CysC (Mg/l) + 4 or: 87 x 1/CsyC (mg/ml) – 6.9

Interstitial nephropathy, especially when caused by indinavir, can present as a sterile leukocyturia, and can also lead to a loss of renal function.

Leukocyturia must be microbiologically clarified (culture of mid-stream urine) in order to initiate treatment with antibiotics according to the resistance situation, whereby a case of bacterial interstitial nephritis may also be in existence. Tuberculosis of the urinary tract should be considered as a possible cause of abacterial leukocyturia.

The symptoms of drug-induced Fanconi's syndrome (***tubulotoxic damage***) are glucosuria + phosphaturia with a normal blood glucose (dropping the renal glucose limit) + hypophosphatemia. The patient feels tired and peaky, the symptoms are non-specific and an increase in serum creatinine is often delayed.

Routine tests for renal impairment

The routine investigation of an HIV-infected person should include tests for sodium, potassium, calcium, phosphate (every three months) and creatinine (creatinine clearance). The urine should be tested for glucosuria, proteinuria, erythrocyturia and leukocyturia every 3 months.

If there is a significant rise in proteinuria or serum creatinine, a nephrologist should be consulted (renal biopsy if necessary).. There is no time to waste in the case of a rapid increase of creatinine (rapid-progressive glomerulonephritis?), an increase of LDH connected with hyperbilirubinemia and thrombocytopenia (hemolytic uremia

syndrome, HUS), or severe electrolyte imbalance (especially hyperkalemia), or acidosis that cannot be controlled, which can also occur on therapy as lactacidosis.

An asymptomatic, slight proteinuria with no rise in creatinine can be treated in almost one third of untreated patients and should be monitored quarterly.

A decrease in renal function in patients with an HIV infection could be interpreted as a symptomatic HIV infection, and antiretroviral therapy might be considered. The use of a contrast medium (CM) for the urinary tract should be avoided, especially in cases of renal insufficiency, proteinuria and all forms of low intravasal volume (including cirrhosis of the liver), in order to avoid causing CM-induced renal failure.

HIV-associated nephropathy (HIV-AN)

HIV-AN is characterized by rapid loss of renal function, which is especially observed in Afro-Americans. At the end of 2005, 56 HIV-positive dialysis patients were registered in Germany (new in 2005: 9 dialysis patients with HIV and 3 HIV patients with a kidney transplant, Quasi Kidney Report 2006). The risk factors are genetic predisposition (97 % Afro-Americans), male gender and drug abuse.

Most patients have a poor immune status with < 100 CD4+ T-cells/µl (only 20 % have normal ranges). Individual cases of sudden renal insufficiency within an acute HIV syndrome have been reported. But there seems to be no correlation with HIV viral load and the duration of the HIV infection.

Nephrotic proteinuria usually presents clinically as more than 3.5 g/day, but a minor proteinuria is also possible. Progression is fast and can lead to end-stage renal disease (dialysis) in less than 10 months (Szczech 2001). The blood pressure is normal or slightly increased; the kidneys are within the normal size range when examined by ultrasound scan. Despite hemodialysis, the one-year-mortality rate is 50 %; on antiretroviral therapy it still reaches around 30 %.

The histological findings in biopsies mostly (70 %) correspond to a focal segmental sclerosing glomerulonephritis (FSGN), which is also frequently observed in “malignant hypertension” in Afro-Americans. However, other causes of a glomerulonephritis, such as an amyloid kidney are also possible with HIV (Daugas 2005). Single case descriptions with the histological course of disease have confirmed the direct infection of the glomerular basal membrane with HIV, and have documented an impressive positive effect of HAART on the histological changes (Winston 2001).

Experience with other FSGN-forms has shown that only early intervention with HAART – before scarring of the glomeruli occurs due to the underlying disease – has a chance of success. This calls for a rapid reaction: HIVAN is independent from CD4 cell count and viral load must be treated.. The use of components of antiretroviral therapy should take into consideration the different means of renal elimination (adaptation of the dosing). ACE-inhibitors (captropil 6.25 to 25 mg bid, then change to a longer-term effective preparation such as enalapril 5 mg) should be added (see also Table 2). The use of steroids is the subject of controversial discussion (1 mg/kg KG/day for 2 to 11 weeks), but is favoured in the USA alongside initiation of a HAART, particularly in cases which take a course similar to lupus (Haas 2005, Gupta 2005).

Post-infectious glomerulonephritis

Many bacteria and viruses are able to trigger or support an acute post-infectious glomerulonephritis or other forms of chronic GN. Viral infections such as CMV, EBV, VZV, influenza, adenovirus, and parvovirus B19 do this as well as HIV. After syphilis and infections with staphylococci, pneumococci, legionella, salmonelli and other infectious agents, an acute post-infectious glomerulonephritis can also occur. An acute HIV infection can cause renal insufficiency.

Membranous glomerulonephritis is a special form of secondary glomerulonephritis, which can appear in malignant tumors and hepatitis (B and C). Chronic hepatitis C can lead to a membrano-proliferative GN, or through cryoglobulinemia can also cause vasculitis with renal involvement.

The most common form of renal disease in Germany is IGA nephropathy, which can also be triggered by an HIV infection, respiratory infections or infection with Hepatitis A. Post-infectious GN is treated specifically (see below); the underlying infection is treated simultaneously.

Irrespective of the liver histology, hepatitis C-associated GN can also be a reason for therapy with interferon/ribavirin (observe adaptation of the dosing intervals). However, ribavirin shouldn't be used if the creatinine clearance is less than 50 ml/min/1.73 m² because of the danger of prolonged anemia. In the case of a nephritic syndrome as a result of cryoglobulin anemia in hepatitis C, a low-dosage interferon maintenance therapy or other anti-inflammatory anti-lymphocyte therapy should be considered.

Principles of therapy of glomerulonephritis

The underlying cause of a post-infectious glomerulonephritis should be treated first, including hepatitis B, C and HIV infection.

Particular attention should be paid to the adjustment of blood pressure: target values are < 130/80 mm Hg or, in the presence of proteinuria < 120/80 mm Hg. ACE-inhibitors as well as AT-II-receptor-antagonists are used to control blood pressure, usually in combination with diuretics.

Proteinuria should be treated with an ACE-inhibitor, also at high doses, if necessary, irrespective of the blood pressure, and should be combined additionally with AT-II-receptor-antagonists if the proteinuria is more than 0.5 to 1 g/day. The protein intake is reduced to 0.6-0.8 g/kg/day (low protein diets like the Mediterranean diet might be helpful).

Fluids should be restricted to 1.5 to 2 l/day and adapted according to the body weight and amount of edema. Forced drinking of large amounts, or rather the alleged "flushing" of the kidneys or the use of high-ceiling diuretics in combination with increased fluid flow rate, has no effect on renal function. Not smoking is of vital importance because nicotine causes an increase in the risk of progression of glomerulonephritis.

Hyperlipidemia should be treated after dietary arrangements have been exhausted. HMG-CoA reductase inhibitors are ideal, provided that they can be combined with the antiretroviral therapy (see chapter on drug interactions). Fibrates or fibrates in

combination with statins may only be used carefully when renal function is reduced (cumulation).

Analgesics should be waived as far as possible, which applies especially to the "small" analgesics, such as ASA and paracetamol.

‚When the creatinine clearance reaches a value of less than 50 ml/min/1.73 m², at the latest, treatment should be managed by a nephrologist.

Treatment of hypertension

Please take note of the specific side effects of antihypertensive drugs. Note hyperkalemia with ACE-inhibitors; at a creatinine count of 1.4 mg/dl do not use potassium-saving diuretics; at creatinine > 1.8 mg/dl high-ceiling diuretics such as furosemid or torasemid should be used.

Table 1: Blood pressure adjustments

Category	**Drug**	**Dosage (examples)**
ACE-inhibitors	Lisinopril, Benazepril-HCL, Fosinopril sodium, Enalapril, etc	Fosnorm® 5 mg (1 x morning, increase slowly to 20 mg/day
Beta-blockers	Metoprolol, Bisoprolol	Beloc-Zok® (mite) 1x1
AT I-receptor-antagonists	Valsartan, Candesatan, Telmisartan, etc.	Blopress® first 2-4 mg/day, increase carefully to 16 mg/day
Diuretics	Hydrochlorothiazide + Triamterene	Dytide H® 1x1
Ca-antagonists	Amlodipine	Norvasc® 5 mg 1x1, after > 1 week increase to 2x1 if necessary

Renal safety of antiretroviral therapy

The spectrum of an allergic or autoimmune reaction in the kidney is no different from the skin or other internal organs. Reactions can be humoral or T-cell-mediated and can lead to renal insufficiency. The spectrum ranges from the type I immune reaction (acute interstitial nephritis after exposure to medication) to the type IV T-cell-mediated reaction (special forms of a chronic interstitial nephritis). It is, therefore, important to know that even the one-off use of an analgesic (e.g. ibuprofen) can lead to renal failure. In principle, this is possible with antiretroviral drugs. Any change of treatment should be followed by a check of renal function, after 14 days in the case of any noticeable renal changes, otherwise every 4 weeks in the first year.

Acute renal failure or acute tubular necroses can also occur during treatment with aciclovir, ganciclovir, adefovir, aminoglycosides or pentamidine. Tubular dysfunctions may also be found with DDI, D4T or 3TC. An acute allergic interstitial nephritis can arise in connection with a hypersentitivity reaction when taking ABC. With patients taking atazanivir and T-20, membranoproliferative glomurelonephritides were observed.

The typical side effects of antiretroviral therapy are:

Indinavir-associated nephropathy

In the indinavir doses used in the past,. the cumulative occurrence of the symptomatic nephrolithiasis was indicated to be over 10 %. .The renal side-effects ranged from asymptomatic crystalluria to renal failure.. Renal problems have become rarer with the boosted doses used today On abdominal x-ray, an indinavir stone is not usually apparent. However, in combination with calcium it can become radio-opaque, and could be confused with a calcium-oxalate-stone. Urate stones are transparent on x-rays.

When evaluating the triggering agent, it must be observed that other medicaments could have caused the crystalluria, and only resulted in nephrolithiasis on combination with indinavir (e.g. ampicillin, acyclovir, aspirine, ciprofloxacin, methotrexate, vitamin C, sulfonamide and also other drugs that lead to an increase in uric acid).

Elevation of creatinine under long-term indinavir therapy was already observed at the end of the 90s (Fellay 2001, Boubaker 2001). Typical signs of ***indinavir nephropathy*** include sterile leukocyturia and an echogenic transformation of the renal parenchyma in otherwise normal kidneys. Discontinuing indinavir leads to a normal function in most cases. One should pay heed to the possibility of tuberculosis in the urinary tract in sterile leukocyturia.

Tubulotoxic damage, *Fanconi's syndrome*

When the substances filtered from the glomerulum in primary urine exceed the transport capacity of the reabsorbing tubular cells, they are excreted with the urine. The most prominent example is the glucose threshold of the kidneys (180 mg/dl). However, a transport dysfunction in the tubular system can also be caused by drugs such as cidofovir, tenofovir and adefovir. This is then known as a secondary (drug-induced) Fanconi's syndrome and is distinguished by a malfunction of the tubular system without there necessarily being any impairment of the GFR. There is an increased amount of phosphate, amino acids and glucose in the urine, whereas phosphate in the blood is reduced. The loss of amino acids, phosphate, glucose, bicarbonate and other organic and inorganic substances, as well as water, can become clinically manifest in the form of increased urination, thirst or tiredness.

In case reports, renal failure was above all described in patients with other reasons for renal insufficiency, mostly under boosted PI-regimes with tenofovir as well as secondary disorders and cirrhosis of the liver or hepatitis. Nephrologists advise caution in selecting antiretroviral therapy for patients with proteinuria, nephritic syndrome, cirrhosis of the liver, and/or dyslipoproteinemia. Nephrotoxic substances such as cidofovir, adefovir and tenofovir should be avoided in these patients. In principle, it is possible to administer NRTIs, and a regime of only two boosted PIs

can be given "as a kidney-neutral solution" in individual cases For patients with healthy kidneys, there are no restrictions at present. However, careful monitoring of serum creatinine, proteinuria, erythrocyturia and serum phosphate can only be recommended.

Tenofovir and the kidney

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In view of the broad application of tenofovir, more attention must be devoted to long-term renal toxicity in the future. Based on 455,392 patient years, the incidence of unwanted renal occurrences at Gilead since drug approval amounted to 29.2 renal events per 100,000 patient years (Nelson 2006). However, unreliable notification performance means that this is not a realistic reflection of the true situation.

The leading renal event when taking tenofovir is Fanconi's syndrome (Incidence: 22.4/100,000 patient years).This was almost always diagnosed in conjunction with hypophosphatemia, glucosuria (renal diabetes mellitus with normal blood sugar), and a mild proteinuria. It occurs on average 7 months after beginning intake and disappears 4 to 8 weeks after discontinuing. (Izzedine 2004). An isolated case of hypophosphatemia without glucosuria in HIV cannot yet be defined as Fanconi's syndrome and can just as well be due to malnutrition, vitamin D deficiency, diuretics or alcohol and doesn't necessarily mean tenofovir must be discontinued.

In the accreditation studies, the incidence of renal events (changes in creatinine clearance, glucosuria, proteinuria, hypokaliemiam acidosis) when taking tenfovir was no higher than in the control groups. With patients treated previously, however, hypophosphatemia was observed in 13% after 24 weeks (113 weeks: 22%). This was more often than in the placebo arm, but not associated with other tubulotoxic symptoms (Gallant 2004 + 2006). The median time up to the occurrence of renal side-effects amounted to 9 months in a study (Izzedine 2004). The risk in increased through the combination with nephrotoxic substances, kidney disease or renal insufficiency in the patient's history, sepsis, dehydration, extremely advanced HIV disease or severe hypertension (Nelson 2006).

Like the other NRTIs, tenofovir is eliminated renally and must be dose-.adapted in cases of renal insufficiency. Contrary to earlier case studies and the fact that ritonavir increases the Cmax and the AUC of tenofovir by about 30%, however, combination with boosted PIs is possible. This is also confirmed by in-vitro studies (Izzedine 2005, Ray 2005).

In the first year of treatment with tenofovir, patients with healthy kidneys should be monitored monthly, thereafter every three months. Patients with kidney dysfunctions are monitored more often. In the case of additional nephrotoxic substances or drugs which are also excreted via the renal transporter (aminoglycosides, amphotericin B, famciclovir, ganciclovir, pentamidine, vancomycine, cidofovir, IL-2), the renal function is monitored at weekly intervals.

Dosage of antiretrovirals in renal insufficiency

In each case, the technical information of the individual substances must be taken into consideration. Because NNRTIs and PIs are almost exclusively hepatically

eliminated, a dose rate adjustment is normally only necessary for the NRTI, unless a coexistent insufficiency of the liver is present.

Within the scope of hepatitis C therapy, ribavirin should be omitted in patients with renal insufficiency (note: prolonged anemia) if the creatinine clearance is under 50 ml/min/1.73 m². T-20 (Fuzeon™) can be used up to an endogenous creatinine clearance of 30 ml/min/1.73 m² without dose reduction; no data is available for more severe renal insufficiency.

Table 2: Dosage of antiretroviral medicaments in renal insufficiency (in each case diurnal dosages, if not otherwise stated) HD=Hemodialysis

Category	Standard dose	CrCl (ml/ min)	Dose in renal insufficiency
AZT (Retrovir®)	2 x 250 mg	> 10	2 x 250 mg
		< 10	300 – 400 mg
3TC (Epivir®)	1 x 300 mg or	> 50	Standard dose
	2 x 150 mg	30 – 49	1 x 150 mg
		< 30	150 mg (15 ml) on day 1; 100 mg (10 ml)/day thereafter
			50 mg (5 ml) on day 1; 25 mg (2,5 ml)/day thereafter
		< 5	
AZT+3TC	2 x 1 Tabl.	> 50	Standard dose
(Combivir®)		< 50	Not recommended
ABC (Ziagen®)	2 x 300 mg	> 50	Standard dose
		< 50	contraindicated
AZT/+3TC+ABC	2 x 1 Tabl.	> 50	Standard dose
(Trizivir®)		< 50	Not recommended
d4T (Zerit®)	2 x 40 mg (> 60 kg)	> 50	Standard dose
	2 x 30 mg (< 60 kg)	30 - 49	half standard dose
		< 30	quarter standard dose
ddI (Videx®)	1 x 400 mg (> 60 kg)	> 60	Standard dose
	1 x 250 mg (< 60 kg)	30 - 59	half standard dose
	(combined with TDF never exceed 1 x 250 mg)	10 - 29	1 x 150 or 100 mg
		< 10	1 x 100 or 75 mg
TDF (Viread®)	1 x 245 mg	>50	Standard dose
		30 - 49	245 mg every 2 days
		10 - 29	245 mg every 72-96 h
		HD patients	245 mg every 7 days past HD
FTC (Emtriva®)	1 x 200 mg	> 50	Standard dose
		30 - 49	200 mg every 2 days
		15 - 29	200 mg every 72 h
		< 15 (incl. HD)	200 mg every 96 h
TDF	1 x 1 tablet	> 50	Standard dose every 24 h
(Truvada®)		30 – 49	1 tabl. Every 48 h
		y 30 and HD	Not recommended

OIs and renal insufficiency

Pneumocystis pneumonia

As cotrimoxazole is nephrotoxic as a high-dose therapy, its use must be carefully considered. Systemic administration of pentamidine should also be avoided in patients with renal insufficiency.

Table 3: PCP treatment in renal insufficiency

	GFR normal	GFR >50 ml/min	GFR 10-50 ml/min	GFR <10 ml/min	Dose adaptation for HD/CAPD/cont. NET
*Cotrimoxazole	960 mg 3 x 3/die (total of 120 mg/kg daily)	(100 % every 12 h)	(100 % every 12-24 h)	(50 % every 24 h)	HD: + half dose after dialysis CAPD: no adaptation CAVH: GFR 10-50 CVVHD: GFR < 10
Dapsone	100 mg every 24 h	50-100 %	50 %	avoid	avoid
Atovaquone	750 mg every 12 h	100 %**	100 %**	100 %**	HD: no adaptation CAPD: no adaptation* CAVH: (GFR < 10)**
Pentamidine	4 mg/kg every 24 h	100 %	100 % every 24-36 h	100 % every 48 h see text !!!	HD: (GFR < 10)*** CAPD: (GFR < 10)** CAVH: (GFR < 10)**

* no studies available, normal dosage recommended,

** no studies available, dosage as for GFR < 10ml/min recommended.

(cont. NET = continuous dialysis, HD = intermittent hemodialysis, CAPD = continuous ambulant peritoneal dialysis; CAVH = continuous arterio-venous hemofiltration, CVVHD = continuous veno-veno hemodiafiltration).

Toxoplasmosis encephalitis

Table 4: Treatment of cerebral toxoplasmosis with renal insufficiency

	GFR normal	GFR > 50 ml/min	GFR 10-50 ml/min	GFR < 10 ml/min	Dose adaptation for HD/CAPD/cont. NET
Pyrimethamine	50-75 mg every 24 h	100 %	100 %	100 %	HD: no adaptation CAPD: no adaptation CAVH: no adaptation
Clindamycin	150-300 mg every 6 h	100 %	100 %	100 %	HD: no adaptation CAPD: (GFR < 10)* CAVH: (GFR < 10)* CVVHD: GFR normal
Sulfadiazine	2 g every 6 h	Avoid	Avoid	Avoid	Avoid

*= no studies available, dosage as for GFR < 10 ml/min recommended.

(cont. NET = continuous dialysis, HD = intermittent hemodialysis, CAPD = continuous ambulant peritoneal dialysis; CAVH = continuous arterio-venous hemofiltration, CVVHD = continuous veno-veno hemodiafiltration).

CMV, HSV, VZV infection

Table 5: Treatment of CMV, HSV, VZV in renal insufficiency

Drug	GFR normal	GFR > 50 ml/min	GFR 10-50 ml/min	GFR < 10 ml/min	Dose adaptation for HD/CAPD/cont. NET
Acyclovir	5-10 mg/kg every 8 h	5 mg/kg every 8-12 h	5 mg/kg every 12-24 h	2.5 mg/kg every 24 h	HD: Dose after dialysis CAPD: GFR < 10 CAVH: 3.5 mg/kg every 24 h CVVHD: 6.5-15 mg/kg every 24 h
Ganciclovir	5 mg/kg every 12 h	3 mg/kg every 12 h if GFR 25-50 ml	3 mg/kg every 24 h if GFR 10-25 ml	15 mg/kg every 24 h	HD: Dose after dialysis CAPD: GFR < 10 CAVH: 3.5 mg/kg every 24 h CVVHD: 2.5 mg/kg every 24 h
Valgan-ciclovir	900 mg every 12 h	GFR 40-59 ml/min 450 mg every 12 h GFR 25-39 ml/min 450 mg every 24 h GFR 10-24 ml/min 450 mg every 48 h for induction		unknown	unknown
Foscavir	90 mg/kg every 12 h	50-100 %	10-50 %	avoid	HD: Dose after dialysis CAPD: 60 mg/kg every 48-72 h CAVH: GFR 10-50
Cidofovir	5 mg/kg every 7 days	100 %	0.5-2 mg/kg every 7 days	avoid	HD: GFR 10-50 CAPD: GFR 10-50 CAVH: avoid
Famciclovir	250 mg every 8 h p.o.	Every 12 h	Every 48 h	50 % every 48 h	HD: Dose after dialysis CAPD: ? CAVH: GFR 10-50

(cont. NET = continuous dialysis, HD = intermittent hemodialysis, CAPD = continuous ambulant peritoneal dialysis; CAVH = continuous arterio-venous hemofiltration, CVVHD = continuous veno-veno hemodiafiltration).

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21. HIV-associated Skin and Mucocutaneous Diseases

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Introduction

Since 1981, when the first reports about AIDS were published in themedical literature, skin and mucocutaneous diseases have played an important role in the clinical diagnosis of acquired immunodeficiency. Kaposi's sarcoma in young homosexual men was the clinical manifestation of AIDS (Friedman-Kien 1981, 1990). Additionally, opportunistic infections of the skin and oral cavity such as herpes simplex and candidiasis were noted to be clinical markers of acquired immunodeficiency (Gottlieb 1981, Siegal 1981). In the early years of HIV infection, a broad spectrum of common cutaneous infections was noted in patients due to viruses, bacteria, fungi, protozoa, and parasites as well as many unusual manifestations of common dermatoses (Friedman-Kien 1989, Farthing 1989, Schöfer 1990, Schöfer 1991, Berger 1997).

The alterations of the cell-mediated immune system enable organisms considered to be non-pathogens to penetrate into the tissue and cause infections. Such opportunistic infections, as well as any other infections in the immunodeficient host, sometimes behave aggressively leading to a life-threatening clinical course.

The most frequent skin diseases documented in a prospective long-term study in HIV-infected patients at the Department of Dermatology and Venereology, University Hospital, Frankfurt/M, Germany, between 1983 and 2004, are summarized in Table 1.

Differences in the prevalence and incidence of mucocutaneous disease between countries may be attributable to climate, endemic diseases, hygienic standards and the availability of specialized medical facilities and drugs, as well as social, economic and cultural factors. The risk groups observed – homosexual men, IVDA, heterosexuals, and children – play an important role in the incidence and prevalence of HIV-associated mucocutaneous diseases.

Among sexually transmitted diseases, chancroid is an important indicator of the spread of the HIV epidemic in tropical and subtropical regions; whereas in Europe and North America, herpes simplex infections and a resurgence of syphilis in homosexual men are more important indicators. Since 2003, there has been increased reporting of lymphogranuloma venereum, an STD caused by Chlamydia trachomatis (L1-3), in homosexual men in the Netherlands, France and several big cities in Germany (Hamburg, Berlin) . It is suspected that the resurgence of STDs is due to the changing sexual behavior of homosexual men during the past 5 to 7 years. Fear of acquiring HIV infection by unsafe sexual practices has lessened as patients live longer, healthier lives on HAART therapy. There may be a sense among patients that HIV infection no longer confers a death sentence because HAART decreases viral loads resulting in fewer diseases. In addition, many men are not aware

of the risk of co- infection through orogenital contact with other STDs such as syphilis. There is an increasing incidence of oral primary chancres.

Table 1: Frequency of skin diseases	No. patients	% of all HIV patients
Oral candidiasis	636	30%
Seborrheic dermatitis	619	28%
Xeroderma	600	28%
Tinea	502	23%
Folliculitis	492	23%
Syphilis (active/seropositive)	485	23%
Kaposi's sarcoma	460	21%
Pruritus	436	20%
Genital warts	368	17%
Candida infections, others	355	16%
Drug eruptions	349	16%
Herpes simplex genitoanalis	349	16%
Herpes zoster	345	16%
Gonorrhea (active/history)	340	16%
Bacterial infections	315	15%
Mollusca contagiosa	301	14%
Warts (HPV)	278	13%
Herpes simplex labialis	214	10%
Oral hairy leukoplakia	188	9%
Hair loss	135	6%
Psoriasis	117	5%
Basal cell carcinoma (BCC)	25	1.2%
Squamous cell carcinoma (SCC)	23	1.1%
Malignant melanoma	9	0.4%
Total number of patients 1982 - 2000	2149	100%

Notice: The frequency of skin diseases listed here mirrors the clinical symptoms of 2149 HIV-infected patients, who visited the Frankfurt University Hospital between 1982 and 2000 because of skin problems. Most of these patients were referred with a known HIV infection. Others were detected to be HIV-positive by their dermatological symptoms, which were interpreted as clinical markers of severe acquired immunodeficiency and led to HIV antibody testing. The majority of these patients (75 %) was seen in the pre-HAART era (between 1982-1996). Since 1996, more than 80 % of the patients living with HIV/AIDS in Frankfurt/M. are on HAART. This led to a significant reduction in opportunistic skin diseases (by 90 %) and Kaposi's sarcoma (by 90 %). The high frequency of skin disease summarized in this table is still seen in patients who are not on HAART or not yet diagnosed to be HIV-infected.

In urban areas, syphilis is now seen 4 to 10 times more frequently in homosexual men compared to 2000. Until today, there has been no observable increase in the incidence and prevalence of syphilis in European women, but it is very likely that the epidemic in homosexual men will be followed by a heterosexual epidemic within a few years. According to the epidemiological data, provided by the Robert Koch Institute in Berlin, the incidence of syphilis in Germany (3.8 per 100 000 in-

habitants per year) exceeded the incidence of newly registered HIV infections (3.2) in 2006 (RKI 2006).

It has become evident that a functional cell-mediated immune system plays an important role in the protection against epithelial tumors. The likelihood of developing squamous cell carcinomas, basal cell carcinomas, lymphomas, or even malignant melanoma is correlated with the length of time HIV-infected immunocompromised patients survive. Nowadays, HIV-infected patients survive longer than patients from the pre-HAART era. For this reason, these patients need to be monitored for primary cutaneous malignancies such as basal cell carcinoma, squamous cell carcinoma, melanoma, and cutaneous lymphomas.

Analogous to the long-term immunosuppressed organ transplant recipient, the HIV-infected patient has to be examined periodically (6 month intervals suggested) for melanoma as well as non-melanoma skin cancers including actinic keratoses (Schöfer 1998, Honda 2006). Factors such as UV-light, smoking and oncogenic viruses (especially mucocutaneous infections with HPV 16 and HPV 18) must be considered as cofactors in carcinogenesis. Skin cancer precursors such as actinic keratoses, bowenoid papulosis, Bowen's disease, and intraepithelial neoplasias of the genital or anal region must be treated early and aggressively. The incidence of anal carcinoma, an epithelial tumor typically found in old men, is now increasing in young HIV-infected homosexual men. Contrary to the manifestation of Kaposi`s sarcoma effective HAART does not reduce the incidence of anal carcinoma. It seems that the total duration, rather than the severity of immunodeficiency is important for the manifestation of these tumors. As in non-immunocompromised patients, risk factors such as pigmentation characteristics, sun sensitivity, sun exposure behavior patterns, and geographic location must be considered in the evaluation.

Dermatological examination and therapy in HIV-infected patients

HIV-infected patients with advanced disease often suffer from common skin diseases (Table 1), but they also present with rare dermatoses, unique to HIV infection. Careful dermatologic evaluation may lead to the diagnosis of serious systemic infections in this population such as cryptococcosis, bacillary angiomatosis, oral hairy leukoplakia, and *Penicillium marneffei* infections of the skin. Common dermatoses often present with atypical findings and may pose diagnostic dilemmas. For example, herpes simplex labialis may present as large superficial erosions or deeply ulcerating lesions rather than the classical small vesicles on an erythematous base. Eruptions of secondary syphilis may ulcerate and form rupial lesions accompanied by high fever and constitutional symptoms (malignant syphilis). It is therefore important to pursue diagnosis of all cutaneous eruptions through appropriate tests such as tissue cultures, biopsy, and swabs of lesions prior to the initiation of therapy.

Because HIV-infected patients are at high risk of contracting other STDs due to the common modes of transmission, they should be screened for them. During the past three years, 39 % of all syphilis patients who attended our Department, had HIV co-infection. Dermatologic evaluation should include complete cutaneous inspection, oral cavity examination, inspection of the anogenital region and palpation of the

lymph nodes. Standard treatment regimens for skin and mucocutaneous diseases may be inadequate in HIV-infected patients due to unusual strains of organisms leading to drug resistance. In these cases, high dose regimens or second and third line therapies may have to be considered (Osborne 2003). Diagnostic and therapeutic regimens of the most frequent HIV-associated skin diseases are compiled in alphabetical order in Appendix 1 of this chapter.

Table 2: Clinical Diagnostic Tools

Indication	Performance	Interpretation
	Biopsy	
Differential diagnosis of tumors, skin lesions without definite clinical diagnosis, or to confirm a clinical diagnosis	Under local anesthesia: 4-mm punch-biopsy; if necessary: excisional biopsy. Fixation of the material in 10 % formalin; for special investigations (immunohistology, electron-microscopy, HPV-typing) use only saline.	Dermatopathologist
	Skin-scraping for KOH examination	
Presumptive diagnosis of dermatophytosis	Clean the skin with 70 % alcohol, let it dry. Use a scalpel or glass slide to scrape scales at the active edge onto a glass slide. A drop 10 - 15 % KOH is put on top of the specimen and covered with a cover slip. After ~ 20 minutes or immediately after gentle heating the specimen can be examined microscopically (10-40x magnification) for fungal elements. The specimen may be cultured as well.	Fungal elements (spores and hyphae) are not digested by KOH and can be visualized with light microscopy.
	Herpes-virus detection	
Presumptive diagnosis of herpes infections (grouped vesicles or ulcers)	A smear of cells from the base of the skin lesion is taken (for culture: special swabs: Culturette™; use pressure to obtain cells). Sample can be put onto a glass slide for immediate direct fluorescent antibody testing (DFA) which will distinguish between HSV and VZV infections.	Tzanck-preparation: multinucleated giant cells (Giemsa- or Wright-stain; 400x magnification) Viral lab, positive culture proves diagnosis; demonstration of DNA or antigen does not differentiate between living and dead viruses
	Allergy testing	
Drug eruptions, presumptive allergic contact dermatitis	Serology: (RAST, lymph. transformation test); skin tests Type I reactions: Prick- and intracutaneous-tests. Type IV reactions: “Scratch”- and patch testing. A specialist in allergy should perform tests and interpretation.	Allergist
	Dark-field microscopy	
Presumptive diagnosis of ulcers (mainly of syphilitic ulcers) Exudative lesions (condylomata lata, possibly secondary syphilis lesions).	Secretion (mechanical pressure, if necessary use ether in local anesthesia) of serous exudate is applied to a glass slide, covered with a coverslip. Examination by dark-field microscopy (1000x). **Lesions in the mouth: examination not possible due to saprophytic bacteria**	Negative test does not exclude syphilis; false negative testing may be due to: prior treatment with antibiotics/ antiseptics A positive test confirms the diagnosis

	Wood`s lamp	
Presumptive diagnosis of dermatophytosis, erythrasma *Malassezia* folliculitis, *Pseudomonas* infections and phorphyria	Skin inspection in a darkened room with a special lamp (Wood`s lamp, 365nm, invisible long-wave ultraviolet light). Shine UV-light closely to the skin area of interest.	Characteristic fluorescence (green, red, orange etc.) of chemicals produced by several fungi and bacteria. False-positive tests by some soaps, deodorants, make-ups etc.

HAART: Influence on (muco-) cutaneous diseases

The introduction of HAART in 1996 revolutionized the dermatological management of HIV-infected patients. Opportunistic infections and Kaposi's sarcoma have decreased to a level of 10 % compared to the pre-HAART era (Reinmöller 1997, Schöfer 1998, Sepkowitz 1998, Calista 2002). An Italian hospital reported that HAART had reduced the total number of HIV patients with skin problems by 40 %. The percentage of patients with cutaneous infections dropped from 66 to 53 %; the percentage of non-infectious, inflammatory diseases from 25 to 21 %; however, the percentage of patients with drug reactions increased from 8 to 23 % (Calista 2002). Appendix 2 is a compilation of antiretroviral drugs, and their cutaneous side effects. Atypical clinical courses of skin diseases and resistance to therapy, which were very common in patients with severe immunodeficiency in the pre-HAART era, are rare conditions now. They still occur, however, in patients not taking antiretroviral therapy (Mirmirani 2001). Cutaneous infections and inflammatory skin diseases have been replaced by drug eruptions caused by 26 currently available antiretroviral drugs. In some patients, immune system reconstitution, following 1 to 3 months after the introduction of HAART, causes clinical disease summarized as immune reconstitution inflammatory syndrome (IRIS).

Drug eruptions have many clinical patterns including macular or maculopapular exanthemas, follicular eruptions, urticaria, and toxic epidermal necrolysis (TEN), . Severe, sometimes life-threatening reactions such as Stevens-Johnson-syndrome or TEN were mainly reported in patients on combination therapy with zidovudine, didanosin, nevirapine, indinavir or amprenavir. In 86 % of these patients, the drug eruptions occurred within the first 4 weeks of treatment (Rotunda 2003). Instead of discontinuing therapy, less severe drug eruptions without mucosal involvement, blistering, or constitutional symptoms (apart from pruritis), may be treated with antihistamines and corticosteroids. This is especially important for patients, whose choice of antiretroviral combination drugs is already limited by drug resistance or severe side effects such as hematotoxicity or polyneuritis. Patients who are "treated through" drug eruptions must be monitored frequently. Corticosteroid treatment should not exceed the equivalent of 1 mg/kg/d bodyweight of prednisone. General considerations about how to recognize and manage drug reactions are updated by Knowles and Shear (2007). Miller and Warshaw (2007) focus on adverse cutaneous reactions to antimicrobials that are commonly used in the management of HIV infected patients.

Blister formation, involvement of the mucous membranes and constitutional symptoms as well as drug reaction with eosinophilia and systemic symptoms (DRESS

syndrome) are absolute indications to stop antiretroviral therapy. TEN (e.g. induced by efavirenz, nevirapine) and hypersensitivity syndrome (e.g. induced by abacavir) may be fatal.

Drug interactions between HAART and agents used to treat cutaneous diseases are frequent and need to be carefully evaluated before being prescribed (see Chapter "Drug interactions", McNicoll 2004 or http://www.hivguidelines.org/Content.aspx?pageID=262). Azole derivatives, retinoids and drugs metabolized via the p450 pathway frequently interact with antiretrovirals.

Immunosuppressive therapies, such as ultraviolet light and cyclosporin, should be limited to a few conditions such as severe autoimmune diseases, and used only with careful clinical and laboratory monitoring. Photo(chemo)therapy is able to provoke viral infections such as herpes zoster and herpes simplex, epithelial tumors, and to increase the HIV viral load. Despite this, we have seen the benefit of narrowband UVB phototherapy in HIV-infected patients with extreme pruritus associated with papular dermatoses or eosinophilic folliculitis, resistant to all other therapies. As long as these patients were under the protection of HAART, UV therapy caused no observable worsening of the immune status.

Eliciting the cause of a drug eruption can be challenging, especially if the patient is taking complementary medication not prescribed by a physician. It is necessary to ask explicitly whether any herbal medicines, vitamins, minerals, or food complements are being taken to improve the general health. Substances with a potential risk of sensitization or toxicity can be the cause of drug reactions (Witkowski 2003). Urticaria, angioedema, and exanthemas due to food complements are reported in the literature (GISED 1996).

The treatment of KS varies with the clinical manifestation of the tumor, the immune status of the patient and his additional symptoms associated with the HIV infection (details see Chapter "Kaposi's sarcoma").

Conclusions

The dermatologist's role in the care of HIV-infected patients is to be familiar with HIV-associated skin and mucocutaneous diseases, their diagnoses, and management. It is also a part of the extensive interdisciplinary knowledge necessary for any physician who takes care of HIV-infected patients.

Considering the lifelong duration of antiretroviral therapy with complications such as drug intolerance, development of epithelial tumors induced by UV-light exposure or oncogenic viruses, it is recommended that patients have a dermatologic consultation before the start of antiretroviral therapy. Complete skin examination with attention to the presence of STDs should be performed. Education should include prevention of photodamage, safe sex practices, and skin care to avoid infections, especially when HIV-associated xerosis is already evident.

Despite the fact that HIV-associated opportunistic infections are less frequent in the HAART era, knowledge about these diseases and adequate treatment is still of high clinical relevance. The full spectrum of these skin diseases is still found in untreated patients around the world.

Dermatological markers of disease of severe acquired immunodeficiency (see Appendix 1) play an important role in this situation (Schöfer 1991), especially if several diseases are diagnosed in the same patient. In the absence of other immunodeficiency, HIV antibody testing must be offered to the patient as a diagnostic tool to elicit the cause of the clinical presentation.

At present, syphilis and HIV co-morbidity is of special interest. The incidence of syphilis in Western Europe has increased 4 to 10 times over the past 4 years. As HIV and *Treponema pallidum* share the same route of transmission, any patient with syphilis must be evaluated for HIV infection. The delayed seroconversion for HIV antibodies should be taken into account and, if initially negative, HIV testing should be repeated after 3 months. Untreated syphilis might result in severe, irreversible damage of multiple organs, accelerate the clinical course of HIV disease and facilitate HIV transmission between sexual partners.

Appendix 1:

Most frequent HIV-associated skin diseases

Acute HIV exanthema: In 40-90 % of all patients infected with HIV-1, an acute, febrile, mononucleosis-like disease with constitutional symptoms and an exanthem occurs (details see Chapter "Acute HIV-1 Infection"). This nonspecific eruption starts 1 to 3 weeks after HIV transmission, and several weeks before HIV seroconversion (Stekler 2007). The macular exanthem favors the upper trunk and is characterized as fairly non-pruritic with erythematous macules from 0.5 to 1 cm in diameter. Morbilliform or rubella-like eruptions and palmoplantar hyperkeratotic eczema occur less frequently. Histopathology reveals a nonspecific perivascular and interstitial infiltrate in the upper and mid dermis (Barnadas 1997). Oral aphthous ulcers, frequently in combination with shallow genital ulcers (bipolar aphthosis) are another important clinical sign (Hulsebosch 1990, Porras-Luque 1998). Differential diagnosis includes other viral infections (EBV, CMV), Mediterranean spotted fever, secondary syphilis, drug eruptions (Hecht 2002, Daar 2001) and Behcet's disease.

Aphthous ulcers and other oral lesions: At least three different kinds of aphthous ulcers occur in the oral cavity of HIV-infected patients. The most frequent diagnosis is recurrent aphthous stomatitis (canker sores) (1) with single or few painful lesions usually localized in the vestibule of the mouth. The ulcers occur at sites of mechanical injuries, are 3 to 10 mm in diameter and heal spontaneously after a few days. Single or multiple large aphthae (2) which are >1cm in diameter and usually persist for several weeks are less common. Both variants are of unknown origin. In a few cases, especially when multiple small lesions occur, herpes simplex viruses can be involved. Large ulcers in combination with severe immunodeficiency can be caused by cytomegaloviruses, which are usually part of a generalized CMV infection. Bipolar aphthosis (3), involving the oral and genital mucosal membranes, is an important clinical symptom of acute HIV infection or Behcet's disease. In addition to these clinical variants of aphthous ulcers, several authors have discussed the di-

rect role of HIV retroviruses in aphthous stomatitis (Kerr 2003). The treatment of recurrent aphthosis is based upon topical anesthetics, and corticosteroids. Large persistent aphthae can require intralesional corticosteroids or systemic prednisone. Immunomodulators, such as thalidomide, are suggested for use as prophylaxis in patients with frequent and painful recurrences(Shetty 2005). The incidence of oral disease has decreased since HAART was introduced (Hodgson 2006). But comparable to the situation in the anal mucosa, high-risk HPV infections, e.g. flat warts of the oral mucosa, oral squamous cell carcinoma and tonsil-related cancers (43% HPV associated) are increasing (Pintos 2007). Differential diagnoses and treatment of oral lesions in HIV infected patients were recently updated by Baccaglini et al (2007).

Folliculitis: Pustular, papular or edematous-papular follicular lesions, involving the proximal limbs and the upper trunk**.** Possible causes include *Staphylococus, Malassezia furfur, Demodex folliculorum*, and drugs such as indinavir. Treatment depends on the etiologic agent detected by bacterial swabs and histopathology if needed. Antimicrobials against staphylococcus, and malassezia, or changing the antiretroviral drug regimen may be required. DADPS, a 10 % crotamiton or polidocanol ointment, or narrowband UVB are effective against severe pruritus in these patients (Ellis 2004). Today, it is well established that HAART naive patients with pruritic eosinophilic folliculitis (Nervi 2006) significantly improve after the initiation of antiretroviral therapy.

Genital warts (condylomata acuminata): Genital warts are sexually transmitted hyperkeratotic and verrucous papules of the anogenital region, caused by a variety of human papilloma viruses (HPV 6, 11, 16, 18, etc.) . HIV-infected patients have a high prevalence of these lesions (17 %), and genital warts are directly related to the number of sexual partners. Genital warts, located in the perianal or intra-anal region are characteristic of receptive anal intercourse. Patients who have anogenital warts, should be offered HIV testing, especially if they have other HIV risk factors.

In general, the clinical manifestations of common genital warts in immunodeficient patients do not differ from those in immunocompetent patients. They are diagnosed by their typical clinical features as condyloma acuminata, condyloma plana, bowenoid papulosis, Bowen's disease and giant condyloma (Buschke-Loewenstein tumor). In contrast to the findings in the immunocompetent population, HPV 16-associated lesions, such as bowenoid papulosis and Bowen's disease (squamous cell carcinoma in situ), which are now classified as anal intraepithelial neoplasias (AIN I-III including the erythroplasia of Queyrat), are more prevalent in immunodeficient patients. These premalignant conditions have a low rate of spontaneous remission and are very resistant to therapy (frequent relapses). It is now accepted, that genito-anal lesions due to oncogenic HPV types, especially HPV 16 and 18, are substantial risk factors for malignant cervical, penile, and anal carcinomas . HPV 16 and 18 are able to immortalize human keratinocytes by downregulating the tumor suppressor genes p53 and pRB. The transformation rate to malignant carcinomas is low in bowenoid papulosis, but almost 30 % in Bowen's disease. In contrast to the beneficial effects of HAART on the incidence and the clinical course of Kaposi's sarcoma and NHL, there is no clear impact on cervical and anal carcinoma. The incidence of these tumors is still increasing (Kreuter 2006). Analogous to cervical intraepithelial

neoplasia (CIN) and cervical cancer in women, regular screening (every 2 to 3 years) for AIN and anal carcinoma is advised for all HIV-infected patients on HAART (Papathanasiou 2003). Screening should include clinical inspection, aceto-white-stain, colposcopy, proctoscopy, cytology (Pap smear) and, if necessary, histopathology (Horster 2003). Due to orogenital sexual contacts HPV 16 and other oncogenic HPV are also found in the oral cavity (Pintos 2007).

Conventional therapy for anogenital warts is destruction by cryosurgery, electrocautery, carbon dioxide, Nd-YAG laser, trichloroacetic acid, or podophyllotoxin. CIN, PIN, and AIN are treated surgically with histological control of the margins to ensure complete removal of the lesion.

All of the destructive treatments have disadvantages. Since virus-harboring keratinocytes can remain in the clinically normal surrounding tissue, relapses are as frequent as 50 % in immunocompetent patients and up to 70 % in immunodeficient patients within 4 months. Alternative therapies with immunomodulatory activity, such as systemic and topical interferons, have shown some efficacy, but the outcome of the studies was closely related to the different treatment regimens and the cost of therapy was extremely high. Topical interferon (IFN-gel with 0,15 Mio IU/g) was only effective in very small warts and as an adjuvant after surgery. The relapse rate could be reduced by almost 50 %.

The immune response modifier imiquimod has been approved for the treatment of genital warts since 1998. As demonstrated in several controlled studies (Yan 2006), imiquimod treatment is safe and effective and has the lowest relapse rate of all treatments (6-13 % in immunocompetent patients, Schöfer 2007). Imiquimod is not approved for the treatment of anogenital warts in immunodeficient patients and intraepithelial neoplasias, but results of several successful treatments of genital warts (Cusini 2004), bowenoid papulosis and Bowen's disease in HIV-infected patients have been published (Kreuter 2004, Klencke 2003, Cooley 2003, Wieland 2006). The only antiviral agent active against HPV is cidofovir, but there is little experience in HIV-infected patients (Snoeck 2001, De Clercq 2007).

Tinea (dermatophytosis, ringworm infections): Infections of the skin, hair or nails with dermatophytes (in Western Europe predominantly *Trichophyton, Microsporum* and *Epidermophyton species*). Tinea has a high prevalence in the general population. There is no significant difference between HIV-negative and HIV-infected adults. The prevalence is dependent upon climate, profession, clothing, and participation in team sports. In homosexual men, the prevalence is 29 to 37 % (Torssander 1988, Schöfer see Table 1).

Typical clinical findings are superficial, scaling, round or oval erythematous plaques, that expand centrifugally with an inflammatory edge and central clearance. Deep infections, with tissue destruction and abscess formation, are rare in Europe and North America, but common in tropical regions. According to Torssander (1988), onychomycosis due to dermatophytes is frequent in HAART-naive patients and difficult to treat. Nails are discolored (white, yellow, green, black), thickened, and show growth disturbances (onychodystrophy). Subungual hyperkeratosis and onycholysis are common.

Psoriasis, yeast infections and trauma can imitate onychomycosis, so it is necessary to identify the causative organisms on KOH and fungal culture. Direct microscopic

examination with addition of 10-15 % KOH solution shows translucent, septated hyphae (mycelium) and arthrospores. Culture on Sabouraud's or Kimmig's medium identifies different fungi by their growth characteristics.

Treatment of superficial fungal infections of the skin is best achieved with topical broad spectrum antifungals such as ciclopirox or azoles, applied twice daily. In severe inflammatory disease, it is helpful to start with combination therapy including topical corticosteroids for 3 or 4 days, to achieve quick relief of discomfort. Deep infections and infections involving terminal hairs (tinea capitis, tinea barbae) require systemic treatment with griseofulvin (500-1000 mg/day), terbinafine (250 mg/day), fluconazole (50 mg/day), or itraconazole (100-400 mg/day). There are different regimens to treat onychomycosis. Itraconazole (pulse therapy) and terbinafine (250mg per day) are typically used for two months for fingernails and three months for toenails. Griseofulvin may be used for up to 9 months or longer, until the infection clears (Aly 1996, Myskowski 1997, Gupta 2000). If only the distal part of the nail plate is infected, topical treatment with nail varnish containing antifungals (e.g. amorolfin, ciclopiroxalamine), which are able to penetrate the nail plate, are advised to avoid drug interactions between systemic antifungals and antiretroviral medications (see Chapters "Drug Profiles" and "Drug interactions"). If systemic therapy is necessary, fluconazole has less drug interactions in HIV-infected patients than the other antifungals mentioned.

Yeast infections (candidiasis etc.) see Chapter "Opportunistic Infections")

Herpes simplex virus infections: Herpetic infections of the skin and mucous membranes are frequent opportunistic infections in HIV-infected patients. The clinical symptoms differ substantially according to the patient's immune status. As long as the cell-mediated immune functions are normal, typical localized infections with itching, erythema and grouped vesicles will appear and heal spontaneously within a few days. In contrast, very painful, deep and large ulcerations of the anogenital region, but also of the face and other parts of the body (e.g. herpetic whitlow) will appear in patients with advanced HIV infection and severe immunodeficiency (CD4+ T-cell count < 100/µl). Clinical diagnosis can be difficult in these patients because grouped vesicles might be absent and only erosions or ulcers might be visible. Along with other STDs, genital herpes plays an important role in the dynamic of the worldwide HIV pandemic. Herpes lesions ease HIV transmission between sexual partners by breaking the epithelial barriers, stimulating HIV reproduction via pro-inflammatory cytokines, and enhancing expression of cellular HIV receptors (CD4, etc.) on the surfaces of immunocompetent cells (Kapiga 2007, Linqappa 2007, Corey 2007) (see Chapter "Opportunistic Infections").

(Herpes) Zoster: Shingles is an early marker disease during the natural course of HIV infection. Frequently, this secondary endogenous *Varicella zoster virus* infection is diagnosed several years prior to any other opportunistic infection. HIV infection or any other kind of acquired immunodeficiency must be suspected in any zoster patient who is (1) younger than 50 years and has no other known cause of immunodeficiency, or (2) shows atypical clinical features such as multisegmental or generalized distribution of normal, hemorrhagic, or necrotic lesions. Latent VZV infections can be activated in the frame of immune reconstitution syndrome a few

weeks after the initiation of effective HAART (See also Chapter "Opportunistic Infections").

Immune reconstitution inflammatory syndrome (IRIS) related skin reactions: HAART recovers the TH-1 immune response and the tuberculin test reactivity (Girardi 2002). In association with this immune reconstitution, clinical manifestations of herpes zoster, mucocutaneous herpes simplex infections, mycobacterial infections, eosinophilic folliculitis, foreign-body granulomas, cutaneous sarcoidosis and aggressive Kaposi`s sarcoma were reported (Handa 2001, Hirsch 2004, Leidner 2005). These infectious, as well as some non-infectious inflammatory skin diseases and tumors, occur within a few days to 3 months after the initiation of HAART. The therapy depends on the severity of clinical manifestations and consists of specific antibiotics, steroidal and non-steroidal anti-inflammatory drugs (For details, see Chapter "IRIS").

Kaposi's sarcoma: See Chapter "Kaposi's sarcoma").

Lipodystrophy and metabolic syndrome: See Chapter "Lipodystrophy syndrome".

Cutaneous lymphomas: Malignant B and T-cell lymphomas are rare in HIV-infected patients (, Biggar 2007). Cutaneous B-cell lymphomas usually grow as red to violaceous nodules, that are easily mistaken for Kaposi's sarcoma. They can also look like persistent hematoma or nonspecific asymptomatic papules. A biopsy should be performed on any clinically unclear tumor of the skin.

Cutaneous T-cell lymphomas are rare malignancies in HIV-infected patients. The prevalence among 2149 HIV patients in Frankfurt/M. was 0.06 %. The clinical course starts with nonspecific eczematous patches (stage I), which are usually not diagnosed as cutaneous lymphoma, even after several biopsies because of the paucity of findings such as cellular atypia. These lesions are usually diagnosed as eczematous dermatitis. A linear pattern of patchy or slightly infiltrated lesions in the relaxed skin tension lines can be an early clinical indication of cutaneous T-cell lymphoma known as parapsoriasis (Munoz-Peres 1999). Histopathology becomes more evident during the plaque stage (stage II), and is striking when in stage III multiple tumors of the mycosis fungoides present. Biggar et al (2007) calculated a relative risk for cutaneous T-cell lymphomas in HIV-infected patients of 15.0 in comparison to the general population. In both HIV-infected and HIV-negative patients, the leukemic phase (Sézary syndrome) is characterized by erythroderma involving the palms and soles. In patients with erythroderma who have darker skin types and lack the histopathological signs of cutaneous T-cell lymphoma, the so-called "pseudo-Sézary syndrome" has to be considered in the differential diagnosis (Picard-Dahan 1996). Therapy with potent topical steroids (e.g. clobetasol) is effective in the patch and plaque stages. Solitary tumors can be controlled by radiotherapy (20-24 Gy) or photodynamic therapy (Paech 2002). Widespread, multiple tumors, and Sézary syndrome are treated with a combination of retinoids and interferons or chemotherapy. Remission of a CD8+ pseudolymphoma treated solely with HAART was reported (Schartz 2003).

Molluscum contagiosum: This is a benign viral infection of the skin, usually seen in children, and often in association with atopic dermatitis. The poxvirus (MCV1-4) causes multiple papular skin-colored lesions with a typical central umbilication. The diagnosis is usually made on clinical grounds. After several weeks or months, an inflammatory reaction indicates the onset of spontaneous healing. In adults, mollusca are detected in the anogenital area and regarded as a sexually transmitted disease . In HIV-infected patients, the clinical manifestations can differ significantly from those seen in the normal host. Spontaneous healing is rare; most patients have high numbers of lesions, typically occurring in the face and neck region, which is otherwise a rare location. The presence of multiple mollusca on the face, is a typical disease marker, indicating advanced cell-mediated immunodeficiency with CD4+ T-cell counts <100/µl (Schöfer 1991, Schwartz 1992). The growth of mollusca in the immunocompromised host is not always exophytic, sometimes endophytic lesions occur. Multiple mollusca have to be differentiated from hematogenous dissemination of cryptococcosis, histoplasmosis, and coccidioidomycosis, which are usually associated with fever, headache, and sometimes pulmonary infiltrates. In such cases, skin biopsies (and tissue culture) and chest x-rays are indicated. Single molluscum can exceed 1 cm in diameter and grow exophytically, which can cause confusion with keratoacanthoma, squamous cell carcinoma, basal cell carcinoma, or common warts.

Mollusca are treated surgically with , electrocautery, curettage, or cryotherapy. Photodynamic therapy with 5-aminolevulinic acid (Moiin 2003, Gold 2004) and imiquimod 5 % cream were effective as well (Jones 2007). Imiquimod is applied by the patient 3x/week (off label use). An inflammatory reaction (erythema), occurring after 3 to 4 weeks of topical treatment, indicates the beginning of the immune reaction, which leads to complete resolution of the mollusca after 6-8 weeks. In a Cochrane review van der Wouden et.al (2006) concluded: "No single intervention has been shown to be convincingly effective in treating molluscum contagiosum."

Oral hairy leukoplakia (OHL): is a clinical manifestation of Epstein-Barr virus infection, which is almost exclusively found in patients with untreated advanced HIV disease. Non-cytolytic viral replication in the glossal epithelium, especially in the lateral parts of the tongue, leads to asymptomatic white verrucous plaques that do not rub off. OHL is diagnosed on clinical findings; initially parallel white or grayish hyperkeratotic rows arranged vertically on the lateral aspects of the tongue are characteristic. Unilateral lesions are seen , but bilateral occurrence of plaques is more typical. Important differential diagnoses include other leukoplakias, lichen planus mucosae and oral candidiasis (Patton 2002, Cherry-Peppers 2003). If the diagnosis is in doubt, a biopsy or cytology can confirm the diagnosis. As the lesions will respond to antiviral drugs such as aciclovir, ganciclovir, or foscarnet (Walling 2003), but not antifungals, treatment can be used as a diagnostic tool to distinguish OHL from candidiasis. Both diseases however, respond well to HAART, which has led to a significant decrease (80-90%) of these oral diseases (Triantos 1997, Ramirez-Amador 2003). Topical treatments with podophyllin resin (25%) with or without acyclovir cream are effective (Moura 2007).

Pruritus: Chronic, often unremitting pruritus is one of the most frequent clinical symptoms of HIV infection. One in three patients is affected. Etiology remains un-

clear in most patients, and therefore only symptomatic treatment can be offered which may be unsatisfying (Moses 2003, Singh 2003). Pruritus in HIV-infected patients can be a complication of infectious diseases. Viral, bacterial, and fungal infections (e.g. *Malassezia furfur* folliculitis) and scabies can cause severe itching. Also, dry eczematous skin (xerosis), papulosquamous skin diseases, systemic lymphomas, renal insufficiency and hepatic disease are causative conditions. Finally, many antiretroviral and other drugs given to the HIV-infected patient can cause pruritus (with or without rash). It has been suggested that a viral load of more than 55 000 copies/ml are associated with pruritus (Zancanoro 2006).

To diagnose idiopathic pruritus, it is necessary to exclude all skin and systemic diseases mentioned above. In patients on HAART, it can be useful to change the treatment regimen. Systemic antihistamines and topical corticosteroids are symptomatic treatment standards. If they are ineffective, or a prolonged systemic treatment is necessary, phototherapy (UVA-1, UVB-311nm) or photochemotherapy (PUVA) is an alternative or adjuvant therapy. (Smith 1997, Gelfand 2001, Zirwas 2001, Singh 2003) Concerning the immunosuppressive effects of ultraviolet light, it seems that patients on HAART are at less risk.

Papular dermatoses: Patients can present either with monomorphic skin colored to red papules (size 2 – 5 mm) or with combined eruptions consisting of papules and pustules (sterile eosinophilic pustulosis Ofuji). There is no special predilection for any site. The etiology of papular eruptions is heterogeneous (Ramos 2006). According to the clinical presentation and to laboratory findings (elevation of IgE, eosinophilia in peripheral blood and affected skin) they resemble the prurigo of atopic dermatitis found in adults. Autoimmune reactions against follicular antigens have also been discussed (eosinophilic folliculitis; Nervi 2006)e). These papules can be due to a *hypersensitivity reaction* to drugs, microbiological agents (viruses, bacteria, fungi), parasites, or saprophytes (*Sarcoptes scabiei*, *Demodex folliculorum*, Malassezia and others). A drug history and microbiological and histological examinations (including special stains such as PAS) are required for a correct diagnosis.

If infections are identified, they are treated with antimicrobials. , . In the case of sterile eosinophilic pustulosis (Ojufi), or papular dermatosis of unknown origin, therapy is symptomatic. Depending on the clinical situation, antihistamines, itraconazole (200 mg/d for 2 weeks), isotretinoin, dapsone, mild PUVA or narrowband UVB or 5 % permethrin-cream can be tried . Topical tacrolimus (0.1 %) also was shown to be effective (Kawaguchi 2004).

Paronychia and ingrown nails: Ingrown toenails and inflammatory reactions of the proximal nailfold are a well known complication in diabetics, but also in patients on beta-blockers, or retinoid therapy. A few cases might be due to local pressure (poorly fitting footwear) or occur spontaneously. Patients on HAART are the most recent group of patients to regularly develop ingrown nails. These are ascribed to retinoid-like side effects of several antiretrovirals, especially indinavir, but also lamivudine and nelfinavir. Usually, the great toenails are involved, but all other toenails and fingernails can be affected. The therapy of choice , is to substitute indinavir or lamivudine with other antiretrovirals. This has led to complete remission in several of our patients. Surgical measures, such as Emmetplasty or its modification

after Hanneke, should only be performed on patients in whom the exchange of HAART medications did not lead to a remission after 3 to 6 months (Tosti 1999, Alam 1999, Garcia-Silva 2002).

Psoriasis vulgaris: Psoriasis is regarded as an autoimmune disease and affects approximately 1 % of the general population. It has multifactorial inheritance with variable penetrance. Physical stimuli such as friction and UV-light, or endogenous factors such as infections, drugs, and "stress" may trigger psoriatic flares. When HIV-infected persons are exposed to such factors, psoriasis may appear for the first time or can be aggravated. The incidence of psoriasis has been reported to be between 2.5 % (and 4.9 % (Schöfer 1990). Being a T-cell mediated disease, the pathomechanisms of severe and recalcitrant psoriasis in HIV infected patients with a substantial decrease in CD4 cell counts, are not well understood (Namazi 2004, Fife 2007). The use of antiretrovirals improves psoriasis.

Typical psoriatic plaques can be eruptive, guttate, or chronic and stationary.) Atypical findings include inverse localization on the palms or soles and in the genital region and axillae, exudative, pustular, or erythrodermic manifestations. In general, the severity of psoriasis parallels the impairment of the immune system. Besides infection, drugs have to be considered as possible triggers. In the final stages of HIV infection, psoriasis can be generalized and extremely resistant to therapy. Alternatively, the disease may disappear completely.

The typical psoriatic plaque is a sharply demarcated, erythematous plaque covered with silvery scales. Clinically and histologically, it may be difficult to differentiate from seborrheic dermatitis.

Triggering factors should be eliminated, if possible. Treatment is more difficult if the immune system is impaired. An antiretroviral therapy should be initiated or optimized. Localized lesions can be treated topically with corticosteroids, anthralins, calcium-agonists (calcipotriol or tacalcitol) or the topical retinoid, tazarotene. The scalp and nails can be treated topically with corticosteroids. Generalized or exudative eruptions are usually treated systemically: acitretin (25 – 75 mg/d) is not immunosuppressive. Methotrexate or cyclosporin are immunosuppressive and should be avoided. In some cases, however, it is necessary to use them. Several years ago, , the successful use of hydroxyurea was reported (Kumar 2001), but no further studies have been published. AZT has a beneficial effect on psoriasis, probably by improving the immune status. To treat refractory psoriasis, experimental therapies such as cimetidine (400 mg, 4x/d) have been tried successfully.

The clinical relevance of immunosuppression by UV-radiation is unknown. At present, it is believed that phototherapy or photochemotherapy have no real detrimental effect for HIV patients (Akarapathanth 1999, Schoppelrey 1999). These treatments are as effective as in patients without HIV-infectionNarrowband UVB) is well tolerated and effective. Broadband UVB can also be used.. In case of treatment failure, photochemotherapy can be instituted (local = bath or cream PUVA, or systemic PUVA). Interactions of the mentioned antipsoriatics with antiretroviral substances are unknown. Recently, several "biologics" were introduced for the therapy of psoriasis. These compounds specifically interact with certain elements of the inflammatory cascade in psoriasis, such as TNF-α and cause additional immunodefi-

ciency. . Although, restricted to exceptional cases, several authors reported promising treatment results. Long-term experiences are lacking (Bartke 2004, Ting 2006, Sellam 2007). **Reiter's syndrome:** Reiter's syndrome is regarded as a variant of psoriasis in patients who carry HLA B27. This rare chronic-relapsing disease mainly affects young men, the incidence being higher in HIV-infected men than in the general population (0.6 to 6 %; Kaye 1989). Recently, it was reported to occur as a symptom of IRIS.

The classical triad consists of: urethritis (sterile yellow urethral discharge), conjunctivitis (serous or purulent) and arthritis (mainly knee-, foot- or sacroiliac joints; causing pain and leading to immobility). The triad is found in about 30 % of patients. Furthermore, constitutional symptoms (attacks of fever, malaise, leukocytosis, elevated ESR) and skin lesions can be found. The skin lesions are characterized by erythema with sterile pustules on the palms and soles, and later, hyperkeratotic, scaling, exudative lesions known as keratoderma blenorrhagicum. Psoriatic plaques can be seen as well as the typical circinate balanitis presenting as crusting, desiccated plaques in circumcised men and shallow, moist, serpiginous, painless ulcers with slightly raised borders in uncircumcised men.

The diagnosis depends on the typical pattern of arthritis plus one or more of the mentioned clinical symptoms. Gonorrhea or Chlamydia urethritis have to be excluded by microbiological methods. Psoriatic arthritis should have other clinical signs of psoriasis (nail changes) and lacks fever.

Initially, symptomatic therapy with non-steroidal anti-inflammatory agents, or possibly corticosteroids (short-term, high-dose pulse-therapy) should be given. Acitretin (25 - 75mg/d) in combination with topical fluorinated corticosteroids has also proved to be effective as has been sulfasalazine.. Arthritis can be treated with oral gold. Doxycyline has been reported to induce remissions (Neumann 2003). There is one report on the successful use of infliximab in a patient with Reiter's syndrome without a negative impact on the HIV viral load (Gaylis 2003).

Scabies: Scabies can be found worldwide; the prevalence varies from < 1 % to 30 % depending on the socio-economic circumstances. Scabies is characterized by extreme pruritus, especially at night.. In the interdigital areas, volar sides of the joints of the hands, breasts, axillae, periumbilical region, or penile shaft, fine red burrows (S-shaped or straight lines) may be found. There may be a small papule or vesicle at one end. Excoriations and/or secondary infections make the identification of burrows difficult. Generalized eczematous eruption may be seen. Typically, in the groin or on the genitals, red-brown pruritic nodules are found. These scabies granulomas can persist for months, even after successful therapy.

In the case of severe cellular immunodeficiency, crusted scabies or Norwegian scabies can occur. Besides HIV-patients, persons with general physical or mental debilitation are affected. Over weeks to months, eczematous lesions covered with asbestos-like crusts extend over large areas and the plaques can be mistaken for psoriasis. Crusted scabies is extremely infectious and carries many more mites than regular scabies – up to 10,000 mites/g scales. The history of unremitting and intractable itching is suggestive of scabies. The diagnosis is made by the clinical picture and proven by the demonstration of the mites, their ova, or fecal droppings in

the scales by light microscopy of KOH treated scales. On histology, the female mite can be visualized in the stratum corneum.

A single application of permethrin 5 % cream is performed (whole body application from chin to toes, usually excluding the face; leave on skin for 8 hrs, then shower off). In cases of crusted scabies, the scales have to be removed over several days (salicylic ointments) and therapy has to be repeated over 3 – 4 days. Alternative therapies are: hexachlorcyclohexane (lindane), benzoylbenzoate, pyrethrum-extracts or allethrin/piperonylbutoxid, which all have to be applied for 3 days. It is important to treat all contactactants at the same time as well!

Linen and bed-clothes have to be changed daily. Depending on the clinical presentation, another treatment one week later is sometimes recommended ("safety-day"). In cases of severe immunodeficiency, the scalp has to be treated too.

If more than 50 % of the skin is affected, or several recurrences have occurred, a combination of keratolytic/topical therapy and systemic treatment with ivermectin is recommended. Oral therapy with 2 tablets (6 mg each; some 200µg/kg) repeated after one week is generally sufficient. But special attention should be payed to nail involvement, which is not treated sufficiently with ivermectin (Ohtaki 2003). Ivermectin is not licensed for this indication. There have been no reports of complications after this therapy in HIV-infected patients (Dourmishev 1998). Hygienic measures to prevent contact infections are extremely critical.

Seborrheic dermatitis: The incidence in the general population is estimated to be 3–5 % of all young men. The liphophilic yeast Malassezia furfur (formerly known as pityrosporum ovale) is believed to be of pathogenetic relevance. Here the specific subtype appears to be more important than the density of colonization. In HIV-infection 20–60 % are affected depending on the immune status. Seborrheic dermatitis appearing de novo or exacerbation of mild seborrheic dermatitis in a known HIV-positive patient could indicate seroconversion from a latency state to a symptomatic state (Ippolito 2000).

Areas rich in sebaceous glands, such as the scalp, forehead, eyebrows, nasolabial folds, over the sternum, between the shoulder blades, external ear canal, and retroauricular area, develop yellowish, oily scales and crusts on mildly erythematous to very red plaques. The lesions may be pruritic.

The clinical picture is typical in most cases. Differentiation from psoriasis may be difficult both clinically and histologically. Initially, other forms of eczema such as allergic contact dermatitis and atopic dermatitis may have similar presentations.

Due to the pathogenic role of pityrosporum ovale, topical antifungals such as ketoconazole cream, other topical imidazoles or triazoles, or alternatively selenium sulfide, metronidazole, and low-dose dithranol or lithiumsuccinate- and zinc-sulfate-creams are used. In addition, pimecrolimus 1% cream is an alternative in patients which do not respond to antifungals (de Moraes 2007). For the scalp, antimycotic shampoos, zinc pyrithione or tar-containing products are used. In severe cases, systemic antimycotics are given: ketoconazole (1 x 200 mg/d), itraconazole (1 x 100 mg/d) or terbinafine (250 mg/d) (Gupta 2004, Kose 2005).

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Syphilis: In general, syphilis in HIV-infected patients is not clinically different from syphilis in the immunocompetent host. In some patients however, atypical findings complicate the clinical and serological diagnosis as well as the treatment. In primary syphilis, painful anal or oral chancres occur. Persistent chancres can still be found when the exanthems of secondary syphilis and symptoms such as generalized lymphadenopathy appear. In secondary syphilis, syphilids can ulcerate and develop thick crusts (rupia syphilitica or rupial syphilid), which are accompanied by high fever and severe illness. This unusual and otherwise rare course of syphilis, which is termed "malignant" syphilis, is found in 7 % of all syphilis associated with HIV infection. In addition, early neurosyphilis and a very short latent period before the onset of tertiary symptoms of syphilis are described. Neurosyphilis is partly due to a reduced blood-brain barrier, and a failure of benzathine penicillin G to prevent neurosyphilis in these patients is reported. The interpretation of syphilis serologies, especially in patients with repeated infections and severe immunodeficiency, can be complicated by false negative results and persistent antibodies. Therefore, it is advisable to verify *T. pallidum* infection in any clinical manifestation suspected to be syphilis by direct proof (dark-field microscopy, direct fluorescent antibody testing of exudates, or biopsy specimens).

The recommended treatment of syphilis, which is penicillin for all stages of the disease, has not changed over the past 60 years. *T. pallidum* has developed some resistance against macrolides (erythromycin, azithromycin), but not against penicillin. Syphilis therapy, as recommended by the CDC, WHO, and the German STD Society (DSTDG) is identical for HIV-infected and non-HIV-infected patients. It is advised however, not to use benzathine penicillin G in patients, in whom early neurosyphilis cannot be excluded. If neurosyphilis is suspected by clinical symptoms, and the patient refuses CSF puncture, high-dose penicillin G (6x5 Mega or 3x10 Mega IV should be given for 2 (early syphilis) or 3 weeks (late syphilis). Ceftriaxone, 1-2g/day IM or IV for 10 days (early syphilis) or 2 weeks (late syphilis) is a widely used, but not approved alternative.

Standard regimens for early syphilis (primary and early secondary syphilis until one year after infection) are procaine penicillin G, 1.2 million units IM/day for 14 days, or benzathine penicillin G, 2.4 million units IM in a single dose, injected into different sites.

Late syphilis (any stage of disease at more than one year after infection and any syphilis of unknown duration, excluding neurosyphilis) is treated like early syphilis, but for three weeks instead of two weeks. (For more details about HIV and T. pallidum coinfection, see Chapter "HIV and Sexually Transmitted Diseases"). HIV-infected patients should be evaluated clinically and serologically for failure of treatment at 3, 6, 9, 12, and 24 months after therapy.

Xerosis/Dry skin: Dry skin is a very frequent complication of any kind of immunodeficiency. In the pre-HAART-era, we diagnosed dry skin in one in three HIV-infected patients (see Table 1). The patients complain of dry, itchy skin, which is exacerbated by a multitude of stimuli. Overall, these skin problems are very much like atopic dermatitis (Rudikoff 2002) and can culminate in acquired ichthyosis. The prevalence of dry skin in HIV-infected patients decreased after the introduction of HAART, but is sometimes seen in patients on indinavir (Garcia-Silva 2000,

Singh 2003). Some years ago, we showed that the lipid film of the skin surface has a different composition in HIV-infected patients, but is not diminished in quantity (C. Semrau: unpublished data, doctoral thesis).

Dry itchy skin is treated with the application of emollients that contain 5 to 10 % urea, or 3 to 4 % lactic acid, and dexpanthenol. If the patients take too many showers, the frequency should be reduced to one shower every (other) day, and 1 to 2 oil baths per week should be recommended. In cases with severe inflammation and fissures (eczema craquele) topical class 3 or 4 corticosteroids are very helpful in reducing the patients symptoms. They should not be used for longer than 3 to 5 days.

Appendix 2:

Skin and mucocutaneous disease related to antiretroviral drugs

1. Nucleoside analog reverse transcriptase inhibitors (NRTIs)

AZT, zidovudine, Retrovir™: Drug eruptions (6 %) mostly macular, rarely severe reactions such as erythema multiforme and Stevens-Johnson syndrome, melanonychia striata medicamentosa, pigmentation and lichenoid eruptions of mucosal membranes, vasculitis, urticaria, pruritus, hyperhidrosis (5-19 %), tongue ulcers.

ddI, didanosine, Videx™: Drug eruptions and itching (4 %), erythema multiforme, oral dryness (30 %), papuloerythrodermia Ofuji.

d4T, stavudine, Zerit™: Drug eruptions with fever.

3TC, lamivudine, Epivir™: Exanthems, vasculitis, light sensitivity, linear nail hyperpigmentation, hair loss, paronychia, ingrown toenails.

FTC, emtricitabine, Emtriva™: Exanthems, especially in combination with ddI and efavirenz (10 %), cause unidentified.

ABC, abacavir, Ziagen™: Maculopapular exanthems, hypersensitivity syndrome (5 %) after 9 (3-42) days, frequently associated with respiratory problems, nausea, and vomiting, increase in liver transaminases. Any suspicion of hypersensitivity syndrome forces immediate cessation of treatment (Clay 2002). Abacavir re-exposure is contraindicated (severe, sometimes lethal reactions). For details of the management of abacavir hypersensitivity syndrome, see alphabetical drug register.

Tenofovir, Viread™: rare exanthemas.

2. Non-nucleoside analog reverse transcriptase inhibitors (NNRTIs)

Nevirapine, Viramune™: frequent drug eruptions (33 %), severe reactions 6 % (mostly within the first 6 weeks of treatment), Stevens-Johnson syndrome 0.5 %, and few cases of toxic epidermal necrolysis. Less frequent drug reactions (22 %), when therapy is initiated with low doses, and very low rate, when HLA-Cw 8 positive patients are excluded from nevirapine therapy (Gatanga 2007). Cetirizine, as a

prophylactic, is not effective (Launay 2004). Treatment must be stopped in 3-5 %. Reasons are severe skin reactions, exanthemas with fever, conjunctivitis, pain of the limbs, meningitis, eosinophilia (DRESS syndrome = Drug rash with eosinophilia and systemic symptoms; Bourezane 1998, Lanzafame 2001), occasionally diffuse loss of hair. Exanthems are 7x more frequent, and therapy has to be stopped 3.5 x more often in women compared to men (Bersoff-Matcha 2001). According to the producer's report (Boehringer Ingelheim, February 2004), complications have to be expected mainly during the first 6 weeks of treatment (up to 18 months). During this period, hepatotoxic reactions with high transaminases and exanthemas are frequent. Patients, especially women older than forty, with residual cell mediated immune functions (CD4 cells > 250/µl), are particularly at risk.

Delavirdine, Rescriptor™: Maculopapular or erythematous rashes, with or without pruritus in up to 50 %, starting 2-3 weeks after initiation of treatment and involving especially the trunk and upper arms. Mild exanthems without other complications can regress spontaneously without a need to discontinue treatment.

Efavirenz, Sustiva™: Frequent macular or urticarial exanthems (11 %). Light exanthems can regress spontaneously without discontinuation of treatment. In case of complications, it is necessary to stop treatment. Fat wasting.

3. Protease inhibitors (PI)

Saquinavir, Invirase™: Aphthous oral lesions (6 %), cheilitis, exanthems- (4 %), rarely Stevens-Johnson syndrome, bullous eruptions, papular pruritic folliculitis.

Ritonavir, Norvir™: exanthems (0.9-2.6 %), papular pruritic folliculitis (8 %), perioral paresthesia (25 %).

Indinavir, Crixivan™: In many patients a sicca syndrome with very dry skin, dry mouth and eyes is observed. In addition, exanthems are frequently papular and intensely itching, involving the lateral parts of the upper arms, the upper trunk and the lateral neck in particular, can occur. Differential diagnosis: papular pruritic eruption (folliculitis). Paronychia (pyogenic granuloma-like) and ingrown toenails, light diffuse loss of hair (12 %), severe and generalized loss of terminal and vellus hair in 1-2 %. Hematoma and hemarthrosis in hemophiliacs. Lipodystrophy ("Crixi-belly", buffalo hump, facial lipotrophy, etc.), metabolic syndrome and asymptomatic hyperbilirubinemia.

Nelfinavir, Viracept™: Exanthems (infrequent), paronychia (single cases, Dominguez 2007).

Amprenavir, Agenerase™: Exanthems (3 %, mostly starting during the 2nd week of treatment, Pedneault 2000), perioral paresthesia.

Atazanavir, Reyataz™: Exanthems (Goldsmith 2003), hyperbilirubinemia, in some cases with jaundice and scleral icterus (Orrick 2004).

Lopinavir/r, Kaletra™: Exanthems (infrequent). Lipodystrophy.

4. Entry-Inhibitors

T-20, Enfuvirtide, Fuzeon™: Erythems and indurations at the injection sites (96%, almost obligatory), exanthems <1% (Ball 2003).

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22. HIV and Sexually Transmitted Diseases

T. Lorenzen and Katrin Graefe

Syphilis

Syphilis, also called Lues, is caused by Treponema pallidum. The risk of transmission is greatest in the early stages of the disease, especially if skin or mucosal ulcers are present. For a single unprotected sexual contact, the risk of transmission is about 30 to 60 %. Like other STDs, syphilis favors the transmission of HIV due to lesions in the genital mucosa. In some European and North-American areas, the incidence of syphilis has increased within the last 10 years to levels last seen in the mid twentieth century. In some metropolitan regions, the rates of newly diagnosed infections has multiplied.. The highest incidence of syphilis in Europe in 2006 was seen in baltic areas.

Symptoms

Classic syphilis progresses in four stages, listed in Table 1:

Table 1: Course of classic syphilis

Stage	Typical clinical appearances	Time since infection
Lues I	Ulcus durum / chancre	approx. 3 weeks
Lues II	Disseminated exanthemas	approx. 6-8 weeks
Lues III	Tuberous syphilis, gumma	several years
Lues IV	Tabes dorsalis, progressive paralysis	decades

In HIV-infected patients, the latency period between stage II and the late stages III and IV may be significantly shorter than usual. In some cases, symptoms of the different stadiums may be present at the same time.

Furthermore, unusual manifestations with dramatic skin ulcers or necrosis, high fever and fatigue are described. Occurrence of these clinical symptoms is called *Lues maligna* (Gregory 1990).

Another unusual aspect in HIV-infected patients is a possible endogenous reactivation after prior Treponema pallidum infection.

Diagnosis

Routine screening for syphilis with TPHA, TPPA or VDRL may not be reliable in HIV-infected patients. False-negative results can be explained by inadequate production of antibodies or by suppression of IgM production due to exorbitant IgG levels. In case of doubt, specific tests such as FTA-ABS (IgG and IgM) or cardiolipin tests should be carried out.

In erosive skin or mucosal lesions, dark field microscopy should be performed to demonstrate Treponema pallidum directly.

In cases where infection has been proven serologically, a neurological examination should be performed, especially on HIV-infected patients because of the merging of clinical stages. Patients with neurological symptoms should undergo cerebrospinal fluid examination, which is particularly important for making decisions regarding the type of therapy (intramuscular or intravenous).

Therapy

Therapy of syphilis should be adapted to the stage of disease.

Recommendations for the early stages of syphilis include three intramuscular injections of benzathine penicillin 2.4 MU administered in weekly intervals (Anglo-American recommendations: only twice).

In cases of penicillin intolerance, doxycycline (2 x 100 mg), tetracycline (4 x 500 mg) or erythromycin (4 x 500 mg) can be administered orally for 4 weeks, but these drugs are considered to be less effective than penicillin. Consequently, patients should be treated with the same scheme used in neurosyphilis.

Neurosyphilis is usually treated with 5 MU benzylpenicillin given intravenously every 4 hours for 21 days. Other recommendations prefer administration of benzylpenicillin for 14 days, followed by three intramuscular doses of 2.4 MU benzathine penicillin given at weekly intervals.

In cases of penicillin intolerance, neurosyphilis can also be treated with 2 g intravenous ceftriaxone once daily for 14 days. Observational studies in small groups suggest ceftriaxone to be as effective as penicillin in the treatment of syphilis. However, cross-sensitivity may occur.

Alternative treatment options are doxycycline 2 x 100-200 mg per day or erythromycin 4 x 500 mg per day for at least 3 weeks. When treating with macrolides, the possible development of resistance should be considered (Lukehart 2004).

On initiation of syphilis therapy, one should be aware of a possible Jarisch-Herxheimer reaction. This reaction is caused by a massive release of bacterial toxin due to the first dose of antibiotic given. By triggering inflammation mediators, patients may experience shivering, fever, arthritis or myalgia. The symptoms of the Jarisch-Herxheimer reaction may be avoided, or at least reduced, by administering 25-50 mg of prednisolone prior to the first dose of antibiotic.

Serological controls should be performed at 3, 6 and 12 months after syphilis therapy. Because of a possible endogenous reactivation or reinfection in some patients, annual controls should be considered.

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Gonorrhea

Gonorrhea, also called the clap, is caused by Neisseria gonorrhea, a diplococcal bacterium. It is typically localized in the genitourinary mucosa, but infection may also occur orally or anally. Transmission is almost exclusively through sexual activity (exception: neonatal conjunctivitis), and the incubation period is about 2 to 10 days. Co-infection with Chlamydia occurs frequently.

Symptoms

In men, primary symptoms are dysuria and urethral pain. A typical symptom is purulent secretion from the urethra, especially in the morning (“bonjour-drop”). Without treatment, the infection can ascend and cause prostatitis or epididymitis, leading to symptoms such as pain in the perineal region or scrotum or swelling of the scrotum.

In women, the course of gonorrhea is often asymptomatic, although vaginal discharge or purulent dysuria may occur. Involvement of the cervix and adnexa is rare, but if left untreated, may lead to pelvic inflammatory disease with subsequent infertility.

Extragenital manifestations of gonorrhea occasionally cause pharyngitis or proctitis. Systemic infections with symptoms such as shivering, fever, arthritis or endocarditis are rare (Rompalo 1987).

Diagnosis

The diagnosis of gonorrhea is confirmed by microscopy. In a dye-staining test with methylene blue or gram stain, the intracellular diplococci of Neisseria gonorrhea are traceable. This kind of diagnosis can directly be performed within several minutes at many sites. Other methods, such as serological examination, PCR or laboratory culture are also accurate, but are more complex and more expensive.

Therapy

An isolated gonorrhea is usually treated with a single dose of ciprofloxacin 500 mg orally. Other effective antibiotics are Levofloxacin 250 mg or Ofloxacin 400 mg.

Recently, some international surveillance authorities reported an increasing number of fluoroquinolone-resistant bacterial isolates. Consequently, the American Centers for Disease Control and Prevention suggest a single dose of cefixime 400 mg orally or ceftriaxone 125 mg as intramuscular injection for the treatment of gonorrhea in high-risk patients. Intramuscular administration of spectinomycin has been an option, but it is effective only in urogenital and anorectal infection, not in pharyngeal gonorrhea (CDC 2004). For these reasons, a pragmatic and sufficient therapy seems to be a single dose of azithromycin 1 g or doxycycline 100 mg twice daily for 7 days. These therapeutic options also treat a possible co-infection with chlamydia species (see following chapter).

In all cases of gonorrhea, the sexual partners should also be screened for infection and treated if necessary.

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Chlamydia infection

Infections with Chlamydia trachomatis are nearly twice as prevalent as gonococcal infections. The serovars D–K cause genitourinary infections and, if vertically transmitted, conjunctivitis or pneumonia in the newborn.

The serovars L1–3 cause Lymphogranuloma venereum. This disease is usually considered to be a tropical disease, rarely occurring in industrialized countries. However, for several years, Lymphogranuloma venereum has undergone a renaissance

in Europe and USA (Gotz 2004, Krosigk 2004). Actually, the described outbreaks are under investigation by international surveillance authorities, which are working on management strategies.

Symptoms

In men, a genital infection with Chlamydia is usually asymptomatic. If symptoms occur, they may be present as urethral discharge, burning or unspecific pain in the genital region. As in gonorrhea, an epididymitis, prostatitis or proctitis may occur. Reiter's syndrome with the triad reactive arthritis, conjunctivitis and urethritis is also possible.

In women, a chlamydial infection often does not cause any symptoms. But in about 20 % of female patients, unspecific symptoms such as discharge, burning or, more often, polyuria may occur as an expression of urethritis or cervicitis. Some of the patients also suffer from pelvic inflammatory disease involving the adnexa. This disease pattern can lead to later complications such as infertility or ectopic pregnancy due to tubal occlusions.

In Lymphogranuloma venereum, a primary lesion occurs at the entry location. Some weeks later, a tender lymphadenopathy develops which is mainly unilateral. These swollen lymph nodes may grow into large bubo that tend to ulcerate, possibly leading to scars and lymphedema.

Diagnosis

A chlamydial infection may be suspected based purely on clinical symptoms. Gene amplification methods (PCR, LRC) are the best procedures for confirming the diagnosis. Sensitivity is superior to, while specificity is nearly equal to results obtained by culture (Morre 2005). To achieve optimum results, a dry cotton wool wad should be used to collect some epithelioid cells, which should be sent to the laboratory in dry storage.

Other direct tests such as ELISA or direct immunofluorescence are also possible, but there is a lack of sensitivity in populations with low prevalence.

Therapy

The therapy of choice is doxycycline, 2 x 100 mg for 7 days. International guidelines also recommend 1 g azithromycin, given as a single dose, as an equally potent therapy, but which costs nearly twice as much as doxycycline in many countries. Alternatively, ofloxacin 2 x 200 mg or erythromycin 4 x 500 mg for 7 days can be given.

Lymphogranuloma venereum requires a longer treatment, with doxycycline being administered for a minimum of 3 weeks.

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Chancroid

Chancroid, also called *Ulcus molle*, is caused by Haemophilus ducreyi, a gram-negative bacterium. It is an endemic infection found primarily in tropical or subtropical regions of the world. In the industrialized countries, it appears to be mainly an imported disease, with only a few cases being reported by the national authorities.

Symptoms

Usually, the incubation period is about 2–7 days. After transmission, one or more frayed-looking ulcers may appear at the entry location, usually in genitourinary or perianal locations. These ulcers are typically not indurated, unlike the primary ulcers of syphilis (therefore the Latin name *Ulcus molle*). Characteristically, they cause massive pain. In about half of the patients the inguinal lymph nodes are swollen and painful, mostly unilaterally. Balanitis or phimosis occurs less frequently.

Diagnosis

Suspected chancroid is difficult to confirm. Clinically, other ulcer-causing STDs such as syphilis or herpes simplex infections have nearly the same symptoms. Microscopy of ulcer smears may demonstrate gram-negative bacteria, but diagnosis should be confirmed from a culture of scrapings from the ulcer or pus from a bubo. Sometimes, a biopsy from the ulcer becomes necessary to differentiate it from a malignoma.

Therapy

Therapy should be conducted using a single dose of 1 g oral azithromycin (Martin 1995). Ceftriaxone 250 mg intramuscularly, as a single dose, is equally potent. Alternative therapies are ciprofloxacin 2 x 500 mg for three days or erythromycin

4 x 500 mg for 4-7 days. In fluctuant buboes, needle-aspiration of pus may be indicated.

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Condylomata acuminata

Condylomata acuminata are caused by human papillomaviruses (HPV). They are usually present as genital warts, but other locations (oral) are known to be involved. HIV-infected patients have a higher risk of acquiring genital warts.

The typical pathogens, human papillomavirus type 6 or type 11, are not normally considered to be cancerogenic. Although, in both male and female HIV-infected patients, epithelial atypia is seen more often than in uninfected persons.

Besides sexual transmission, infection with papillomavirus may be possible via smear infection and perhaps through contaminated objects. But the primary risk factor remains the number of sexual partners (Karlsson 1995).

Symptoms

Generally, genital warts remain asymptomatic. Pruritus, burning or bleeding is rare and generally caused by mechanical stress.

Malignant degeneration of genitourinary papillomavirus infections (HPV 16, 18, etc.) is the most important complication. In contrast to HPV-associated cervical carcinoma, genital or anal carcinoma rarely develops on underlying Condylomata.

Diagnosis

Condylomata acuminata is a clinical diagnosis. Further diagnostic tests should be considered in case of persistence despite therapy or an early relapse. In addition to histological examination, direct HPV detection, including subtyping, is possible to differentiate between high and low risk types. Actually, this procedure is mainly instrumental in gynecology in case of ambiguous histologies (Ledger 2000).

Therapy

Treatment of genital warts is performed surgically by electrosurgery, cryotherapy, curettage, or laser. Chemical interventions with podophyllin or trichloroacetic acid are also possible. Other methods have been recommended. In daily clinical practice, a surgical intervention followed by adjuvant immunotherapy with interferon beta or (possibly more effective) with imiquimod reduces the rate of relapse and seems to be the best choice for patients.

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23. HIV and Cardiac Diseases

Till Neumann

Metabolic abnormalities are common side effects of antiretroviral therapy. It is expected that the incidence of premature cardiac and cardiovascular diseases will rise due to the elevated cardiovascular risk profile and increased life expectancy of HIV-infected patients (Fisher 2001, Neumann 2002a). Therefore, diagnosis and therapy of HIV-associated cardiovascular diseases have to be an inherent part of current medical concepts of HIV infection.

Coronary artery disease (CHD)

Premature atherosclerosis in HIV-infected patients was described shortly after the introduction of antiretroviral therapy. The observations were affirmed by an autopsy trial, reporting a significant increase of atherosclerotic plaques over the last two decades in HIV-infected individuals (Morgello 2002) and byan augmented rate of coronary artery calcification in HIV patients treated with protease inhibitors (Robinson 2005, Meng 2002).

In contrast to case reports and autopsy trials analyzing the influence of antiretroviral therapy on myocardial infarction rate, the results of clinical observations appear to be inconsistent. At present, two major clinical trials have been published, and in one of these trials, a retrospective analysis of 36,500 patients, no rise in cardiac or cardiovascular events was detected (Bozzette 2003). Nevertheless, in the second trial, the most extensive prospective study to date, including more than 23,000 patients, a 26 % increase in the incidence of myocardial infarction was found with each year of antiretroviral therapy (Friis-Moller 2003). The increased risk of myocardial infartion was associated with an increased exposure to protease inhibitors, which is partly explained by dyslipidemia (Friis-Møller N 2007).

Today most trials indicate an effect of ART on medical infarction (Obel 2007). Therefore, it could be estimated, that the interruption of ART might reduce the rate of cardiovascular events. Yet, the SMART trial found an elevated rate of cardiovascular events in patients with interruption of antiretroviral therapy compared with a group of patients without interruption of medical therapy, which makes the answer of the impact of ART on myocardial infarction even more complex (El-Sadr WM 2006). However, the total incidence of myocardial infarction was small in all trials. Therefore, current treatment regimens for HIV infection might have no considerable impact on myocardial infarction rate and the concerns of cardiovascular complications have to be balanced against the marked benefits of antiretroviral treatment. Nevertheless, prevention of coronary heart disease should be integrated into current treatment procedures of HIV-infected patients.

Prevention

Prevention is crucial, as the occurrence of cardiovascular disease is strongly related to lifestyles and modifiable risk factors. It has been shown that HIV-infected patients exhibit a marked cardiovascular risk profile (Neumann 2003, 2004a, 2004b).

Most notably, in some countries the cigarette consumption is two- to three-fold higher than in the non-HIV-infected population.

Furthermore, an association between antiretroviral drugs and lipid concentrations, i.e. hypercholesterolemia and hypertriglyceridemia, has been reported (Stocker 1998, Sullivan 1997). These lipid alterations might jeopardize the benefits of antiretroviral therapy by increasing the risk of coronary disease (Grover 2005). Lipid alterations were first shown with protease inhibitors, but there is now evidence that some NRTIs and NNRTIs have an unfavorable effect on lipids too. In addition to hyperlipidemia, insulin resistance has also been described in association with PIs (Behrens 1999, Noor 2001). However, new PIs such as atazanavir have a considerably more favorable lipid profile. Other authors presume an effect of virus antigens on the development of atherosclerosis (Hsue 2007),

Prevention of coronary heart disease is based on the guidelines for non-HIV-infected patients (De Backer 2003; Table 1). Cessation of smoking and healthy food choices are the first steps in the therapy of hypercholesterolemia. The consumption of fruits, vegetables, whole grain bread and low fat dairy products in an energy balanced diet should be encouraged. The second step relies on lipid lowering drugs (Dube 2003). Good results were observed using a combination of statin (atorvastatin 10 mg/d) and fibrate (gemfibrozil 600 mg bid) (Henry 1998). However, an increased risk of rhabdomyolysis is suspected, and thus caution is required.

Table 1: Prevention of coronary heart disease

1)	**Cease Smoking**	
2)	Make healthy food choices	
3)	Normalization of lipids	
	a. LDL-Cholesterol:	
	- low risk (0-1 risk factors):	< 160 mg/dl (4.14 mmol/l)
	- intermediate risk (2 or more risk factors):	< 130 mg/dl (3.36 mmol/l)
	- high risk (i.e. CHD or diabetes mellitus):	< 100 mg/dl (2.59 mmol/l)
	b. HDL-Cholesterol:	> 35 mg/dl (0.90 mmol/l) (increased risk > 40 mg/dl)
	c. Triglycerides:	< 200 mg/dl (5.17 mmol/l) (increases risk < 150 mg/dl)
4)	Optimize blood glucose value (HbA1c < 6.5 %)	
5)	Reduce alcohol consumption (< 15 g/d)	
6)	Regular exercise training (1-2 h per week)	
7)	Normalization of weight (BMI of 21-25 kg/m²)	
8)	Optimize blood pressure (systolic: < 130 mmHg, diastolic < 85 mmHg)	

Furthermore, statin therapy might interact with the metabolism of common antiretroviral drugs. In particular, several PIs act as substrates for isoenzyme 3A4, a subgroup of the cytochrome p450 system. Inhibition of isoenzyme 3A4 by antiretroviral drugs can increase the blood concentration of statins and, therefore, induce side effects (Dube 2000). In contrast to most other statins, pravastatin and fluvastatin are

not modulated by isoenzyme 3A4. Therefore, these two drugs are preferred by some authors for the therapy of HIV-infected patients being treated with antiretroviral drugs.

Diagnosis

HIV-infected patients with cardiovascular risk factors or of elevated age should undergo an annual cardiac check-up, including a resting ECG and estimation of the cardiovascular disease risk with the help of the SCORE system (De Backer 2003). The time between two cardiac controls should be shortened in case of high cardiovascular risks. Symptomatic patients also need further detailed cardiovascular examinations (exercise ECG, stress echocardiography, laboratory work-up and, in some cases, scintigraphy of myocardium or coronary angiography). Clinical symptoms of coronary heart disease mostly occur due to a critical stenosis of more than 75 %. Therefore, the onset of new cardiac symptoms or an increase in gravity, duration or frequency, referred to as acute coronary syndrome, needs direct and immediate clarification (Erhardt 2002).

Therapy

In randomized clinical trials, low-dose aspirin (100 mg/d), or in some cases clopidogrel (75 mg/d), β-blockers, ACE inhibitors, and statins, decreased the risk of mortality and re-infarction. A calcium antagonist and/or nitrate can be supplemented for symptomatic treatment.

The indication for vascular intervention (coronary angiography, including percutaneous transluminal catheter angioplasty and stent implantation) depends on the current guidelines (see http://www.escardio.org/knowledge/guidelines). Clear indications for invasive diagnosis are a documented exercise-induced ischemia, typical clinical symptoms together with ST-alterations in the ECG, increases in cardiac enzymes and/or a marked cardiovascular risk profile. It is worth emphasizing that HIV infection is not an exclusion criteria for invasive procedures. Successful cardiac interventions have been performed on HIV-infected patients, including catheter procedures and coronary artery bypass operations (Escaut 2003, Bittner 2003, Ambrose 2003).

Congestive heart failure

Congestive heart failure includes a variety of myocardial alterations. In HIV-infected patients, the HIV-associated dilated cardiomyopathy is of major interest and a significant clinical problem in HIV-infected patients (Twagirumukiza 2007).

Etiology

Myocarditis is still the most thoroughly studied cause of dilated cardiomyopathy in HIV disease. Until now, a variety of pathogens has been found in the myocardial tissue of HIV-infected patients (Patel 1996, Wu 1992). Furthermore, human immunodeficiency virus itself appears to infect myocardial cells in a patchy distribution. Although it is unclear how HIV-1 enters CD4-receptor-negative cells such as car-

diomyocytes, reservoir cells may play a role in the interaction between HIV-1 and myocytes.

In addition to a direct impact of the human immunodeficiency virus or other pathogens, dilated cardiomyopathy was reported in association with an autoimmune reaction. Cardiac-specific autoantibodies (anti-α-myosin antibodies) have been reported in up to 30 % of HIV-infected patients with cardiomyopathy. However, several studies also indicate that in HIV-infected patients, dilated cardiomyopathy is associated with cardiotoxic agents (e.g. pentamidine, interleukin-2, doxorubicin), cytokines (Monsuez 2007) or as the sequelae of malnutrition (Nosanchuk 2002). Furthermore, it is expected that antiretroviral therapeutic drugs may induce cardiac dysfunction due to mitochondrial toxicity (Lewis 2000, Frerichs 2002).

The frequency of clinical, symptomatic dilated cardiomyopathy is estimated to be between 1 and 5 %. However,in one study, only 30 % of HIV-infected individuals with ventricular malfunction could be identified by characteristic clinical symptoms (Roy 1999). In African countries, HIV-associated cardiomyopathy is a significant clinical problem in up to 18% (Twagirumukiza 2007). Thus, reliance on clinical features of heart failure only, will fail to identify patients who might benefit from treatment.

Diagnosis

The diagnosis of chronic heart failure is based on clinical findings and symptoms. In addition to exercise intolerance, patients often exhibit dyspnea and edema. Nocturia, nightly cough (cardiac asthma), peripheral cyanosis and an increase of weight may also occur. In these cases, ECG, chest x-ray and echocardiography may lead to the diagnosis of heart failure.

A new parameter in the diagnosis of heart failure is the b-type natriuretic peptide (BNP) or NTproBNP. This peptide has the power to distinguish between lung and cardiac malfunction.

Exercise intolerance can be determined by a 6-minute walk test, exercise ECG or spiroergometry. In some cases, further diagnosis can be performed with magnetic resonance tomography (MRT) or computer tomography (CT) revealing information about etiology and type of cardiomyopathy (Breuckmann 2007). Invasive diagnosis including myocardial biopsies is often recommended in unknown cases of chronic heart failure. Stable chronic heart failure patients in a low stage should be controlled annually. In a higher stage, the controls should include ECG, echocardiography and occasional BNP measurements every 6 months.

Therapy

The therapy of congestive heart failure depends on current guidelines (www.escardio.org/knowledge/ guidelines) and begins with moderate and regular exercise in combination with a healthy diet, including a reduced fluid and salt intake. Non-steroidal anti-rheumatics (NSAR), class I antiarrhythmics and calcium antagonists (verapamil, diltiazem and short-acting dihydropyridine derivates) should be used carefully.

Treatment of congestive heart failure includes:

- from NYHA I (asymptomatic heart failure):

ACE inhibitor or AT1-antagonists (control blood pressure and renal function)

beta-blocker for patients after myocardial infarction (beginning with low dose therapy under regular control of blood pressure and heart rate. If a low-dose therapy is tolerated, the beta-blocker medication should be increased slowly).

- from NYHA II (slight limitation of physical activity):

  beta-blockers for all patients, digitalis glycosides and diuretics.
- from NYHA III (marked limitation of physical activity):

  spironolactone (low dose with controlled potassium).
- from NYHA IV (unable to carry out any physical activity)

  reinforce medical treatment (combination of diuretics), consider heart transplantation (Jahangiri 2007), reconsider any surgical improvement and device implantation

NYHA III and NYHA IV require cooperation with a cardiologist. In the presence of ventricular arrhythmia, the indications for an implantable cardioverter defibrillator (ICD) have to be considered.

Therapeutic options that could eliminate the causes of heart failure (such as operative valve replacement in the case of a primary vitium or intensive antibiotic therapy for bacterial myocarditis) have priority. In these cases, cooperation with a specialized center is recommended.

Prognosis

Chronic heart failure is associated with a reduced life expectancy. In cases of NYHA III-IV, the annual mortality rate rises by up to 30 %. While in some cases, a total recovery was described (Fingerhood 2001, Tayal 2001), the majority of patients with HIV-associated dilated cardiomyopathy still have a progression of left ventricular dysfunction (Felker 2000). It is still unclear whether antiretroviral medication has an influence on the recovery of ventricular function. Early diagnosis and conventional therapy seem to be the most promising ways to reduce the progression of disease.

Pericardial effusion

Before effective antiretroviral drugs were available, pericardial effusion was the most frequent cardiac manifestation. In clinical trials, the incidence of pericardial effusions was recognized to be as high as 11 % per year (Heidenreich 1995). However, the majority of HIV-associated pericardial manifestations are described as asymptomatic. Nevertheless, the spectrum ranges from acute or chronic pericarditis to an acute pericardial tamponade (Silva-Cardoso 1999) and may result in constrictive pericarditis (Sa 2006). Pericardial diseases could be caused by HIV itself, further pathogens, or neoplasms (Stotka 1989). In a recent report from South Africa, where pericardial effusion is obviously still more common than in Europe or North America, 96 % of HIV patients with large pericardial effusions had tuberculous pericarditis (Reuter 2005). However, non-HIV-associated causes of pericardial effusion, such as uremia, trauma, irradiation, and drugs, have to be considered. In

some cases of lipodystrophy an increase in the cardiac lipid tissue could simulate an extensive pericardial effusion (Neumann 2002c).

Echocardiography is referred to as the standard method for diagnosis and control of pericardial diseases. Nevertheless, further diagnosis should be performed by computer tomography and/or magnetic resonance tomography when a neoplasm or an increase in the cardiac lipid tissue is suspected. Pericardial puncture has to be considered for symptomatic patients. If possible, a causative therapy should be applied. Pericardiotomy might be an option in palliative care.

Cardiac arrhythmias

Cardiac arrhythmias can depend on medication (Anson 2005). Antiretroviral drugs, e.g. atazanavir, efavirenz, foscarnet, pentamidine, or co-therapy with methadone, are expected to prolong the QT interval, an alteration in ECG, which might cause "Torsade de pointes" tachycardia (Castillo 2002, Chinello 2007, Ly 2007). Further drug combinations such as a macrolide and a chinolone may have the same effect on the QT interval.

Initiation or change of medication, which might influence the QT interval, should be controlled daily by ECG. In case of arrhythmias, electrolyte and glucose concentrations have to be determined and corrected if necessary. Magnesium may be used for termination of torsades de pointes tachycardia.

Valvular heart disease

Valvular heart disease of HIV-infected patients occurs as a bacterial or mycotic endocarditis. In fact, the hypothesis that HIV infection alone makes a subject more susceptible to infective endocarditis could not be validated. However, intravenous drug abusers have a ten- to twelve-fold increased risk for infective endocarditis than non-intravenous drug abusers (Nahass 1990). The most frequent germ is staphylococcus aureus, being detected in more than 40 % of HIV-infected patients with bacterial endocarditis. Further pathogens include Streptococcus pneumoniae and Hemophilus influenzae (Currie 1995). Mycotic forms of endocarditis, which may also occur in patients who are not intravenous drug abusers, mostly belong to Aspergillus fumigatus, Candida species or Cryptococcus neoformans and are associated with a worse outcome (Martin-Davila 2005).

Even if non-drug-abusing HIV patients are not more susceptible to infective endocarditis, the clinical course of the infection is more severe and the outcome worse than in a non-HIV-infected population (Smith 2004).

Signs of infective endocarditis include fever (90 %), fatigue, and lack of appetite. An additional heart murmur may also be present (30 %). In these cases, repeated blood cultures should be taken and transesophageal echocardiography is mandatory (Bayer 1998). Due to the fact that the detection of the infectious agent is often difficult, an antibiotic therapy has to be started early, even without the microbiology results.

In most cases, previously damaged valves are affected. Therefore, antibiotic prophylaxis is recommended in all persons with a previously damaged endocardium and planned interventional procedure, e.g. dental work or operations on the respi-

ratory or gastrointestinal tract. For diagnosis, antibiotic prophylaxis, and choice and length of antibiotic treatment, please refer to your local cardiologist and to the European guidelines for infective endocarditis (http://www.escardio.org/knowledge/guidelines/).

Further cardiac manifestations

Heart neoplasms are rarely found in HIV-infected patients. These manifestations occur predominantly in the advanced stages of the disease. On autopsy, the rates of cardiac-localized Kaposi's sarcoma and lymphoma are less than one percent.

Some infections of the heart in HIV-positive subjects may not only result in myocarditis but in abscesses. Several opportunistic pathogens including toxoplasma and trypanosomes have been reported to causes abscesses in the heart. These manifestations are believed to decrease with the introduction of HAART.

As well as neoplasms and abscesses, vascular alterations including vasculitis and perivasculitis have been described as further cardiovascular manifestations in HIV-infected patients. In particular, the function of the pulmonary vessels can deteriorate, resulting in pulmonary arterial hypertension and, consequently, right heart failure (Mehta 2000). For further information on pulmonary arterial hypertension see the chapter "HIV-associated pulmonary hypertension (PAH)".

Table 2. Cardiac diseases in HIV-infected patients

Pericardial diseases
▪ Pericardial effusion
▪ Pericarditis (viral, bacterial, mycotic)
▪ Neoplasm (Kaposi's sarcoma, lymphoma)
Myocardial diseases
▪ HIV-associated dilated cardiomyopathy
▪ Myocarditis (acute or chronic)
▪ Neoplasm (Kaposi's sarcoma, lymphoma)
▪ Drug side-effects (especially by antiretroviral therapy)
Endocardial diseases
▪ Infective endocarditis (bacterial, mycotic)
▪ Nonbacterial thrombotic endocarditis
Vascular diseases
▪ Atherosclerosis
▪ Vasculitis, perivasculitis
▪ Pulmonary arterial hypertension

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24. HIV-associated Pulmonary Hypertension

Georg Friese, Mirko Steinmüller and Ardeschir Ghofrani

Pulmonary hypertension is a severe life-limiting disease, often affecting younger patients. The connection between HIV infection and the development of pulmonary hypertension is well documented (Mette 1992, Simonneau 2004). However, the underlying pathobiology still remains unclear. Given that the prognosis of HIV infection has been improved by HAART, severe pulmonary hypertension is becoming a life-limiting factor (Nunes 2002).

Etiology, pathogenesis, classification

Pulmonary hypertension can be caused by vasoconstriction, reduction of arterial elasticity by structural remodeling of the vessel wall, obstruction of the vessel, and vessel rarification. All forms show the development of functional alterations (reversible vasoconstriction) and structural changes (vascular remodeling), and often occur in combination with intravasal thrombosis. The increase in right ventricular afterload induces right ventricular hypertrophy and/or dilatation.

Chronic pulmonary hypertension is classified using five groups according to the classification developed at the *World Symposium on Primary Pulmonary Hypertension* 1998 in Evian (modified in Venice 2003). HIV-associated pulmonary hypertension belongs to group number one (PAH):

Pulmonary arterial hypertension (PAH)

1.1 Primary pulmonary hypertension

a) Sporadic disorder

b) Familial disorder

1.2 Associated with

a) Collagen vascular disease

b) Congenital (right-left) systemic-pulmonary shunt

c) Portal hypertension

d) **HIV-associated pulmonary hypertension**

e) Drugs

f) Persisting PAH of the newborn

Pulmonary hypertension is classified into three clinical stages:

Latent pulmonary hypertension is characterized when mean pulmonary arterial pressures (PAP) are below 21 mmHg with an exercise-induced increase to values above 30 mmHg. The patients suffer from dyspnea upon exercise. In **manifested pulmonary hypertension**, the mean PAP exceeds 25 mmHg at rest. Patients already suffer from dyspnea on light exercise. **Severe pulmonary hypertension** is characterized by a severely reduced cardiac output at rest, which cannot be increased upon exercise, due to the increase in right ventricular afterload. Thus, patients are unable to perform any physical activity without distress.

Diagnosis

Right heart catheterization

For diagnosis of chronic pulmonary hypertension, right heart catheterization is still considered to be the gold standard. It allows the essential parameters of pulmonary hemodynamics to be evaluated. The main parameter is pulmonary resistance, which can be abnormal even without affecting pulmonary arterial pressure. A test for reversibility of vasoconstriction should be performed at the stage of manifested pulmonary hypertension, to identify patients responding to vasodilative therapy. These "responders" are identified using oxygen insufflation or vasodilators during right heart catheterization. For example, during inhalation of nitric oxide, these patients show a decrease in pulmonary arterial pressure of 30 % and a simultaneous normalization of cardiac output.

ECG

ECG alterations induced by pulmonary hypertension are present after a two-fold increase in right heart musculature. Typical signs are:

- right axis deviation (mean QRS-axis > + 110°)
- RS-ratio in lead V6 < 1
- S wave in lead I and Q wave in lead III
- S waves in lead I, II and III
- increased P-wave amplitude (not obligatory).

Chest radiography

Pulmonary hypertension can be inferred by chest radiography observations:

- Enlarged right descending pulmonary artery (diameter > 20 mm)
- Central pulmonary arterial dilatation in contrast to narrowed segmental arteries
- Pruning of peripheral pulmonary blood vessels
- Enlargement of transverse heart diameter and increase of retrosternal contact area of the right ventricle

Echocardiography

Echocardiography allows recognition of right ventricular dilatation and estimation of systolic pulmonary arterial pressure. Typical signs are:

- right ventricular myocardial hypertrophy
- abnormal septum movements
- abnormal systolic intervals
- abnormal movement patterns of the pulmonary valve
- altered ejection flow profile of the right ventricle (transthoracic Doppler echocardiography).

Ventilation-perfusion scan, pulmonary angiography and CT scan

These radiological techniques are used to identify or exclude chronic thromboembolic pulmonary hypertension (CTEPH) and may guide operative treatment. CTEPH is an important differential diagnosis in intravenous drug abusing HIV-patients suffering from recurring thromboembolisms (Figure 1).

Therapy

General treatment

Various modalities of general treatment have been established for the therapy of pulmonary hypertension on the basis of empirical data. These are:

1. Diuretics

In the later stages of pulmonary hypertension, volume retention may cause an enormous increase in the right ventricular preload followed by congestive hepatomegaly, edema and ascites formation. Volume retention is not only caused by chronic right heart failure but also by stimulation of the renin-angiotensin system followed by elevated aldosterone levels. For this reason, a combination of loop diuretics (e.g. furosemide 20-80 mg per day) and aldosterone antagonists (e.g. aldactone 50-200 mg per day) has proved to be successful. The usual contraindications, as well as the risk of dehydration followed by a critical decrease of right ventricular preload, have to be considered. A preload of about 6-10 mmHg is needed for optimal right ventricular performance.

2. Digitalis

The use of digitalis is still much debated. According to a randomized placebo-controlled double-blinded trial, only patients simultaneously suffering from Cor pulmonalis and decreased left ventricular function benefit from digitalis medication. However, digitalis medication is always justified in the case of tachycardic atrial arrhythmias. It has to be considered that digitalis has a high arrhythmogenic potential in combination with hypoxemia, which might lead to severe complications.

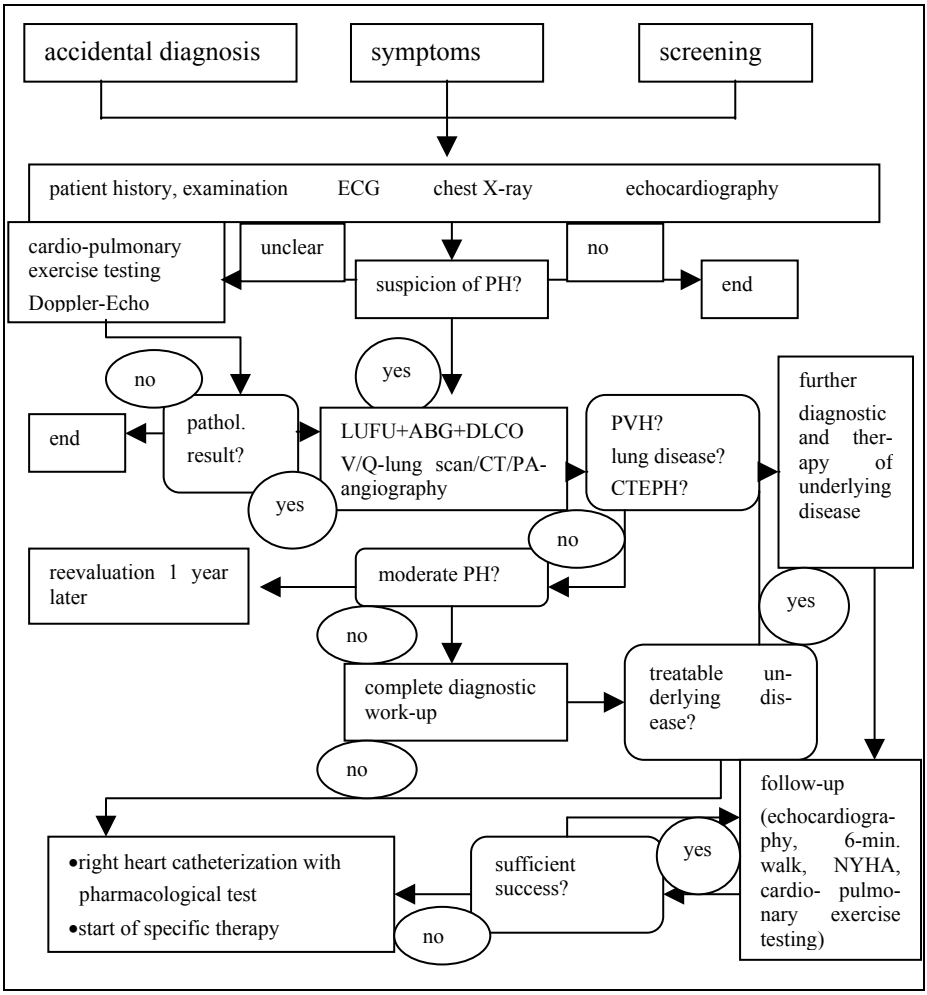

FIGURE 1. Diagnostic and therapeutic algorithm: suggestion for diagnostic procedures on suspicion of pulmonary hypertension (adapted from Arbeitsgemeinschaft Pulmonale Hypertonie). LUFU: lung function test; ABG: arterial blood gases; DLCO: CO diffusion capacity.

3. Anticoagulation

After considering the contraindications, the application of heparin or oral anticoagulants such as phenprocoumon and warfarin, are an established treatment for chronic pulmonary hypertension. Long-term anticoagulation therapy addresses the following aspects of the pathophysiology of PAH:

- increased risk of in-situ thrombosis caused by altered blood flow in narrowed and deformed pulmonary vessels
- increased risk of thrombosis caused by peripheral venous stasis, right ventricular dilatation and reduced physical exercise

- decreased levels of circulating thrombin and fibrinogen degradation products, which are supposed to act as growth factors in vascular remodeling processes.

The dose of anticoagulants should be adjusted to maintain the prothrombin time at an international normalized ratio (INR) of 2.5.

4. HAART

HAART is considered as a general treatment for HIV-associated pulmonary hypertension. According to the CDC classification, pulmonary hypertension is a symptomatic complication and therefore classified as category B. This is independent of CD4 cell numbers and virus load, indicating an obligation for antiretroviral treatment. Evidence shows that the prognosis of HIV-associated pulmonary hypertension is improved upon effective antiretroviral therapy (Zuber 2004). Furthermore, the immune status of this high-risk group has to be stabilized to prevent systemic infection, especially pneumonia.

Specific treatment

The aim of specific therapy is to decrease pulmonary arterial pressure, thereby reducing the right ventricular afterload. Substances that currently used for the treatment of pulmonary hypertension or tested in clinical studies are:

- Calcium channel blockers
- Prostanoids (intravenous, inhalative, oral, subcutaneous)
- Endothelin receptor antagonists (selective, none-selective)
- Phosphodiesterase-5 inhibitors

In addition to the immediate effect of muscle relaxation, some vasodilators (especially prostanoids and phosphodiesterase-5 inhibitors) seem to have a sustained antiproliferative effect.

1. Calcium channel blockers

Currently nifedipine and diltiazem are the most commonly used calcium channel blockers. Around 5-10 % of primary pulmonary hypertension patients are so-called responders. The response to calcium channel blockers should be evaluated during right heart catheterization.

The major disadvantage of oral calcium channel blockers is their effects on the systemic circulation. Peripheral vasorelaxation causes hypotension and the negative inotropic effect of calcium channel blockers leads to a reduction in cardiac output. Furthermore, non-selective vasodilation in the pulmonary circulation may have disadvantageous effects on gas exchange by increasing ventilation-perfusion mismatches. For long-term therapy, up to 250 mg nifedipine or 720 mg diltiazem is used. The dose must be increased slowly over weeks to the correct treatment dosage.

2. Intravenous prostacyclin

Reduction of endothelial prostacyclin synthesis in lung tissue has been described in patients suffering from pulmonary hypertension (Christman 1992, Tuder 1999). Therefore, substitution of exogenous synthetic prostacyclin is an obvious therapeutic option. Due to its short half-life, iloprost is continuously infused intravenously

using a portable pump via a catheter or an implanted port. The intravenous dosage of iloprost is slowly increased to a usual dose of between 0.5 and 2.0 ng per kg bodyweight per minute.

The treatment of outpatients with intravenous prostacyclin is today an established treatment for long-term therapy of severe pulmonary hypertension (Barst 1996, Sitbon 2002). Long-term therapy with intravenous prostacyclin induces a sustained hemodynamic benefit in the treatment of primary pulmonary hypertension (e.g. HIV-associated pulmonary hypertension).

The disadvantages of intravenous prostacyclin are:

- systemic side effects of non-selective vasodilators, e.g. arterial hypotension, orthostasis, skin hyperemia, diarrhea, jaw- and headache
- risk of acute right heart decompensation due to application failures
- possible catheter infection
- tachyphylaxis

Tachyphylaxis is observed in long-term application of intravenous prostacyclin and requires increased doses.

Conclusion: experiences with prostacyclin in HIV-associated pulmonary hypertension are based on smaller, uncontrolled trials. However, these studies suggest an improvement in the prognosis of affected patients (Aguilar 2000, Cea-Calvo 2003).

3. Inhalative prostanoids

Many disadvantages of intravenous application can be avoided by using aerosolized prostanoids (e.g. the recently approved prostanoid Ventavis™). Alveolar deposition of prostanoids stimulates a selective intrapulmonary effect. Repeated inhalation of iloprost has proved to be effective and safe in HIV-negative patients in a recent multi-centric, randomized placebo-controlled trial (Olschewski 2002). Iloprost-treated patients showed a significant improvement in exercise capacity, as measured by a six-minute walk test, as well as in NYHA classification.

The effect of this treatment on HIV-associated pulmonary hypertension was demonstrated in a further clinical trial at our center (Ghofrani 2004). Disadvantages of this form of therapy include the sophisticated aerosolation technology, the short duration of action after a single application (60-90 min), requiring frequent inhalations (6-9 per day), and the therapy-free interval during the night. Per day, 25-75 µg iloprost are given in 6-9 inhalations.

4. Endothelin receptor antagonists

Several experimental trials have proved the effectiveness of selective and non-selective endothelin antagonists. A phase III trial on the orally administered endothelin antagonist bosentan showed an improvement in physical exercise capacity and an increase in complication-free survival time of PPH patients (Rubin 2002). Applied doses vary between 62.5 and 125 mg twice daily. The major side effect of this therapy is an elevation of liver enzymes. Therefore, stringent controls of liver enzymes are necessary. The use of bosentan in patients suffering from HBV or HCV/HIV co-infection has to be considered carefully.

Based on these data, bosentan was approved for the treatment of pulmonary arterial hypertension in Europe. Due to the potential increase in liver enzymes, frequent controls of liver enzymes are required. An uncontrolled study has reported initial experiences in using bosentan to treat HIV-associated pulmonary hypertension (Sitbon 2004).

5. Phosphodiesterase-5 (PDE5)-inhibitors

Sildenafil (Revatio™) is the first phosphodiesterase-5 inhibitor approved for the therapy of pulmonary hypertension. Revatio™ is also approved for use in HIV-associated pulmonary hypertension, although combination with protease inhibitors is not recommended because of possible interactions due to the same metabolic pathway (cytochrome P450 cyp 3A).

Considering the association of the groups of pulmonary arterial hypertension (Venice 2003), a similar therapeutic regime to that used for idiopathic pulmonary hypertension can be applied, depending on the clinical severity of the disease (Figure 2). A daily dose of 25-150 mg sildenafil is usually given in two or three single applications.

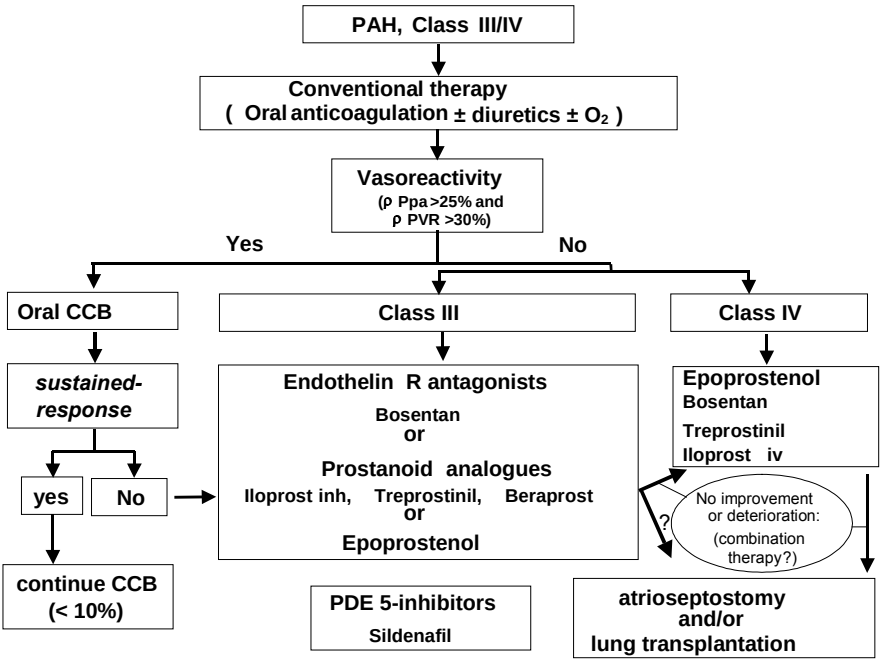

Figure 2. Therapeutic algorithm of pulmonary arterial hypertension depending on severity and vasoreactivity (adapted from World symposium on pulmonary hypertension, Venice 2003). Class I-IV: NYHA classification; Ppa: Pulmonary arterial pressure; PVR: pulmonary vascular resistance; CCB: Calcium channel blocker; PDE 5: Phosphodiesterase 5.

Conclusion for clinicians

HIV-patients suffering from exercise-induced dyspnea should be tested for pulmonary hypertension when other pulmonary or cardiac diseases (e.g. restrictive or obstructive ventilation disorders, pneumonia, coronary heart disease) have been excluded. The incidence of pulmonary hypertension is elevated by a factor of 1,000 in HIV patients compared to the general population, excluding estimated numbers of unreported cases.

A suspected diagnosis of pulmonary hypertension can be substantiated by non-invasive diagnostic methods (e.g. echocardiography). Since new therapeutic options have recently become available, correct diagnosis is essential.

Further diagnosis and treatment of patients suffering from every kind of pulmonary hypertension should be performed in specialized centers with experience in the treatment of pulmonary hypertension and HIV infection.

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25. HIV and Pulmonary Diseases

Sven Philip Aries and Bernhard Schaaf

The spectrum of lung diseases in HIV-infected patients encompasses complications typical for HIV such as tuberculosis, bacterial pneumonia, lymphomas and HIV-associated pulmonary hypertension, but also includes typical everyday pulmonary problems like acute bronchitis, asthma, COPD and bronchial carcinomas (Table 1). Classical diseases such as PCP have become rarer as a result of HAART and chemoprophylaxis (Lazarous 2007), so that other complications are on the increase (Grubb 2006). None other than acute bronchitis is the most common cause of pulmonary problems in HIV patients (Wallace 1997). However, particularly in patients with advanced immune deficiency, it is vital to take all differential diagnoses into consideration. Anamnestic and clinical appearance are often essential clues when it comes to telling the difference between the banal and the dangerous.

Table 1: Pulmonary complications in patients with an HIV infection

Infections	Neoplasia	Other
Pneumocystis jiroveci	Kaposi sarcoma	Lymphocytic interstitial pneumonia
Bacterial pneumonia	Non-Hodgkin's lymphoma	Non-specific interstitial pneumonia
S. pneumoniae	Hodgkin's lymphoma	
S. aureus		Pulmonary hypertension
H. influenzae	Bronchial carcinoma	
B. catarrhalis		COPD
P. aeruginosa		
Rhodococcus equi		Bronchial hyperreactivity
Nocardia asteroides		
Mycobacteria		
M. tuberculosis		
Atypical mycobacteria		
Other		
Cytomegalovirus		
Aspergillus spp.		
Cryptococcus neoform.		
Histoplasma capsulatum		
Toxoplasma gondii		

This chapter presents an outline of differential diagnoses in patients with respiratory complaints. PCP, mycobacterioses and pulmonary hypertension are covered in detail in chapters elsewhere.

Anamnesis

What are the previous illnesses of the patient?

Someone who has suffered from a PCP once is at a higher risk of having another one. A patient with hyperlipidaemia and carotid stenosis might have coronary heart disease.

What medication does the patient take?

Taking cotrimoxazol regularly makes a PCP unlikely, and the risk of bacterial pneumonia may also be reduced (Beck 2001). In the case of PCP prophylaxis with Pentamidine inhalation, however, atypical, often apically pronounced manifestations of a PCP are to be expected.

Has the patient recently started HAART?

Particularly HAART can induce pulmonary problems:

During a newly begun course of treatment with abacavir, asthma could also be due to hypersensitivity. Dyspnea (13 %), cough (27 %) and pharyngitis (13 %) are common symptoms (Keiser 2003). Some patients even develop pulmonary infiltrates.

T-20 seems to increase the risk of bacterial pneumonia, at least among smokers.

Dyspnea and tachypnea are also seen in lactic acidosis secondary to nuke therapy.

In addition, pulmonary symptoms after institution of HAART might result from the Immune Reconstitution and Inflammatory Syndrome (IRIS). The list of etiologies includes a number of infective and non-infective causes (Grubb 2006). Low CD4+ T-cell count and high viral load are risk factors. In a retrospective analysis, IRIS was seen in 30 % of patients with TB, atypical mycobacteriosis and cryptococcosis (Shelburn 2005).

Does the patient smoke?

Although smoking is more harmful to HIV-positive than to HIV-negative persons, it is still more common among HIV-positives (Royce 1990). All HIV-associated and HIV-independent pulmonary diseases are more common in smokers than in non-smokers. This starts with bacterial pneumonia and PCP, but also applies to asthma, COPD and pulmonary carcinomas (Hirschtick 1996). Smoking promotes the formation of a local immune deficit in the pulmonary compartment: it reduces the number of alveolar CD4+ cells and the production of important pro-inflammatory cytokines such as IL-1 and TNF-α (Wewers 1998). Furthermore, smoking suppresses the phagocytosis capacity of alveolar macrophages. This effect is more pronounced in HIV patients than in HIV-negative patients. HIV infection itself, however, does not seem to have any direct influence on the capability for bacterial killing (Elssner 2004).

Motivating the patient to restrict nicotine intake is thus an important medical task, particularly in HIV consultation. Strategies which promise success and are supported by the evidence of studies include participation in motivational groups, nicotine substitutes and taking Buproprion, whereby interactions, particularly with Ritonavir, should be taken into consideration.

Where does the patient come from?

Another important question is that of the travelling history and/or the origin of the patient. There are places where disease such as histoplasmosis and coccidiomycosis occur endemically. Histoplasmosis, for example, is more widespread in certain parts of the USA and in Puerto Rico than PCP, while it is rare in Europe.

Tuberculosis plays a greater role among immigrants.

How did the patient become infected with HIV?

Intravenous drug users suffer more often from bacterial pneumonia or tuberculosis (Hirschtick 1995). Pulmonary Kaposi's sarcomas are almost exclusively found in MSM (men who have sex with men).

What are the symptoms?

Occasionally, some valuable information can be gained above the more uniform symptoms such as coughing and shortness of breath, which might be useful for differentiation between PCP and bacterial pneumonia. Thus, for example, it is typical for the onset of bacterial pneumonia to be more acute. Patients usually go to the doctor after only 3-5 days of discomfort, whereas patients with PCP suffer from symptoms for an average of 28 days (Kovasc 1984). PCP patients typically have dyspnea and a non-productive cough. A large quantity of discoloured sputum is more likely to indicate a bacterial cause or a combination of infections.

What does the chest X-ray look like?

Table 2: Chest X-ray findings and differential diagnosis

Chest X-ray	Typical differential diagnosis
Without pathological findings	PCP, asthma, KS of the trachea
Focal infiltrates	Bacterial pneumonia, mycobateriosis, lymphoma, fungi
Multifocal infiltrates	Bacterial pneumonia, mycobacteriosis, PCP, KS
Diffuse infiltrates	PCP (centrally pronounced), CMV, KS, LIP, cardiac insufficiency, fungi
Miliary image	Mycobacteriosis, fungi
Pneumothorax	PCP
Cavernous lesions	Mycobacteriosis (CD4 > 200), bacterial abcess (Staph., Pseudomonas)
Cystic lesions	PCP, fungi
Pleural effusion	Bacterial pneumonia, mycobacteriosis, KS, lymphoma, cardiac insufficiency
Bihilar lymphadenopathy	Mycobacteriosis, KS, sarcoidosis

The most important question: What is the immune status?

The number of CD4+ T-cells provides an excellent indication of the individual risk of a patient to suffer from specific opportunistic infections. More important than the nadir is the current CD4+ T-cell count. In patients with more than 200/µl, infection with typical opportunistic HIV-associated diseases is very unlikely. Here, as with HIV-negative patients, one generally tends to expect more „normal" problems like acute bronchitis and bacterial pneumonia. However, tuberculosis should always be considered. Although the risk of becoming infected with tuberculosis grows along

with increasing immunodeficiency, more than half of all tuberculosis infections in HIV patients occur at a CD4+ T-cell count of above 200/µl (Lange 2004, Wood 2000).

At less than 200 CD4+ T-cells/µl, PCP and, more rarely, pneumonia/pneumonitis with cryptococci, occurs. At this stage too, however, bacterial pneumonia is the most common pulmonary disease overall.

Below 100 CD4+ T-cells/µl, there is an increase in the number of pulmonary Kaposi sarcomas and toxoplasma gondii infections. At a cell count of under 50/µl, infections with endemic fungi (histoplasma capsulatum, Coccidioides immitis), non-endemic fungi (Aspergillus, Candida species), atypical mycobacteria and different viruses (mostly CMV) occur. Especially in patients with advanced immunodeficiency, it must be remembered that pulmonary illness may only represent an organ manifestation of a systemic infection. Rapid, invasive diagnostic procedure is thus advisable in such patients.

Pulmonary complications

Bacterial pneumonia

Bacterial pneumonia occurs more often in HIV-positive than in HIV-negative patients, and, like PCP, leaves scars in the lung. This often results in a restriction of pulmonary function which goes on for years (Alison 2000). Although bacterial pneumonia occurs in the early stages of HIV infection, the risk grows along with increasing immunosuppression. A case of bacterial pneumonia significantly worsens the long-term prognosis of the patient (Osmond 1999). Thus, contracting bacterial pneumonia more than once a year is regarded as AIDS defining. The introduction of HAART went hand in hand with a significant reduction in the occurrence of bacterial pneumonia (Jeffrey 2000).

Clinically and prognostically speaking, there is no great difference between bacterial pneumonia in HIV-infected patients and pneumonia in an immunocompetent host. However, the HIV-patient more often presents with less symptoms and a normal leucocyte count (Feldman 1999). Etiologically, pneumococci and haemophilus infections are most common. In comparison with immunocompetent patients, infections with *Staphylococcus aureus*, *Branhamella catarrhalis,* and in the later stages (< 100 CD4+ T-cells/µl) *Pseudomonas spp*. occur more often. In the case of slow-growing, cavitating infiltrates, there is also the possibility of rare pathogens such as *Rhodococcus equi* and nocardiosis. Polymicrobial infections and co-infections with *Pneumocystis jiroveci* are common (10-30 %), which makes clinical assessment difficult (Miller 1994).

What is also important for the risk stratification of the patient, in addition to the usual criteria [pO2, extent of infiltrate, effusion and the CRB-65 score (Confusion, Respiratory rate, Blood pressure, > 65 years, Lim 2003)] is the CD4+ T-cell count. The mortality of patients with < 100 cells/µl is increased more than sixfold. Therefore it probably makes sense when dealing with patients with a pronounced immune defect not to rely on the risk scores validated for immunocompetent patients and to admit apparently less severely ill patients to the hospital for treatment (Cordero 2000).

Should there be no suspicion of mycobacteriosis, a calculated antibacterial treament of patients with a CD4+ T-cell count of > 200/µl with medication effective against *S. pneumoniae, H. influenzae* und *S. aureus* is indicated. However, there are no controlled studies available to support this. In accordance with recommended therapies for community acquired pneumonia with co-morbidity, the prescription of a Group 2 Cephalosporin such as Cefuroxim or group 3a such as Cefotaxim/Ceftriaxon, or an aminopenicillin with betalactamase inhibitor (Ampicillin/Sulbactam or Amoxicillin/clavulanic acid, e.g. Augmentan™ 875/125 mg, twice daily) can be recommended. In the case of regionally increased incidence of legionella infection, combination with a macrolide is advisable (e.g. Klacid™ 500 mg twice daily). Once positive culture results have been obtained, the patient should receive further specific treatment. With advanced immunodeficiency (CD4+ T-cells < 200/µl), primary consideration should be given to bronchoscopic diagnostics, due to the broader spectrum of pathogens (Dalhoff 2002). In patients with a high risk of pseudomonas infection (low CD4 count, nosocomial infection, sepsis) initial therapy should include antibiotics active against pseudomonas. Patients with severe Pneumonia should be treated with combination therapy including a makrolide or quinolone.

Pneumococcus vaccination is recommended. At a CD4+ T-cell count lower than 200/µl, however, there is no proof of vaccination benefit. Due to the frequency of secondary bacterial infections, an annual influenza vaccination is also advisable.

Which diagnostic strategy makes sense with pulmonary infiltrates?

The intensity of the diagnostic workup in a patient with pulmonary infiltrates is based on the HIV stage and the expected spectrum of pathogens. With a CD4+ T-cell count of > 200/µl, non-invasive basic diagnostics and a calculated antibiotic therapy are justified. This basic diagnostic investigation includes taking two blood cultures and a microscopic and cultural sputum examination. The bacteremia rate seems to be higher than in immunocompetent patients (Miller 1994). The main value of sputum culture is the demarcation of mycobacterial and aspergillus infections.

In individual cases the possibility of antigen detection in the urine should be considered (e.g. pneumococcus, legionella. cryptococcus, histoplasma). The determination of the cryptococcus antigen in serum has a high predictive value for the detection of invasive cyptococcosis (Saag 2000). A chest CT is sometimes helpful in the diagnostic workup (high-resolution CT, HR-CT). A PCP, for example, might be depicted in an HR-CT, but might be missed in a conventional chest X-ray.

In advanced stages (< 200 CD4+ T-cells/µl), bronchoscopic investigation is primarily recommended (Dalhoff 2002). The diagnostic success rate of a bronchoscopy in HIV-infected patients with pulmonary infiltrates is 55-70 % and rises to 89-90 % when all techniques including the transbronchial biopsy are combined (Cadranel 1995). The sensitivity of a bronchoalveolar lavage (BAL) amounts to 60-70 % in bacterial pneumonia (patients without previous antibiotic treatment), and 85-100 % in PCP (Baughman 1994). Due to the high sensitivity of the BAL, transbronchial biopsy with possible complications is only recommended in the diagnosis of PCP if there is a negative initial diagnostic workup and in patients taking chemoprophylaxis (Dalhoff 2002). If invasive pulmonary aspergillosis or CMV is considered, a

transbronchial biopsy should be the preferred method in order to differentiate between colonisation and tissue invasion. Surgical open biopsies and CT-controlled trans-thoracic pulmonary biopsies are rarely necessary.

Asthma bronchiale

One would think that an immunosuppressing disease like HIV infection would at least protect patients from manifestations of exaggerated immune reaction such as allergies and asthma. However, the opposite is the case: in a study from Canada concerning HIV-infected men, more than 50 % had suffered an episode of wheezing within the previous 12 months, and nearly half of those showed evidence of bronchial hyperreactivity. These findings were particularly distinct among smokers (Poirer 2001). As the disease progresses, it probably comes to an imbalance between too few „good" TH1 cells producing interferon and Interleukin 2, and too many „allergy-mediating" TH2 cells with an increased total IgE. In cases of unclear coughing, dyspnoea or recurrent bronchitis, the possibility of bronchial hyperreactivity, asthma or emphysema should be kept in mind.

Emphysema

Smokers with HIV infection develop pulmonary emphysema more often than non-infected smokers. It is possible that a pathogenetic synergy arises from smoking and the pulmonary infiltration with cytotoxic T-cells due to HIV infection (Diaz 2000). Smoking crack increases the risk of pulmonary emphysema even more. Here, it seems that superficial epithelial and mucosal structures are destroyed (Fliegil 1997). Furthermore, cocaine can lead to unusual manifestations with pneumothorax or alveolar infiltrates.

Lymphoid interstitial pneumonia (LIP):

LIP is a form of pneumonia which takes a chronic or subacute course and is extremely rare in adults. Radiologically, its reticulonodular pattern makes it similar to PCP. This illness occurs paraneoplastic, rarely, idiopathic and as in HIV and EBV disease parainfectious. In contrast to PCP, patients with LIP usually have a CD4+ T-cell count of > 200/µl and normal LDH values. A CD8-dominated lymphocytic alveolitis with no pathogen detection is characteristic. Definite diagnosis often calls for an open pulmonary biopsy. LIP is considered sensitive to steroids. The role played by HAART is unclear, especially as LIP has occasionally been observed in the context of immune reconstitution during HAART.

Bronchial carcinoma

HIV patients are at considerably higher risk of bronchial carcinoma. A retrospective analysis covering 8,400 patients from the years 1986-2001 showed an eightfold increased incidence of bronchial carcinoma in the period after 1996 than that for the normal smoking population. Interestingly, the majority of bronchial carcinomas are, histologically, adenocarcinomas, which results in discussion of whether HIV infection itself leads to a genetic instability (Bower 2003, Kirk 2007). Patients with bronchial carcinomas and HIV are younger, the disease is often more advanced at presentation and takes a more aggressive course than in HIV-negative patients

(White 1996, Karp 1993). Whether to treat with chemotherapy, and what kind, has to be decided for each case individually. A small cohort study has shown that HIV-infected patients with advanced bronchial carcinoma have a similarly bad prognosis to that of HIV negative patients, regardless of immune status during HAART and chemotherapy (Powles 2003).

Less common opportunistic infections

The detection of CMV in BAL repeatedly gives rise to discussion regarding clinical relevance. Seroprevalence is high (90 %), and colonisation of the respiratory tract is common. CMV pneumonia is the primary reason for 3.5 % of pulmonary infiltrates in AIDS patients. The significance of the pathogen in the later stages may well be underestimated, since histological examination of autopsy material showed pulmonary CMV infections in up to 17 % (Afessa 1998, Waxman 1997). Regarding invasive pulmonary aspergillosis, which only occurs in the late stages and usually in conjunction with additional risk factors such as neutropenia or steroid therapy (Mylonakis 1998), please refer to the OI-Chapter.

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26. HIV-1 associated Encephalopathy and Myelopathy

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HIV encephalopathy

The primary cause of HIV encephalopathy (HIVE) is the infection of the CNS caused by HIV. If untreated, some 15-20 % of patients will eventually develop the disease. The incidence is similar in western and african populations, but may be lower in asian populations (such as Thailand). Since the introduction of highly active antiretroviral therapy (HAART) the incidence of the disorder has decreased. Other terms used for this condition with largely the same significance are AIDS dementia complex, AIDS dementia, HIV dementia, and HIV associated cognitive motor complex. HIVE mainly occurs in the later stages of the HIV infection when there is a profound immune suppression (CD4+ T-cells < 200/µl). The incidence of HIVE will likely increase in the developed countries as a consequence of increasing life expectancy (Valcour 2004 diese Literaturstelle muß wieder in die Zitateliste unten, wenn dieser Satz stehen bleiben soll!).

With the widespread use of HAART the incidence of HIVE has declined, but less so than the incidence of other AIDS-defining illnesses (Dore 1999). Risk factors for HIVE are co-infection with HCV, drug abuse, age and a variety of genetic factors involving TNF-alpha and MCP-1.

In HIVE there is a high level of replication of HIV in macrophages and microglial cells of the brain. Neuronal cells have not consistently been shown to be infected. However, different immunopathological mechanisms lead to functional and structural damage of these cells. With respect to viral replication and viral quasispecies the CNS is partially independent from the hematolymphatic compartment (Eggers 2003). In HIVE the viral load in the brain parenchyma and the cerebrospinal fluid have been shown to be high, and to loosely correlate with the extent of the disease. The histopathological finding of amyloid plaques and elevated CSF levels of ß-amyloid-peptides and the *tau* protein suggest some common pathogenic features with Alzheimer's disease.

In the HAART era the clinical phenotype of HIVE has changed to a somewhat more cortical-type dementia and to lesser dementia grades (Brew 2004). HIVE now develops in earlier stages of HIV infection, with less decreased CD4+ cell counts, and may be seen in patients with a well suppressed plasma viral load. The cause of this is unclear, but a low level viral replication in the CNS and immunopathogenic mechanisms independent of viral replication may be a component.

Clinical manifestation

HIVE is considered to be a mainly a subcortical dementia. HIVE emerges over the course of weeks and months. Acutely developing symptoms point out to another etiology. Fever, exhaustion, the effects of tranquilizers and reduced physical condition, e.g. with opportunistic infection, may all mimic dementia. In these cases, di-

agnosis of HIVE can only be made after repeat examinations when the condition mimicking dementia has improved.

Symptoms are occasionally noted earlier by relatives than by the patient himself. This is why a history given by these persons is of utmost importance. Typical complaints are slowing of reasoning, forgetfulness, difficulties concentrating, lack of energy drive, mild depressive symptoms and emotional blunting. For symptoms and signs see Tables 1 and 2.

Impairment of alertness, neck stiffness and focal or lateralising neurological signs (e.g. hemiparesis, aphasia) are not typical for HIVE. Psychotic symptoms without cognitive or motor disturbance do not warrant a diagnosis of HIVE. The coincidence of psychosis with HIVE is rare. Focal and generalized epileptic seizures are rare manifestations of HIVE.

The severity of HIVE may functionally be categorized according to the Memorial Sloan Kettering scale (Table 3) (Price 1988).

Table 1: Symptoms of HIVE including history given by close relatives or companions

Cognition	Forgetfulnes, difficulties concentrating, mental slowing (apprehension, processing)
Emotional	Loss of drive and initiative, withdrawal from social activities, failure to manage the financial and administrative aspects of one's life. Depressive mood, emotional blunting
Motor	Slowing and impairment of fine movements (e.g. typing, buttoning up), and disturbance of gait
Autonomous	Impaired micturition (urgency), loss of sexual libido, erectile dysfunction

Table 2: Signs with HIVE

Neurological findings	Early stages: impaired gait, slowing of rapidly alternating movements, hypomimia, occasionally tremor and short stepped gait
	Later: brisk tendon reflexes, positive Babinski sign, slowing of gaze saccades, sphincter impairment including incontinence. Palmomental, grasp and glabella reflexes. Occasionally accompanying polyneuropathy
	In the terminal stages spastic tetraplegia and dual incontinence
Neuropsychological findings	Slowing of psychomotor speed (e.g. naming the months in reverse), impairment of short term memory (recall of verbally presented items, digit span), and mental flexibility (spelling simple words backwards)
Psychological findings	Early stages: emotional blunting, disappearance of strong personality traits, distractability, loss of initiative
	Later: problems with recalling events in the correct time order, disorientation to time, space and situation. Finally mutism

Table 3: Severity of HIVE	
Stage 0:	(normal) normal mental and motor function.
Stage 0,5:	(equivocal/subclinical) no impairment of work or capacity to perform activities of daily living (ADL); normal gait; slowing of ocular movements and movements of extremities may be present
Stage 1:	(mild) able to perform all but the more demanding aspects of work or ADL, but with unequivocal signs or symptoms of functional, intellectual or motor impairment; can walk without assistance
Stage 2:	(moderate) able to perform basic activities of self-care, but cannot work or maintain the more demanding aspects of daily life; able to walk, but may require a single prop
Stage 3:	(severe) major intellectual incapacity (cannot follow news or personal events, cannot sustain complex conversation, considerable psychomotor slowing); motor disability (cannot walk without assistance, usually manual slowing and clumsiness
Stage 4:	(end stage) almost mutistic. Intellectual and social comprehension and output are at a rudimentary level; almost or completely mute; paraparetic or paraplegic with urinary and fecal incontinence

Diagnostic workup

Making an HIVE diagnosis requires a synopsis of clinical information and the results of laboratory tests. No laboratory test result on its own warrants the diagnosis of HIVE. Rather, the diagnosis requires the exclusion of other conditions (Table 3).

Clinically, the cognitive and psychological signs and symptoms are invariably accompanied by motor signs, although these may be subtle (Table 2). The International HIV dementia scale (Sacktor 2005) is an easy-to-use bedside instrument for the detection and quantification of the cognitive impairment of HIVE.

Laboratory tests are mainly employed to exclude differential diagnoses. MRI should be preferred to CT. MRI often shows patchy, diffuse, hyperintense and relatively symmetrical lesions in the white matter. These changes indicate leukoencephalopathy. In addition, atrophy with enlargement of the ventricles and the extraventricular CSF is often seen. However, none of these findings are specific for HIVE, and the disease may be present with a normal MRI. Unlike in PML the white matter lesions do not affect the cortical U-fibers, i.e. they don't reach the cortical ribbon. Edema, space occupying lesions and frank asymmetry of the white matter lesions *(dies wollte Christian H. so haben in der letzten deutschen Fassung)* are not typical for HIVE and should raise suspicion of other conditions. There may be some faint contrast enhancement symmetrically in the basal ganglia. More advanced techniques like MR spectroscopy, diffusion tensor imaging and magentization transfer imaging are promising, but so far have no place in clinical routine. *(Diesen Satz könnt Ihr auch rauslassen, da er vielleicht zu sehr einen review-Charakter hat.)*

CSF analysis shows a normal to even decreased white cell count. In contrast, total protein and albumin concentrations may be slightly elevated (blood-brain-barrier disruption). Oligoclonal bands and increased IgG-index indicate autochthonous

immunoglobulin production within the CNS. However, these findings are unspecific and are frequently present in the asymptomatic stages of HIV infection. Although there is a statistically significant correlation of a higher CSF viral load with HIVE, this association is of little value in the context of an individual patient. The EEG shows no or only mild signs of generalized slowing. Moderate or severe slowing or focal arrhythmic delta activity are atypical for HIVE.

Treatment

According to the pathogenesis of HIVE, treatment should aim at suppressing the viral replication in the CNS. It is an unresolved issue whether the antiviral compounds need to penetrate into the CSF. A variety of clinical (Letendre 2004), virological (de Luca 2002), pathological and electrophysiological studies suggest that substances reaching higher CSF concentrations are more effective. In contrast, we found no association of the number of CNS-penetrating substances and their actual CSF levels with the magnitude of CSF viral load suppression (Eggers 2003). HAART-induced neurocognitive improvement correlates more closely with viral load suppression in the CSF than in the plasma (Marra 2003).

In the absence of prospective, controlled, and randomized studies with clinical end points, we consider it important that any antiretroviral regimen in patients with HIVE includes as many as possible CNS-penetrating substances. We suggest any of the following: zidovudine, lamivudine (high concentrations in *ventricular* CSF; unpublished observations), nevirapine and indinavir. With the substances approved for clinical use in the recent years, CNS penetration is low or unknown. Lopinavir and atazanavir exceed, after all, the minimal inhibitory concentration in the CSF ([IC50]). In view of the low protein content of the CSF, the non-protein bound fractions of these two substances might reach effective levels.

Table 4: Differential diagnoses of HIV encephalopathy and diagnostic workup

Condition	adequate diagnostic step (commentary)
Neurosyphilis	Antibody testing and CSF analysis (pleocytosis >15/µl) (serological findings may be atypical for active neurosyphilis)
CMV encephalitis	CSF (pleocytosis, potentially granulocytic; decreased glucose elevated total protein)
	PCR for CMV in CSF, CMV antigen (pp65) in blood antibody testing in blood and CSF (IgG and antibody index may be increased)
	MRI (potentially subependymal hyperintensity and contrast enhancement)
	Occurs mostly in association with manifestation of other organs (retinitis, colitis, pneumonitis, esophagitis)
Toxoplasmosis	CT / MRI (single or multiple lesions found most frequently in basal ganglia or thalamus, space occupying effect, edema, frequently with contrast enhancement (patchy or ring-shaped))
	Presence of toxoplasma specific IgG in blood and CSF (rarely total seronegativity)
	(may rarely present as diffuse microglial nodule encephalitis)
Primary CNS lymphoma	CT / MRI (single or multiple lesions most frequently adjacent to ventricles, space occupying effect, edema, almost invariably intense contrast enhancement (patchy more than ring-shaped))
	CSF cytology
	EBV PCR in CSF (HIV-associated CNS lymphomas EBV induced)
	PET or SPECT (tracer enhancement in lesion)
VZV encephalitis	CSF (marked inflammatory signs)
	VZV specific IgG in blood and CSF (IgM may be absent)
	VZV PCR in CSF
	Mostly antecedent or accompanying cutaneous zoster lesions
Cryptococcal meningitis	CSF (opening pressure frequently elevated, cell count and protein may be normal), India ink stain
	Cryptococcal antigen in blood and CSF, fungal culture
Tuberculous meningitis	CSF, culture, PCR for mycobacteria
and other bacterial infections	appropriate tests
Progressive multifocal leukoencephalopathy (PML)	MRI (single or multiple lesions of white matter, no space occupying effect, no edema, no contrast enhancement)
	PCR for JC virus in CSF
Intoxication	Determination of drug levels / screening for illicit drugs
Metabolic encephalopathy and impaired general physical condition	Determination of electrolytes, renal and hepatic markers, hormones (thyroid, cortisol), blood count
	Hypoxaemia? (blood gas analysis)
	Reduced physical state? (bed ridden, wasting, pyrexia)
Depression with „pseudo dementia“	Psychiatric examination
Other „subcortical“ dementia forms	Normal pressure hydrocephalus, Parkinsonian syndroms, other neurodegenerative conditions, subcortical arteriosclerotic encephalopathy

A number of small studies investigated the effect of Selegelin, Nimodipin, Lexipafant, and valproic acid for treatment of HIVE. These drugs act on the molecular pathogenesis of HIVE and are used in conjunction with antiretroviral treatment. Although a trend for clinical and neuropsychologic improvement was seen with some substances, none of them can be recommended for clinical routine.

Prognosis: An optimal HAART may lead to significant clinical improvement of HIVE. The extent of improvement includes restoration of working ability in patients previously dependent on caregivers. This effect can be observed for up to five years, in parallel with sufficiently suppressed plasma viraemia (Cysique 2005). During the first months of treatment, the radiological signs of leukoencephalopathy may become more prominent, but eventually regress over the following one to two years.

Autopsy studies and clinical case series show, however, that some patients develop a clinically apparent CNS disease despite effective HAART-induced suppression of plasma viral load (Brew 2002; own unpublished observations). Even with rapid decrease of plasma viraemia during HAART, many HIVE patients show a significantly protracted decrease of the CSF viral load (Eggers 2003). On these grounds we recommend that in patients with HIVE, the CSF viral load be determined during the first one or two years of HAART. Modification of the antiviral regimen should be considered when clinical and virologic studies suggest ongoing CNS viral replication with complete suppression of plasma viraemia.

HIV-associated myelopathy

Clinical characteristics

HIV-infected patients may develop a myelopathy without the neuropsychological signs and symptoms of HIVE, labelled HIV associated myelopathy (HIVM). The histopathological hallmark are vacuoles most prominent in the cervical and thoracic parts of the spinal cord and lipid-laden macrophages, hence the term “vacuolar myelopathy” (Petito 1985). These changes are reminiscent of severe combined degeneration and may occur with HIV-negative patients. As HIV viral products have only inconsistently been shown to be part of the lesions, the role of the virus for the disease is uncertain. Pathogenetically, a disturbance of cobalamin-dependent transmethylation has been discussed. Like HIVE, HIVM occurs mainly with advanced immunosuppression. Only a proportion of patients with the autoptic finding of vacuolar myelopathy shows clinically apparent myelopathy during life (dal Pan 1994).

Diagnostic workup

A patient may be suspected of having HIVM if he has a spastic-atactic gait, hyperreflexia with positive Babinski sign, disturbance of sphincter control, erectile dysfuntion, and slight signs of sensory dysfunction in a glove and stocking distribution. The diagnosis of an independent HIVM should only be made when a concomittant cognitive impairment is significantly less prominent than the myelopathy. Electrophysiological tests which show increased latencies of somatosensory evoked

potentials (SEP) and the motor evoked potentials on transcranial magnetic stimulation are compatible with the diagnosis. CSF, microbiological and spinal imaging studies are inconspicuous or unspecific, and they have their importance in the exclusion of differential diagnosis, as listed in Table 4. Spinal imaging should include MRI of the cervical and, possibly the thoracic cord.

Table 5: Differential diagnoses of HIV myelopathy and diagnostic workup

condition	adequate diagnostic step (commentary)
Mechanic compresssion of the myelon (cervical myelopathy, disk herniation)	degenerative changes of the cervical spine MRI shows reduced CSF spaces around the spinal cord with hyperintense lesions of the cord parenchyma
Neurosyphilis	Antibody testing and CSF analysis (pleocytosis >15/µl) (serological findings may be atypical for active neurosyphilis)
CMV myelopathy	CSF (signs of inflammation) PCR for CMV in CSF antibody testing in blood and CSF (IgG and antibody index may be increased)
Toxoplasmosis	contrast enhancing cord lesion on MRI
VZV myelitis	CSF (marked inflammatory signs) VZV specific IgG in blood and CSF (IgM may be absent) VZV PCR in CSF Mostly antecedent or accompanying cutaneous zoster lesions
HSV myelitis	CSF (inflammatory signs may be absent), HSV PCR in CSF
HTLV-1 (tropical spastic paraparesis)	travel to the Carribean, West Africa or East Asia slow evolution of symptoms, bladder dysfunction characteristic, CSF inflammation, HTLV-1 specific antibodies
Severe combined degeneration	Vitamin B12 levels, increased erythrocyte volume
heredo-degenerative diseases (hereditary spastic paraparesis, adrenoleukodystrophy, Friedreich ataxia etc.)	appropriate tests

Treatment

Early observations of significant improvement with zidovudine monotherapy (Oksenhendler 1990) were later confirmed with HAART. This is why any patient with HIVM should be offered effective HAART. A controlled trial showed L-methionin to bring about improvement on electrophysiological but not clinical parameters.

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27. Neuromuscular Diseases

Thorsten Rosenkranz and Christian Eggers

Polyneuropathy and polyradiculopathy

Peripheral neuropathies may complicate all stages of HIV infection. During the early asymptomatic stages peripheral neuropathies are uncommon, but electrodiagnostic testing reveals subclinical evidence of peripheral nerve involvement in about 10 % of cases. In later stages, symptomatic neuropathies occur in some 30-50 % of patients. Neuropathological studies have shown pathological changes with a prevalence approaching 100 % in patients with AIDS.

The neuropathies can be classified as primary HIV-associated or as secondary diseases caused by neurotoxic substances or opportunistic infections. Although neuropathies related to HIV infection have been on the decline since the introduction of HAART, there has been an increase in the prevalence of toxic neuropathies (Authier 2003). Different types of peripheral neuropathies can be distinguished on the basis of when they occur with respect to the stage of HIV disease, and by the clinical course, major symptoms and electrophysiological and neuropathological features.

Clinical features

Acute inflammatory demyelinating polyneuropathy (AIDP), Guillain-Barré syndrome (GBS)

AIDP usually occurs at seroconversion or at asymptomatic stages of HIV infection. In addition, it seems to be rarely associated with immune reconstitution (Piliero et al. 2003). The typical clinical presentation is that of areflexia, symmetrical ascending weakness and relative sparing of sensory nerve fibers. Involvement of cranial nerves and cervical and thoracic spinal nerves leads to respiratory insufficiency, dysarthria and dysphagia. Parasympathetic and sympathetic nerve involvement may cause life threatening cardiac arrhythmias and severe arterial hypo- or hypertension.

Cerebrospinal fluid (CSF) typically shows a raised concentration of protein caused by the dysfunction of the blood-CSF-barrier. In contrast to HIV-negative patients with AIDP, a moderate pleocytosis of up to 50 leucocytes/µl CSF is found in most HIV-positive patients.

The progressive stage is followed by a few days or weeks of stable disease until recovery begins. If secondary axonal damage has occurred, recovery can last up to two years. A persistent disability of varying degrees develops in about 30 %.

Table 1: Polyneuropathies and polyradiculopathies in HIV infection

Type	HIV infection	Clinical features	Findings
Primary HIV-associated polyneuropathies			
Acute, inflammatory, demyelinating polyneuropathy (Guillain-Barré syndrome, GBS)	Seroconversion, asymptomatic, no or beginning immunosuppression	Symmetrical weakness > sensory loss, areflexia	ENG with demyelinating features, elevated CSF protein and moderate CSF-pleocytosis (< 50 c/µl)
Chronic demyelinating inflammatory polyneuropathy (CIDP)	Asymptomatic beginning immunosuppression, rarely AIDS	Distal and proximal weakness > sensory loss, areflexia	ENG with demyelinating features, elevated CSF protein and moderate CSF-pleocytosis (< 50 c/µl)
Vasculitic neuropathy	Asymptomatic no or beginning immunosuppression, rarely AIDS	Mostly asymmetric, acute loss of function of single nerves, rarely distal symmetrical sensory and motor disturbances	Elevation of ANA, cryoglobulinemia, hepatitis C virus coinfection; vasculitis in nerve biopsy but also in muscle, kidney and other organs
Neuropathy in diffuse, infiltrative leukocytosis syndrome (DILS)	Moderate immunosuppression	Mostly asymmetrical weakness and sensory loss, rarely distal symmetrical disturbances	Disease resembling Sjögren's syndrome; CD8+ cells > 1200/µl
Distal symmetrical sensory polyneuropathy (DSSP)	AIDS or advanced immunosuppression	Distal symmetrical sensory loss, paresthesia and pain of the legs	ENG with axonal features predominantly involving sensory nerves of the legs
Secondary polyneuropathies			
Medication–related toxic neuropathy	Beginning or advanced immunosuppression	Distal symmetrical sensory loss, paresthesia and pain of the lower legs	Treatment with ddI, ddC, d4T, vincristine, dapsone
Acute neuromuscular weakness syndrome	Beginning or advanced immunosuppression	Acute progressive tetraparesis	Lactic acidosis during NRTI treatment, axonal nerve damage, additional myopathy
Mononeuritis multiplex in CMV-infection or non-Hodgkin lymphoma	AIDS	Asymmetric, acute loss of function of single nerves	CMV infection of other organs, CMV DNA detection in plasma; non-Hodgkin lymphoma
Polyradiculitis in CMV or M. tuberculosis infection or due to meningeal lymphoma	AIDS	Flaccid paraparesis, sensory loss, bladder dysfunction	CMV or mycobacterial infection at other sites, detection of mycobacteria in CSF, malignant cells in CSF

Chronic, inflammatory, demyelinating polyneuropathy (CIDP)

Whereas AIDP is a monophasic, self-limiting disease, the course of CIDP is chronic progressive or relapsing-remitting. Weakness and sensory disturbances commonly develop over several months. In some cases, relapses, incomplete remissions and periods of stable disease alternate with each other.

In CIDP, as in AIDP, the CSF is abnormal with an elevated protein level. A moderate pleocytosis is often found instead of the classical acellularity. The underlying pathological mechanisms of both AIDP and CIDP seem to be macrophage and complement-mediated demyelination. The reason why a chronic persistence of the autoimmune process occurs in CIDP is unknown.

CIDP is a rare complication of seroconversion or the early stages of infection before AIDS.

Vasculitic neuropathy

Necrotizing vasculitis with involvement of peripheral nerves is a rare cause of neuropathy in HIV infection. Most patients develop a mononeuritis multiplex characterized by acute, relapsing dysfunction of individual peripheral nerves. The prognosis of the disease is determined by the involvement of other organs such as heart, kidneys or muscles in the vasculitic process. An immune complex attack associated with Hepatitis C virus infection or cryoglobulins appears to play an essential role in the pathological mechanism.

Diffuse infiltrative lymphocytosis syndrome (DILS)

DILS is a rare cause of distal symmetrical and often painful neuropathy. It resembles Sjögren's syndrome, but has multivisceral infiltration characterized by CD8 hyperlymphocytosis (CD8+ T-cell count >1000/µl). Sicca syndrome with parotidomegaly, lymphadenopathy, splenomegaly, pneumonitis and renal dysfunction may occur in association with axonal neuropathy (Gherardi 1998).

Distal symmetrical sensory polyneuropathy (DSSP)

DSSP is the most common neuropathy in HIV-positive patients and becomes symptomatic in the later stages of infection when the CD4+ T-cell count is at or below 200/µl. The clinical course is predominated by slowly progressive sensory symptoms such as numbness, dys- and paresthesia of feet and lower legs (Table 2). Approximately 30-50 % of patients complain of burning, lacerating or stabbing pain. It mainly involves toes and soles and sometimes makes walking difficult. Leading clinical findings are depressed or absent ankle reflexes, an elevated vibration threshold at toes and ankles and decreased sensitivity to pain and temperature in a stocking distribution, whereas proprioception is usually normal. Weakness and atrophy of intrinsic foot muscles are mild and are not features of the disease. The fingers and hands are rarely involved.

Involvement of the upper legs and trunk, significant weakness of leg muscles or decreasing proprioception are not typical for DSSP and should raise suspicion of other disorders, for instance a conjoined myelopathy. Loss and dysfunction of small sympathetic and parasympathetic nerve fibers may cause postural hypotension, erectile dysfunction, gastroparesis and alterations of skin or nails in many DSSP patients.

Table 2: Clinical features of distal symmetrical sensory polyneuropathy

Numbness, pain, dys- and paresthesia of the feet and lower legs
Decreased or absent deep ankle tendon reflexes
Decreased or absent vibratory sense of the toes and ankles
No or only minimal motor dysfunction
No or only minimal involvement of the hands and arms
Slowly progressive course
Electrodiagnostic studies with features of axonal nerve damage
Autonomic dysfunction: orthostatic hypotension, erectile dysfunction

Medication-related toxic neuropathy

A distal symmetrical sensory peripheral neuropathy occurs in about 10-30 % of patients treated with ddI, d4T or ddC. It is indistinguishable from HIV-induced DSSP on clinical examination or in electrodiagnostic studies. The only difference is in the exposure to neurotoxic nucleoside antiretroviral medication. Brew et al. (Brew 2003) found an elevation of serum lactate in over 90 % of patients with d4T-related neuropathies.

Nucleoside neuropathy develops after a mean of 12–24 weeks of treatment. After withdrawal, there can be a temporary worsening for 2–4 weeks and improvement usually begins after 6–12 weeks. In several cases the restitution remains incomplete. In these cases there may have been an additional pre-existent damage to the peripheral nerves due to the HIV infection. Subclinical disturbance of peripheral nerve function confirmed by pathological findings in electrodiagnostic studies elevates the risk of developing NRTI-related neuropathy.

In the American TORO-1 study, 11 % of patients treated with T-20 (enfurvitide) developed neuropathy versus 5 % in the control group (Lalezari 2003), but the European TORO-2 study did not confirm these results (Lazzarin 2003). Whether protease inhibitors (indinavir, saquinavir, ritonavir, and atazanavir) increase the risk of neuropathy, is still a matter of debate (Crabb 2004, Pettersen 2006)

Table 3: Neurotoxic drugs frequently used in HIV medicine

NRTI	ddI, ddC, d4T
Antibiotic	dapsone, metronidazole, isoniazid
Cytotoxic	vincristine

Acute neuromuscular weakness syndrome

In the course of a NRTI-induced lactic acidosis a life threatening tetraparesis resembling AIDP may occur. In most cases axonal peripheral nerve damage was found, but in a few patients demyelination was also detected. In addition, muscle biopsy revealed myositis or mitochondrial myopathy in some cases (Simpson 2004).

Table 4: Diagnostic work-up

Procedure	Findings	Condition
Basic examinations (recommended for all cases)		
Medical history	Drugs	Medication-related toxic PNP
	Opportunistic diseases	Neuropathy associated with CMV infection or lymphoma
	Alcohol abuse	Alcoholic PNP
Neurological examination	Clinical type of PNP (distal symmetrical, mononeuritis multiplex, etc.)	Symptoms not due to myelopathy or myopathy
Electromyography Electroneurography	Confirmation of neuropathy	Symptoms not due to myelopathy or myopathy
	Demyelinating features	AIDP, CIDP
	Axonal features	DSSP, Multiplex Neuropathy, DILS
Blood tests	HbA1c, glucose	Diabetic polyneuropathy
	Vit B12, B1, B6, Fe, ferritin	PNP due to malnutrition or malassimilation
	ANA, cryoglobulins, HCV-serology, circulating immune complexes, ANCA	Vasculitic neuropathy
	TPHA	Neurosyphilis
	CD8+ T-cells > 1200/µl	Neuropathy associated with DILS
	lactate	NRTI-induced toxic neuropathy
	CMV DNA (if CD4+ T-cells < 100/µl)	Mononeuritis multiplex due to CMV-infection
Additional tests (necessary only in particular cases)		
CSF	Elevated total protein	AIDP, CIDP
	Pleocytosis (granulocytes), CMV DNA	Polyradiculitis due to CMV infection
	Lymphoma cells, EBV DNA	Lymphomatous meningitis
	Elevated IgA, acid fast bacilli, mycobacterial DNA	Tuberculous polyradiculitis
Autonomic tests (sympathetic skin reaction, heart rate variability)	Involvement of sympathetic or parasympathetic nerves	Additional autonomic neuropathy
MRI (lumbar spine)	Compression of the cauda equina	Spinal lymphoma
		Spinal toxoplasmosis
Nerve and muscle biopsy	Necrotizing vasculitis	Vasculitic neuropathy
	Perivascular CD8 infiltration without necrosis	DILS-associated neuropathy

Polyneuropathy and polyradiculopathy due to other diseases

In patients with advanced HIV disease, mononeuritis multiplex may be caused by CMV infection or non-Hodgkin lymphoma. Acute or subacute polyradiculopathies of the cauda equina with rapidly progressive flaccid paraparesis of the legs, bowel dysfunction and sensory disturbances occur in the course of opportunistic infections (CMV, M. tuberculosis) or meningeal non-Hodgkin lymphoma. Other important causes of a polyneuropathy are alcohol abuse, diabetes mellitus, malnutrition in patients with long lasting gastrointestinal diseases, neoplastic diseases or cachexia.

Diagnosis

A diagnosis of neuropathy can usually be made based on medical history and clinical examination. Electrodiagnostic studies may be performed for confirmation and for differentiation from other diseases such as myelopathy. Cerebrospinal fluid analysis may be necessary if there is a suspicion of infection with, for example, CMV or syphilis. Sural nerve and muscle biopsy may only be necessary in atypical cases – for instance painful DSSP with a high CD4+ T-cell count and low viral load and without neurotoxic medication or other risk factors. Table 4 gives some recommendations for practical purposes in clinical practice.

Treatment

Causative treatment options only exist for some of the rare neuropathies or polyradiculopathies. Intravenous immunoglobulins and plasmapheresis have been proved effective in the therapy of AIDP. Corticosteroids are also effective in CIPD. In clinical trials on the treatment of CIDP, no difference in the efficacy of immunoglobulins, plasmapheresis or corticosteroids has been shown. However, an individual patient may just respond to one out of the three procedures. In patients who only respond to higher dosages of corticosteroids, other immunosuppressive agents such as azathioprine, low dose weekly methotrexate or cyclosporin may replace long term steroid therapy. We have seen CIDP patients who were in partial remission after temporary steroid therapy and who have remained stable for years with ART alone.

In medication-related neuropathy the offending agent should be withdrawn. However, replacement of ddI or d4T might be difficult in some cases of multiple drug-resistant HIV infection. In this situation, the reduction in the quality of life by neuropathic symptoms must be balanced against the risk of deterioration of immunological and viral parameters. A small open-label study with 2 x 3,500 mg L-acetyl-carnitine resulted in peripheral nerve regeneration, demonstrated in skin biopsies, and in improvement of neuropathic symptoms induced by neurotoxic NRTI (Hart 2004). Two small open studies confirmed the effectiveness of L-acetyl-carnitine in reducing pain in patients with neurotoxic neuropathy (Herzmann 2005, Osio 2006), but a randomized controlled trial is still lacking.

A causative treatment for DSSP does not exist. ART might improve the function of sensory nerves in a few cases, and therefore starting ART or optimizing a current ART should be considered in newly diagnosed DSSP. In most cases the neuropathic symptoms still persist.

Symptomatic treatment is directed at irritative symptoms such as pain and paresthesia. It is not effective against deficits of nerve function including sensory loss or weakness.

Table 5: Causative treatment of polyneuropathies and polyradiculopathies

Condition	Treatment
AIDP	Intravenous immunoglobulins 0.4 g/kg daily for 5 days *or*: plasmapheresis (5 x in 7-10 days)
CIDP	Intravenous immunoglobulins 0.4 g/kg daily for 5 days *or:* plasmapheresis (5 x in 7-10 days) *or:* prednisone 1-1.5 mg/kg daily for 3-4 weeks with subsequent tapering for 12–16 weeks
Vasculitic neuropathy	Prednisone 1-1.5 mg/kg daily for 3-4 weeks with subsequent tapering for 12–16 weeks
Neuropathy due to DILS	Start or improvement of ART plus prednisone 1-1.5 mg/kg daily for 3-4 weeks with subsequent tapering for 12–16 weeks
Distal symmetrical sensory polyneuropathy	A causative treatment is not known, ART may improve nerve function, for symptomatic treatment. See table 6
Medication–related toxic neuropathy	Withdrawal of the neurotoxic substances, if possible.
Mononeuritis multiplex or polyradiculitis due to CMV-infection	Intravenous foscarnet 2 x 90 mg/kg daily plus intravenous ganciclovir 2 x 5 mg/kg daily.
Lymphomatous meningitis	Start or improvement of ART plus intrathecal methotrexate (intraventricular shunt or lumbar puncture) 12-15 mg 2 x/weekly until CSF is free of malignant cells, subsequently 1 x/week for 4 weeks and subsequently 1 x/month plus 15 mg oral folinate after each injection plus systemic treatment of lymphoma (see chapter “Malignant Lymphoma”)
Polyradiculitis due to infection with M. tuberculosis	Treat tuberculosis (see chapter “OIs”)

The agents listed in table 6 are recommended because they have proved useful in daily practice and because they interfere only slightly and in a predictable way with ART. A controlled study showed that lamotrigine was effective in reducing the symptoms of neurotoxic neuropathy (Simpson 2003). The drug is well tolerated if one adheres to the slow dose escalation regimen and stops treatment or reduces the dose when a skin reaction occurs. In a small study, gabapentin was shown to be effective in reducing DSSP-induced pain (Hahn 2004). The advantages of this substance are good tolerability and lack of interference with ART. Pregabalin, an anticonvulsant drug similar to gabapentin, has recently been approved for the treatment of painful neuropathy. It effectively relieves pain in studies of patients with painful diabetic peripheral neuropathy. Like gabapentin, it does not interfere with ART and is well tolerated. We are successfully treating an increasing number of patients with DSSP and neurotoxic neuropathy with this new substance.

A randomized controlled trial could not detect a therapeutic benefit of lidocaine 5 % gel for the treatment of pain in HIV-associated neuropathy (Estanislao 2004).

Table 6: Symptomatic treatment of painful neuropathy

	Treatment	Adverse effects
Step 1:	Physical therapy, supporting measures (wide shoes, etc.), L-acetyl-carnitine 2 x 2–4 g	Rarely allergy, mild diarrhea
Step 2:	Temporarly 3-4 x 1000 mg paracetamol *or* 2-3 x 50 mg diclofenac *or* 4 x 40 drops novaminsulfone for 10-14 days	Nausea, vomiting, allergy (rarely)
Step 3:	Gabapentin 300 mg at night, dose escalation of 300 mg a day every third day up to a maximum of 3 x 1200 mg *or*	Sedation, nausea, dizziness, rarely pancreatitis
	Pregabalin 2 x 75 mg for 1 week, dose escalation to 2 x 150 in 2nd week, possible escalation up to 2 x 300 mg *or*	Nausea, vomiting, diarrhea, allergic drug rash
	Lamotrigine 25 mg at night, dose escalation of 25 mg every 5 days up to 300 mg *or*	Allergy, sedation, cephalgia, nausea
	Amitriptyline 25 mg at night, dose escalation of 10-25 mg every 2-3 days up to 3 x 50 mg *o* *r*	Sedation, orthostatic hypotension, constipation, dizziness, dry mouth, dysrhythmia, retention of urine, caveat: glaucoma
	Nortriptyline 25 mg in the morning, dose escalation of 25 mg every 2-3 days up to 2-3 x 50 mg *or*	Orthostatic hypotension, constipation, dizziness, dry mouth, dysrhythmia, retention of urine, caveat: glaucoma
	Duloxetine 1 x 60 mg in the morning	Nausea, diarrhoe, agitation
Step 4:	Flupirtine 3 x 100, dose escalation up to 3 x 600 mg *or*	Sedation, constipation, nausea
	Retarded morphine 2 x 10 mg gradual escalation up to 2 x 200 mg	Sedation, constipation, nausea
General practice	Proceed one step if symptoms persist. Substances within step 3 may be combined (for instance an anticonvulsant and an antidepressant), substances of step 3 and step 4 may also be combined (for instance flupirtine and an anticonvulsant). If a rapid relief of symptoms is necessary, treatment should be started with step 4 substances and a low dose step 3 drug should simultaneously be started with slow escalation. The slower the escalation the greater the possibility of reaching an effective dosage.	

The tricyclic antidepressants amitriptyline and nortriptyline both have significant anticholinergic side effects. The dose necessary for reducing neuropathic pain is in the same range as for treating depression and many patients do not tolerate these

dosages. However, lower dosages have proved ineffective in DSSP. Nortriptyline has no sedative side effects. We use this substance with good success rates, although clinical trials for its use in HIV-associated neuropathy are lacking. Duloxetine is the first of the new antidepressants that has proved effective in painful diabetic neuropathy. In our first experience, it seems to be also effective in HIV-related DSSP and toxic neuropathy. The anticonvulsant carbamazepine is widely used for the treatment of neuropathic pain. However, it induces some enzymes of the CYP450 system and interferes significantly with ART. Thus its use in HIV medicine is very limited. Potent opioids may be used to manage moderate or severe pain if a slow dose esca-lation of an antidepressant or anticonvulsant is not possible and an immediate anal-gesic effect is desired (Sindrup 1999). Even in cases of substituted or non-substituted drug abuse, opioids should be used (Breitbart 1997). Sometimes, the dosage of methadone must only be moderately increased for a sufficient analgesic effect.

Myopathy

Myopathies occur in 1-2 % of all HIV patients. They may appear at any stage of the disease. Table 7 gives a synopsis of the most important types of myopathy in HIV infection.

Polymyositis mediated by cytotoxic T-cells is the most common HIV-associated myopathy. AZT-induced myopathy occurs very infrequently with the AZT dosages used today. Some substances commonly used in HIV medicine (ddI, cotrimoxazole, pentamidine, sulfadiazine, lipid lowering drugs) may rarely cause acute rhabdomyolysis with tetraparesis and marked elevation of serum CK levels. Notably, PIs raise the serum concentration of statins increasing the risk of statin-induced myopathy and rhabdomyolysis (Hare 2002).

An elevated serum CK activity is frequently observed during treatment with TDF, especially in patients with HBV- or HCV-coinfection. This is due to a type 2 macroenzyme creatine kinase (Macro CK) and must not lead to suspicion of ischemic or muscular disease. The accumulation of this liver-derived isoenzyme seems to be the result of an insufficient Macro CK2 clearance capacity mediated by TDF (Schmid 2005).

Clinical features

Myopathy in HIV infection usually presents with exercise-induced myalgia of proximal muscles followed by slowly progressive, symmetrical weakness and atrophy of proximal muscles. Limb girdle muscles are most commonly involved, but distal muscles and muscles of trunk, neck, face or throat may also be affected.

Diagnosis

Myalgia, fatigue and elevated serum CK levels are frequently found in HIV infection. But these unspecific symptoms and signs on their own do not warrant the diagnosis of myopathy. The diagnosis of probable myopathy requires weakness, muscle atrophy or myopathic features demonstrated by electromyography. A muscle biopsy confirms the diagnosis and may give some additional clues to the classification and pathogenesis of the muscle disease.

Table 7: Myopathies in HIV infection

Primary HIV-associated	Secondary
Polymyositis	AZT myopathy
Nemaline (rod body) myopathy	Vasculitic myopathy
Vacuolar myopathy	Lymphomatous muscle infiltration
Inclusion body myositis	Infectious myositis
	Medication-related toxic rhabdomyolysis

Treatment

Moderate myalgia may respond to non-steroidal anti-inflammatory drugs.

Prednisone (100 mg daily for 3-4 weeks, subsequent tapering) or intravenous immunoglobulin (0.4 g/kg for 5 days) have been shown to be effective in treatment of polymyositis (Espinoza 1991, Viard 1992).

The treatment of AZT myopathy is cessation of the drug. Myalgia usually resolves within 1-2 weeks. If symptoms persist for 4-6 weeks, prednisone as described above may be effective.

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28. HIV and Psychiatric Disorders

Susanne Tabrizian and Oliver Mittermeier

Psychiatric disorders occur frequently in HIV-infected patients but the reported prevalence rates differ considerably, depending on the stage of infection and study population. Fact is, though, that there are multiple factors that can have an impact on comorbid psychiatric illness: psychiatric disorders, e.g. substance abuse, can be an independent risk factor for HIV infection. Furthermore, there are the neuropathological effects of the virus itself, and there is evidence that the infection of microglia leads to neuronal damage due to the excretion of neurotoxins. Additionally, opportunistic infections and some of the antiretroviral drugs may cause psychiatric symptoms.

Apart from the affection of the patient's well-being, psychiatric disorders may lead to problems in antiretroviral therapy: adherence to antiretroviral medication becomes poorer. Therefore, early diagnosis and therapy of psychiatric disorders are of vital importance for HIV-positive individuals (Angelino 2001).

Major depression

Major depression is the most frequently occurring psychiatric disorder in HIV patients. Reports on prevalence rates differ substantially and reach up to 40 % (Angelino 2001). Major depression is a severe illness with serious complications: up to 15-20 % of all patients with recurrent depressive episodes commit suicide. Further common complications are physical, social or role model function impairment (Low-Beer 2000).

Major depression interferes with all aspects of being and may have a severe impact on quality of life. It is characterized by depressed mood, decreased energy and loss of interest. Patients tend to be unable to experience joy or satisfaction in activities that would usually generate these feelings; they may feel ill, lack energy and experience a sense of doom. Also feelings of guilt, a lack of self-esteem and self-reproach are frequent (Angelino 2001). Additionally, neurovegetative symptoms such as loss of appetite and sleep disturbances with so-called early morning wakening or fatigue are common. Furthermore, depressed patients describe somatic symptoms such as pain or vertigo. Often the severity of symptoms changes during the day with greater severity in the morning and relief in the evening. Poor concentration and cognitive impairment, the so-called pseudodementia in depression may also occur. The individual presentation of these symptoms varies notably and may therefore make diagnosis difficult.

Two simple questions, though, may provide valuable hints:

1. During the past month have you often been bothered by feeling down, depressed or hopeless?
2. During the past month have you often been bothered by little interest or pleasure in doing things?

These two questions are being recommended by the U.S. Preventive Services Task Force for screening for depression in primary care. If at least one of the two ques-

tions is confirmed by the patient, further diagnostic testing is recommended (Pignone 2002). This screening can be improved by simply inquiring wether help is needed. Asking "is this something with which you would like help?" improves the specificity of general practitioners diagnosis for major depression significantly (Arroll 2005).

The following criteria of ICD-10 should be explored when making a diagnosis of depression:

a) Pervasive low mood (see above)

b) Loss of interest and enjoyment (see above)

c) Reduced energy, diminished activity

d) Disturbed or increased sleep

e) Diminished or increased appetite

f) Poor concentration and attention

g) Poor self-esteem and self-confidence

h) Ideas of guilt and unworthiness

i) Psychomotor retardation or agitation

j) Ideas or acts of self-harm or suicide

Therapy is indicated if symptoms last for more than two weeks and when at least two of the first three symptoms in addition to at least one of the other symptoms are reported by the patient.

All of these symptoms might occur as a reaction to a stressful life event or sad circumstances. In these cases treatment is not immediately necessary. If the symptoms persist for an unreasonable period of time – more than a couple weeks – a depressive episode might have been triggered. This should then be treated accordingly (Ebert 2001). Aggressive treatment is also obviously necessary in suicidality. HIV-positive patients are more at risk than the general population. The highest rate of suicidal thoughts and attempts occur approximately one to two years after diagnosis of HIV infection. Altogether, though, the rate of suicide among HIV patients has dropped recently – probably due to the improvement of therapy since the beginning of the HAART era (Einsiedel 2001).

Treatment

Treatment of depression is based on two principles: medication and psychotherapy. Since we cannot discuss different aspects of psychotherapy in this article, we will focus on pharmacological treatment. In general, treatment of depressed HIV-infected patients does not differ from that of other patients. It is shown in various studies, that antidepressant medication is efficacious in treating depression among depressed, HIV-positive individuals (Himmelhoch 2005). Medication should therefore always be part of a therapeutic regimen. It should consist of acute phase therapy, maintenance therapy and prophylaxis of a relapse of depression. The goal of treatment should be the complete remission of depressive symptoms. After alleviation, treatment should be continued for at least six months. At the end of treatment, medication should be reduced slowly over a period of weeks.

Once antidepressant medication has been initiated, it may take two weeks for patients to experience a benefit. Side effects, however, might occur earlier, and patients should be informed about this. A non-response to treatment is considered when – given a standard dose of medication or therapeutic serum levels have been attained – there is no relevant benefit for the patient after four to six weeks (Benkert 2003).

At such time, a switch to an antidepressant of another class should be considered. Another period of two to four weeks latency for the therapeutic effect has to be taken into account. Alternatively, an augmentation strategy – added medication with e.g. lithium or thyroid preparations – could be started, since effects might be seen earlier. Sometimes the combination of two antidepressants might bring relief. These strategies should only be provided by experienced therapists. Without thorough experience in treating psychiatric disorders, one should concentrate on three to four antidepressant drugs. In this way, side effects and therapeutic benefits can be more easily observed.

The choice of the appropriate antidepressant can be based on the side effect profile, e.g. sedating vs. activating. Previous therapies are important too: a drug that previously had beneficial results in a patient will be effective in this patient again (Ebert 2001).

Selective serotonin (5-HT) re-uptake inhibitors

So-called serotonin (5-HT) re-uptake inhibitors (SSRI) are considered to be first-line medication in depressed HIV-positive patients since they are effective and well tolerated. Starting with low doses reduces the probability of adverse effects.

Recently, there have been reports on SSRI medication precipitating suicide, especially in children and adolescents. When looking at available data though, these findings are not consistent and are not easily transferable to adults. In most countries, population suicide rates have fallen in the last years even though significantly more antidepressants - and especially SSRIs - have been prescribed. Furthermore, it is difficult to show effects of medication on suicide since suicide is rare, even among depressed patients, and it is therefore difficult, especially in short clinical trials, to assess the risks of medication-related suicides statistically. However, long-term studies are required to gain further information on benefits and risks of antidepressant medication (Gunnel 2004).

Overall, the risk of suicide for adults does not seem to be increased by medication with SSRIs. This is for instance supported by a recent swedish database study, examining nearly 15000 suicides that found no increased risk for the treatment of depressed individuals with SSRIs (Isacsson 2005). Nonetheless, doctors should closely monitor patients with psychiatric disorders, regardless of their medication, for suicide risk, and, if indicated, ask for suicidal thoughts or self-harm in order to react promptly.

Table 1: Selective Serotonin (5-HT) Re-uptake Inhibitors (SSRI) *

Drug (Trade name™)	**Dosage / day (generally once daily administration)**	**a) Interactions with HAART b) Evaluation / comments c) Selected side effects**
Citalopram (Cipramil™, Sepram™)	20 mg in the morning, therapeutic dose is 20-60 mg	a) Lopinavir/r, ritonavir increase citalopram levels b) effective, well tolerated, non-sedating antidepressant c) Initially diarrhea, nausea, decreased sexual arousal / erection
Fluoxetine (e. g. Fluctin™, Prozac™)	10 mg in the morning for 2-3 days, then 20 mg	a) Increased levels of amprenavir, delavirdine, efavirenz, indinavir, lopinavir/r, nelfinavir, ritonavir and saquinavir. Nevirapine decreases fluoxetine levels b) Activating; most clinical trials conducted with fluoxetine c) see above
Fluvoxamine (Fevarin™, Fluvoxamin-neuraxpharm™)	50 mg in the morning, after 3-4 days increase dose to 100-200 mg	a) Increased levels of amprenavir, delavirdine, efavirenz, indinavir, lopinavir/r, nelfinavir, ritonavir and saquinavir. Nevirapine decreases fluoxetine levels b) Potent inhibitor of CYP1A2 c) see above
Paroxetine (Seroxat™, Tagonis™)	10 mg in the morning for 2-3 days, therapeutic dose is 20 mg	a) Lopinavir/r, ritonavir increase paroxetine levels b) Somewhat sedating, administration at bedtime if possible c) see above
Sertraline (Gladem™, Zoloft™)	25-50 mg in the morning, lowest effective dose 50 mg, maximum 150 mg	a) Lopinavir/r, ritonavir increase sertraline levels b) Non-sedating. In agitation, akathisia, or insomnia, combination with benzodiazepine possible – applicable for all SSRIs c) see above

* Note: SSRIs should not be combined with monoamine oxidase inhibitors (MAOI) e.g. Moclobemid (Aurorix™). Adjustment of dosage is required in renal or hepatic disorder. (Angelino 2001, Benkert 2001, Einsiedel 2001)

Tricyclic antidepressants

Tricyclic antidepressants (TCAs) – named after their chemical structure which contains three rings – are effective and, in HIV patients, well studied agents. However, side effects are more frequent in this class of antidepressants. Their anticholinergic effects need to be pointed out: they are contraindicated in patients with urinary retention and closed-angle glaucoma and they should be avoided in patients with bundle branch blocks. Furthermore, TCAs are easier to under- or overdose than SSRIs. Serum levels should therefore be obtained if possible.

Table 2: Tricyclic antidepressants

Drug (Trade name™)	**Dosage/day**	**a) Interactions with HAART b) Evaluation/comments c) Selected side effects**
Amitriptyline (e. g. Saroten™, Laroxyl™, Novoprotect™, Amineurin™)	Initially 2-3 x 25 mg usual therapeutic dose 3 x 50 mg or 2 x 75 mg	a) Lopinavir/r, ritonavir increase amitriptyline levels b) Promotes sleep. Weight gain, constipation – might be desired side effects c) Delirious syndrome when fast dose increase
Clomipramine (Anafranil™, Hydiphen™)	2-3 x 25 mg for three days usual therapeutic dose 3 x 50 mg or 3 x 75 mg	a) Lopinavir/r, ritonavir increase clomipramine levels b) Initially possible agitation, combination with benzodiazepine possible, also see above c) Effective in chronic pain
Doxepin (Aponal™, Sinquan™)	Initially 3 x 25 mg usual therapeutic dose 3 x 50 mg or 3 x 75 mg	a) Lopinavir/r, ritonavir increase doxepin levels b) see above c) Often orthostasis
Imipramine (Tofranil™, Pryleugan™)	2-3 x 25 mg for three days usual therapeutic dose 3 x 50 mg or 3 x 75 mg	a) Lopinavir/r, ritonavir increase imipramine levels b) see above c) Especially at the start of therapy anticholinergic adverse effects

For further reading see Angelino 2001, Benkert 2001, Einsiedel 2001

Other drugs / therapies

There are numerous other antidepressants but at the time being there is not much data on their use in HIV-infected patients. These include the noradrenergic and serotonergic drug mirtazapine (unlike SSRIs and tricyclic agents, there are so far no reports on sexual dysfunction with this drug) and the combined serotonin-noradrenaline re-uptake inhibitor venlafaxine. The selective noradrenaline re-uptake inhibitor reboxetine seems to be interesting in the therapy of HIV-infected patients since it is not metabolized via cytochrome P450 (CYP450) (Carvalhal 2003).

Table 3: Other antidepressants

Drug (Trade name)	**Dosage / day**	**a) Interactions with HAART b) Evaluation / comments c) Selected side effects**
Mirtazapine (Remeron™)	Initially 15 mg at bedtime usual therapeutic dose 30-45 mg	a) not known b) Sedating, promotes sleep, weight gain no sexual dysfunction c) Cave!: not in leukopenia!
Reboxetine (Edronax™)	Initially 2 to 4 mg maintenance therapy 8 mg to 12 mg	a) not known b) not sedating c) Dry mouth, insomnia, sweating, tremor and urinary retention. Cave!: Dose reduction (2 x 2 mg) in renal or hepatic insufficiency
Venlafaxine (Trevilor™)	Initially 37.5 mg in the morning administer twice daily maintenance therapy 75 to 375 mg/day	a) Lopinavir-ritonavir, ritonavir increase venlafaxine levels b) Extended release formulation with lesser side effects. Effective in anxiety c) Initially high rates of gastrointestinal side effects. RR ↑, allergic skin reactions, delayed ejaculation

For further reading see Angelino 2001, Benkert 2003

New formulations of existing antidepressants are being developed: intravenous formulations with a faster onset of antidepressant action or a once-weekly administered SSRI. (Norman 2004). Furthermore, single enantiomers have been introduced in several countries, e.g. the S-enantiomer of the SSRI citalopram, escitalopram. It is more than twice as potent at inhibiting serotonin uptake and is supposed to maintain therapeutic efficacy at a lower effective dosage. Pharmacokinetic interaction with ritonavir – a CYP3A4 substrate and prototype CYP3A4 inhibitor – which may potentially affect plasma concentrations of escitalopram, was not clinically significant (Gutierrez 2003). None of these agents, however, will be a sovereign remedy, and one should, especially when experience in psychiatric care is limited, only use a few drugs and know them well instead of trying all available substances.

In addition to the above, herbal medicines are also in use, even though there is an ongoing discussion about their effectiveness. There were great expectations espe-

cially about St. John's wort – a herbal substance without serious adverse effects – when clinical trials demonstrated an antidepressant effect in mild to moderate depression (Linde 1996). Unfortunately hopes have fallen somewhat since St. John's wort did not show an advantage above placebo in further clinical trials (Hypericum Depression Trial Study Group 2002). Remarkably enough, though, the SSRI in this trial was not very effective either and merely showed a positive trend above placebo in effectiveness.

In addition to the above, there are more therapeutic options aside from medication, e.g. controlled sleep withdrawal, where the patient has to stay awake throughout the night. Following this procedure, there is a significant reduction of symptoms the next day in about one half of treated patients– but only until the next night's sleep. Repeated sleep withdrawal, though, might reduce the duration of a depressive episode. Phototherapy, especially in seasonal depression, and electroconvulsive therapy carried out in specialized centers for non-responding patients, are therapeutic options too. There are no data on these therapies in HIV patients. Evidence does exist, however, from small clinical trials for a therapeutic effect of exercise in HIV patients (Neidig 2003). Three times a week jogging for half an hour is a good antidepressant and a therapeutic chance that is possibly not tried often enough.

Psychotic disorders

Psychotic means the occurrence of delusions or prominent hallucinations, and typically the patient has no insight into their pathologic character. The prevalence of psychotic disorders in individuals with HIV or AIDS is rather unclear: rates vary between 0.2 and 15 % (Sewell 1996). Basically, psychotic disorders can be classified into two different forms:

Primary psychotic disorders

Psychosis that occurs independently of infection with HIV is to be seen as a comorbid condition. Diseases such as schizophrenia, schizophreniform disorder and brief psychotic disorder can be classified into this group. Typical symptoms are delusions, hallucinations, disorganized speech (e.g. frequent derailment or incoherence) or grossly disorganized or catatonic behavior. Etiopathogenetically, a biopsychosocial concept, the vulnerability-stress-coping model, is assumed. It is thought that genetic and psychosocial factors determine a predisposition or an increased vulnerability for psychotic decompensation.

Therefore, an infection with a neuropathological virus such as HIV could trigger a pre-existing psychosis (Einsiedel 2001).

Secondary psychotic disorders

Characteristic symptoms of a secondary psychotic disorder are prominent hallucinations or delusions. They are caused by an organic disorder of the central nervous system (CNS) as a consequence of a general medical condition. In HIV patients this could, for example, be an opportunistic infection, cerebral lymphoma or HIV encephalopathy. In addition to that, psychotic symptoms can be caused by medications or drug-drug interactions e.g. in HAART (Foster 2003). Therefore an exact

history of medication and especially recent changes in medication are of vital interest.

The occurring delusional themes are numerous, including somatic delusions, delusions of grandeur, religious delusions, and, most frequently, paranoia or persecutory delusions. Diseases that affect subcortical structures or the temporal lobes are more frequently associated with delusions than others. In hallucinations, every sensory quality (auditory, visual, olfactory, gustatory or tactile) might be affected.

Patients with a previously undiagnosed general medical condition, such as HIV infection, might develop an acute psychiatric condition due, for example, to HIV encephalopathy, brain damage from an opportunistic CNS infection such as toxoplasmosis, neoplasms involving the CNS, or metabolic dysfunction. In all acute psychotic disorders, a magnetic resonance image of the brain (more sensitive than computed tomography) and examination of cerebral spinal fluid should therefore be carried out as soon as possible. HIV infection does not show any specific psychopathological findings (Röttgers 2000).

Treatment

While in organic psychosis, the causative general medical condition must be treated first, in primary psychosis, according to its multifactorial etiology, therapy should consist of a combination of pharmacological, psychotherapeutic, psychoeducational and sociopsychiatric intervention.

Symptomatic treatment with neuroleptics is initially the most important line of treatment in the acute phase of primary psychotic disorders. In principle, the pharmacological treatment of HIV patients does not differ much from that of other populations, but it should be started at low doses and titrated cautiously (Farber 2002), since a dysfunction of the blood brain barrier and consequently a higher rate of medication side effects is to be expected: start low, go slow!

In acute psychotic disorder, regardless of the etiology, the use of a conventional antipsychotic agent, e.g. haloperidol 5 mg PO or IM, is usually successful. For additional sedation in cases with more severe agitation, comedication with a benzodiazepine is possible. When aggressive behavior is present, diazepam 5 to 10 mg PO or IM is a good choice; if fear or anxiety is the leading symptom, lorazepam up to 2.5 mg is indicated. In the further course of treatment, change to an atypical antipsychotic agent (see below) is recommended.

In less acute symptomatic psychotic disorders and in primary comorbid psychosis the use of atypical antipsychotic agents is again the treatment of choice, due to various reasons: atypical antipsychotic agents cause significantly less extrapyramidal symptoms (EPS) and tardive dyskinesia (TD) than typical antipsychotic drugs. Furthermore, they might provide an advantage in non-responding patients and in the treatment of negative symptoms: *asociality*, the withdrawal from relationships; *avolition*, the loss of initiative and drive; *affective flattening* or inappropriateness; *alogia*, a poverty of speech production and content; *anhedonia*, difficulty experiencing pleasure. These are often the most debilitating symptoms in psychotic disorders. Because of the lower risk of developing EPS and TD – for which HIV-infected patients are more susceptible than others – treatment with atypical antipsychotic agents might improve adherence to psychopharmacological treatment

too. In case of insufficient effectiveness, a different atypical antipsychotic agent should be selected after approximately four weeks.

Table 4: Atypical antipsychotic agents

Drug (Trade name)	Dosage/day	a) Interactions with HAART b) Evaluation/comments c) Selected side effects
Amisulpirid (Solian™)	twice daily positive symptoms: 400-800 mg negative symptoms: 50-300 mg maintenance therapy: 200-400 mg	a) No interaction to be expected b) Nearly complete renal elimination, poses advantage in patients with liver damage c) EPS in doses > 400 mg/d possible, usually not severe
Clozapine (Leponex™)	prescribing doctor needs to register at manufacturers start with 6.25-12.5 mg, increase every 1-2 days by 25 mg to max. 600 mg. maintenance therapy: 100-400 mg	a) Because of risk of agranulocytosis (1-2 %) in HIV patients not recommended b) Atypical antipsychotic agent with significance for non-responding schizophrenia and in patients with non-tolerable EPS c) Agranulocytosis; seizures; sedation; weight gain and hyperglycemia
Olanzapine (Zyprexa™)	starting dose 5 mg h.s. maintenance 5-20 mg when sedation during daytime is wanted: two to three doses/day	a) No interaction with PIs b) Good antipsychotic effect. Few EPS when < 20 mg. Trials with HIV patients available. Side effects, weight gain (depending on dosage) and/or sedation might be favorable. c) In 1-10 %: EPS (e.g. akathisia), drowsiness, orthostasis, liver enzymes↑. Cave!: hyperglycemia possible
Quetiapine (Seroquel™)	start with 25 mg slow titration to 300 to 450 mg divided into two doses/day	a) Contraindication in combination with ritonavir, macrolide antibiotics and ketoconazole. b) No trials with HIV patients published. c) Common (>10 %) sedation, drowsiness. Occasionally orthostasis, liver enzymes↑, weight gain. Cave!: Leukopenia
Risperidone (Risperdal™)	slow titration over one week start with 0.5-2 mg maintenance dose: 4-6 mg divided into two doses/day in renal or hepatic insufficiency do not exceed 4 mg/day !	a) NRTIs increase risperidone plasma level. b) Good antipsychotic effectiveness. Dose dependent EPS: seldom when ≤ 6 mg. Trials with HIV patients published. No influence on blood count, no increase in seizures. First atypical antipsychotic agent available in long acting formulation (twice weekly). c) Orthostasis, especially in the beginning and at high doses – titrate slowly!

Table 4: Atypical antipsychotic agents

Drug (Trade name)	Dosage/day	a) Interactions with HAART b) Evaluation/comments c) Selected side effects
Ziprasidone (Zeldox™)	start with 2 x 20 mg Maximum dose is 2 x 80 mg IM administration possible.	a) Not examined b) So far no trials with HIV population. Contraindicated in patients with long QT interval, cardiac arrhythmias, myocardial infarction. EPS rates not higher than in placebo. Only minimal weight gain. c) Cave: QTc prolongation! > 1 %: drowsiness, hypotension, sedation

Acute treatment in psychiatric emergency

Most important: de-escalation by "talking down" – this includes measures such as staying in contact with the patient, taking him seriously and adopting a non-confrontational position. Should the use of restraints be necessary, stay calm but act firmly. Always leave the patient the chance to correct inappropriate behavior and always use the least possible restrictive method of restraint.

Table 5: Psychiatric emergency (Benkert 2003; Currier 2004)

Diagnosis	Psychopharmacological treatment
Agitation in acute psychosis	Haloperidol 5-10 mg PO or IM, may be repeated after 30 min, maximal 50 mg in the first 24 hrs. Cave: EPS – then 2.5-5 mg (1/2-1 Amp.) biperidene (Akinethon™) IV or IM.
Agitation and aggression in mania Acute intoxication with psychoactive drug	**plus** oral or IV application of 2 mg lorazepam, when panic is predominant; maximum dose 10 mg / day (inpatient) **or** diazepam, when stronger sedation is needed; in aggressive patients: 10 mg PO, IM or slowly IV. Repetition after 30 min possible. Maximum dose 40-60 mg parenteral or 60-80 mg oral (inpatient). Cave: hypotension, respiratory depression **alternatively** oral treatment with 2 mg of risperidone plus 2 mg of lorazepam (Currier 2004)
Delirium due to general medical condition (e.g. infection, exsiccosis, electrolyte metabolism disorder)	treatment of general medical condition if necessary antipsychotic agent e.g. melperone 50-100 mg for sedation or haloperidol (especially in psychotic symptoms) 2-5 mg PO or IM.
Drug-induced delirium (e.g. antidepressants, antibiotics, rarely efavirenz or others)	change or reduce causative substance in accordance to severity of symptoms, if necessary antipsychotic agent e.g. melperone 50-100 mg for sedation or haloperidol 2-5 mg PO or IM in hospitalized patients if necessary clomethiazole 2 capsules every 2 hours, maximum dose 20 capsules/day. Cave: respiratory depression, hypersecretion; strictly for inpatients only!

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29. Sexual Dysfunction in HIV/AIDS

U. Fritz Bredeek and Christoph Mayr

Introduction

In the "Multinational Survey of Aging Males' (MSAM), the 14,254 interviewed men age 40 to 70, voiced continuous interest in sexual activity: 83 % rated sexual desire and interest as an important to very important component of their lifes. The mean number of sexual intercourse was 5.8 per month in that age group. On the other hand studies have shown that erectile dysfunction has serious impacts on the overall quality of life (Feldman 1994).

Various factors affect sexual function and overall satisfaction not at least age (Feldman 1994). HIV infection may lead to sexual dysfunction because of well known interactions between the immune system and the reproductive, endocrine and the neuroendocrine systems. The impact of the knowledge of HIV infection on the psyche cannot be underestimated, and furthermore long-term highly active antiretroviral therapy (HAART) might additionally have negative psychological effects on sexual health. Lipodystrophy Syndrome can be caused by HAART,which shares some characteristics of the classic metabolic syndrome, for instance the increased insulin resistance, excess weight, dyslipidemia or hypertension. The clear association between metabolic syndrome and erectile dysfunction (ED) makes ED a predictive marker for the metabolic syndrome (Shabsigh in 2005).

Still, many questions remain regarding the causes of sexual dysfunction in HIV and its treatment.

Definitions

Erectile dysfunction or Impotentia coeundi is defined as the "constant or repeated appearance of an inability to attain or maintain an erection sufficient for satisfactory sexual intercourse," (NIH 1993). The diagnosis requires a minimum of 6 months of ongoing problems with 70% or more of the attempts for sexual intercourse unsuccessful.

Important is the differentiation between ED and libido disturbance, defined as a decreased or entirely absent sexual drive or desire, and ejaculation disturbance, with its main signs of Ejaculatio praecox or tarda.

Etiology of sexual dysfunction in HIV/AIDS

Causes of sexual dysfunction (SD) are plentifold. A paradigm shift has taken place since 1980: Improved diagnostic tests and increasing knowledge of the aging processes in men have led to the conslusion that 80% of ED have some organic component and 50% are exclusively organic in nature. A truely only psychological cause is responsible for just 20% of cases (NIH in 1993). A disease-specific peculiarity of HIV is the fact that the probability of a SD is not only increased by the chronic

illness but also by comorbidities associated with HIV, i.e. the aging patient population, psychosocial stressors and the need for polypharmacy (Crum 2005).

Age

The most important biological cause of ED is age. ED exists in variable degrees, from light (17 %) to moderate (17-34 %) to complete (5-15 %) in 52 % of all men aged 40 to 70 years (Feldman 1994). The overall prevalence of ED ranges from 7 % in men aged 18-29 years (Braun 2000) to 85 % in men aged 76-85 years.

Both the increased lifespan and the higher quality of life in HIV patients have an increasing influence on the incidence of SD. Changes that occur with age, like the declining testosterone production, decreasing sensitivity of the erectile tissues secondary to decreasing neural or hormonal activity and vascular problems are further boosted in the context of HIV infection and its therapy.

Risk factors: diseases and comorbidities

Important ED risk factors coexist frequently in HIV patients, including excessive alcohol consumption, smoking and other recreational drug use; metabolic disorders (hyperlipidemia, diabetes mellitus); and cardiovascular disease, with hypertension being of particular importance. Pathophysiologically, most cases of ED are caused by neuronal (polyneuropathy) and vascular (micro- and macroangiopathy) changes; however, ED can also be an early sign of a metabolic syndrome.

Other possible risk factors are endocrine disorders, various neurological problems (i.e. disc prolapse) or infectious diseases. Frequent causes of ED in young men are chronic kidney or liver dysfunction (hepatitis, cirrhosis). Psychosocial problems, relationship conflicts and psychiatric illnesses (e.g., depression) are frequently related to sexual dysfunction. As a consequence, HIV patients have an increased risk for erectile dysfunction.

Table 1: Substances/Substance classes which may cause Erectile Dysfunction

Alcohol	Nicotine
Antihypertensives	Antidepressants
Diuretics	Antirheumatics (NSAR)
Lipid lowering agents	H2-Antagonists, proton pump inhibitors
Anticonvulsants	Tranquilizers
Opiates	Gestagens/estrogens
Chemotherapeutics, HAART	Amphetamines, hallucinogens

Medications

Many drugs have a negative impact on sexual function, mainly on libido and the arousability. Table 1 lists an overview of relevant drug classes in this context. Antiretroviral medications are also associated with SD; and both duration and combination of therapies have an accelerating effect. In a standardized survey on 78 HIV-infected men who have sex with men (MSM), conducted by Cove in London in 2004**,** 69 % reported on at least one occasion dysfunction and 38 % indicated ED.

All antiretroviral drugs can decrease sexual function. Some studies (Colson 2002, Schrooten 2001, Martinez 1999) mention Protease Inhibitors (PI's) to be the main culprit, but this was unble to be confirmed by Lallemand, 2002. Furthermore, our own studies suggest that combinations of NRTIs and PIs may cause this problem equally.

Ongoing research

An increased prevalence of SD, up to 50%, was observed in HIV-infected men in the early 1990s (Tindall 1994). Similar results were seen in HIV-positive women (Goggin 1998). A clear increase in prevalence of both libido loss (48%) and ED (25%) was seen by Lamba in 2004 in HIV positive MSM on HAART, compared to HIV positive MSM not on HAART (both at 26%) or HIV negative MSM (2% and 10% respectively).

A European study (Schrooten 2001) on 904 HIV-infected men and women showed that libido loss and ED is significantly more common in patients on a PI containing HAART regimen compared to patients not taking PIs (40% vs. 16% for LL and 34% vs. 12% for ED, respectively). In a multivariate analysis, the following factors were identified for libido loss: Current or past use of a PI, symptomatic HIV infection, age, and MSM. Additionally, taking tranquilizers was found to be an independent risk factor for ED.

The impact of PIs in SD was also seen by Collazos (2002) in a prospective study of 189 patients. No correlation could be found between measured sex hormone levels and incidence of SD. Interestingly, in subjects taking a PI-containing regimen, testosterone levels were significantly higher compared to NNRTI-containing regimens in which 17ß-estradiol levels were significantly elevated**.**

In a standardized questionnaire of 156 MSM, no role for PIs as the cause of SD could be ascertained (Lallemand 2002). 71% of the participants indicated signs of SD since initiation of ART; however, in therapy stratified groups (PI: 71%, without PI: 65%, no PI in the last 4 weeks: 74%) there were no significant differences seen between patients taking or not taking a PI. 18% of the participants had already suffered from SD before the diagnosis of HIV infection, and 33% before the initiation of ART. The impact of psychological factors is highlighted by one study, in which the rate of HIV-positive MSM with ED rose from 38 to 51% with the use of condoms (Cove in 2004).

More recent research impressively underscores the positive effect of testosterone substitution in HIV-infected hypogonadotropic men (Rabkin 2000, Grinspoon 1998). Testosterone deficiency can cause weight loss, loss of muscle mass, osteopenia, and depression (Grinspoon 1996, Huang 2001).

Diagnosis of sexual dysfunction

A diagnostic work-up for the causes of SD is required before therapy. This includes a complete anamnesis with emphasis on sexual, social and family history as well as social (recreational drug use) and familiar risk factors (i.e. diabetes mellitus), and a complete medication history. A thorough physical examination is obligatory. A diagnostic test of the morning blood level of testosterone is of central importance to

determine the testicular endocrine function. The calculated index of free testosterone is the recommended parameter to follow, since this index reflects the real biological activity of testosterone. The direct determination of free testosterone by the lab has been identified as being unreliable (www.issam.ch).

Table 2: Laboratory diagnostics for erectile dysfunction

Special hormone diagnostics	General work-up
Testosterone (free circulating testosterone)	CBC
Luteotropic hormone	Glucose, HbA1c
Follicular stimulating hormone	Lipid panel
Poss. LHRH	
Poss. HCG	possible: TSH
Poss. Prolactin, PSA	Urine analysis

Low testosterone level requires maesurement of LH and FSH. Further work-up may require an LH or FSH stimulating test, usually handled by an endocrinologist, to exclude secondary hypogonadism. NPT (nocturne penile tumescence measurement) is considered minimally invasive and measures nocturnal erections. 3-6 erections per night of at least 70 % rigidity, lasting 10 minutes, are considered normal values. The question of morning erections can serve as critical criterion for the sexual anamnesis.

Further andrological diagnostics include sonography of the scrotum and, if the mammary glands are enlarged or involvement of the hypophysis is suspected (i.e. by an increased prolactin or estrogen level), an MRI of the Sella turcica is indicated. Other diagnostic tests used for the vascular work-up include Doppler sonography of the penis and pharmacocavernosography; and for the neuro-physiological work-up a Cavernosum EMG, vibrometry, sphincter- and N. pudendus-EMG. These are rarely necessary and left to the urologist.

Therapy for sexual dysfunction

General overview

Phosphodiesterase 5 inhibitors (PDE-5 inhibitors: sildenafil, vardenafil, tadalafil) have substantially improved the therapy of ED. They are simple to take, effective and, in general, relatively well tolerated. However, with the exception of a few private insurance companies, PDE-5 inhibitors are not covered by insurance plans. and so must be paid for by the patients themselves. With the introduction of PDE-5 inhibitors, intra-cavernous erectile tissue injection or the intra-urethral application of vasoactive prostaglandins has clearly receded into the background. Today, surgical interventions, such as penile vein surgery, revascularization surgery or prosthodontics, also no longer play a role.

For HIV physicians the interactions between PDE-5 inhibitors and HAART (particularly protease inhibitors and the NNRTI delavirdine) are important factors. Through the inhibition of the cytochrome p450 enzyme system (CYP3A4) plasma levels of PDE-5 inhibitors are increased. This needs to be discussed with the pa-

tient. In particular, for patients using a boosted PI regimen PDE-5 inhibitors need to be started at a lower dose. We specifically recommend a mini test dose at the beginning (e.g., 1/4 of a tablet of sildenafil 50 mg) and increase according to the success and side effects. Our experience indicates that a significant proportion of patients have the desired success with such a low dose. However, some patients do not achieve any effect with these low dosages (HIV infection of several years, multimorbidity, and psychological overlap). In these patients, the approved maximum dose should not be exceeded. Simultaneous administration of nitrate containing medications or substances containing nitrites ("poppers"!) is contraindicated since it may cause therapy-resistant hypotension.

Sexual activity is physically tiring and can be a strain on the cardiovascular system. If it is not clear whether a patient has an underlying cardiovascular problem, it is advised to screen for it before prescribing ED drugs. This is particular true if unstable angina is suspected.

Apomorphine is a centrally effective dopamine receptor agonist. It is less effective and so less important in the treatment of ED, but should be considered in patients with contraindications to PDE-5 inhibitors (APO-go ampullae, max. 100 mg s.c.). Apomorphine seems to be particularly helpful in psychogenic ED and light organic ED. Miscellaneous herbal substances (Yohimbine, Maca, Turnera diffusa) might have a positive effect on sexual function. However, systematic studies have not been performed. These substances have few side effects, but monitoring for possible interactions with HAART is advisable. For psychosocial problems, relationship conflicts or depressive disorders, psychotherapeutic support and if necessary a sexual-medical discussion are advised.

PDE-5 inhibitors

Sildenafil (Viagra™)

Sildenafil was licensed in the USA in 1998, and shortly afterwards in Europe, as the first PDE-5 inhibitor. Sildenafil is available in dosages of 25, 50 and 100 mg. The first effects are seen between 12 and 40 mins (mean 25 mins) after taking the medication. This can be delayed if a fatty meal or alcohol is consumed simultaneously. The maximum plasma concentration is reached after approx. one hour, the clinical time of effectivity lies within approx. 8 – 12 hours.

The response rate is dependent on the etiology of ED, but varies between 43 and 83%. The most frequent side effects seen are headaches (11%), flushes (11%), dyspepsia (3%), dizziness (3%), rhinitis (2%) and color blindness (1%).

Because of synergistic effects of PDE-5 inhibitors with nitrates and NO-donators (e.g. molsidomin) the simultaneous consumption of those two substance classes can lead to vasodilatation and therefore to severe hypotension. The combination is absolutely contraindicated. Clarification with the patient is needed, since the use of amyl nitrates ("poppers"), or similar substances used as sexual stimulants, is prevalent in some of the groups more affected by the HIV epidemic (i.e. the gay scene).

Epidemiologic studies have so far not shown a statistically increased likelihood of angina pectoris, myocardial infarct or deaths under sildenafil use.

Vardenafil (Levitra™)

Vardenafil was licensed in 2003. Phosphodiesterase 5 or the hydrolysis from cGMP is restrained approx. tenfold greater than by sildenafil, but the bioavailability, at 15%, is low. Vardenafil is available in a dosage of 10 and 20 mg. First effects are seen approx. 15 to 30 mins after taking the medication; maximum plasma concentrations are reached after 60 mins. The clinical effect can last up to 12 hours.

Randomized, placebo-controlled studies, evaluating satisfaction with the amount of erection, showed a response rate of between 48 and 80%. The response rate for successful sexual intercourse with ejaculation was approx. 75 %. Vardenafil is well tolerated by patients on antihypertensive therapy and is effective in these patients.

The same contraindication for the combination with nitrates and NO-donators exists. Adverse events include – as with sildenafil – headache (10-21%), erythema (5-13%), dyspepsia (1-6%) and rhinitis (9-17%).

Tadalafil (Cialis™)

Tadalafil was licensed in 2003. Dosages of 10 and 20 mg are available. Compared to other PDE-5 inhibitors the maximum plasma concentration is reached at 2 hours, the first effect is noticeable after 15 to 20 minutes. Since the plasma half-life is approx. 17.5 hours, the medication is effective up to 36 hours after intake. Personal observations point to the fact that these circumstances promote the popularity of tadalafil in the gay scene ("weekend pill").

Headache (7-21%), dyspepsia and heartburn (1-17%), myalgia (3-7%), back pains (4-9%), rhinitis (5%) and flushes (1-5%) are the most frequently observed side effects. Clinical influences on the cardiovascular system could not be observed; an increased incidence of myocardial infarction was not seen in any study.

Recent studies with MSM suggest a connection between the intake of drugs, the intake of PDE-5 inhibitors and sexual risk behavior (Swearingen 2005, Jackson 2005, Spindler 2006).

Testosterone

Substitution therapy is indicated for a deficiency of testosterone with clinical symptoms. Options include intramuscular injections (testosterone depot 250 mg i.m. with an interval of 14 to 21 days) and application in the form of a gel (e.g., testogel 25 mg/50 mg daily). Oral substitution is possible (e.g., andriol testocaps), but has not proved itself in clinical everyday life. The depot injection of 1,000 mg testosteroneundecanoat (Nebido™) has recently been recommended in intervals of 3 months with an increasing dose 6 weeks after the initial one. Advantages of the depot injection lies in the more even serum concentrations of testosterone. In times of limited recourses, it is advisable to document the testosterone deficit and the appropriate clinical symptoms precisely.

It has been pointed out that testosterone injections may promote growth of a carcinoma in situ of the prostate. Yearly PSA measurement during therapy, and a baseline physical examination before starting substitution is recommended, although this may not be covered by health insurance plans. Moreover, with a positive family anamnesis, a urological consultation is advisable before the beginning of the substitution.

Hair loss, skin irritation (with the gel!), increase in serum liver enzymes, the lipid panel and the e-phoresis, as well as water retention in tissues, have been described as relevant side effects.

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30. HIV and Wish for Parenthood

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Introduction

The optimization of antiretroviral therapy has led to great improvements in both the quality of life and life expectancy of people living with HIV/AIDS, at least in countries where HAART is widely available. A growing number of men and women living with HIV/AIDS feel encouraged to include parenthood in the planning of their lives. Procreation without risk, or at very low risk of infection for the uninfected partner or prospective child, is now an option for couples in which one or both partners are HIV-infected. The low materno-fetal transmission rate that can be achieved today has added to the acceptance of planned motherhood in seropositive women.

Procreative options for HIV-affected couples theoretically vary from unprotected intercourse to several techniques of assisted reproduction, donor insemination or adoption. Usually, couples are advised against unprotected intercourse, as the priority is to prevent infection in the uninfected partner or child.

Average transmission rates for unprotected heterosexual intercourse are hardly useful in individual counseling situations. They can vary greatly depending on the stage of HIV disease, viral load or presence of other sexually transmittable diseases (Wawer 2005). Data hint to a low risk of transmission in case of totally suppressed viral load but are still limited. HIV can sometimes be detected in semen or genital secretions even when viral load in blood plasma is below the limit of detection. In other words, couples should not risk unprotected intercourse only on the basis of the infected partner having an undetectable load. Consistent use of condoms can decrease the transmission risk in heterosexual relationships by 80-85 % (Davis 1999) and abstention from condom use, restricted to the time of ovulation, has been proposed as an option for discordant couples. Mandelbrot et al. (1997) reported a transmission rate of 4 % in 92 couples using carefully timed, but unprotected intercourse to conceive. Infections were restricted to couples who also reported inconsistent use of condoms outside the fertile period. In a small retrospective Spanish study (Barreiro et al. 2006) no infections occurred in a cohort of 62 HIV discordant couples who conceived by timed intercourse. All HIV-infected partners had a viral load below detectability. . These data so far cannot support unprotected intercourse limited to ovulation time without further protection as being a safe option for couples.

Donor insemination is an alternative safe option for a small number of couples, but due to legal restrictions it is only offered in a minority of centers. In the UK, for example, there are no restrictions on donor insemination, whereas in Germany the access is limited. In addition, most couples wish for a child that is the biological offspring of both parents. Adoption in many countries is merely a theoretical option: HIV infection of one partner usually renders this procedure very difficult, or even impossible in most countries.

To minimize the risk of HIV transmission, the following options are recommended:

- Self-insemination or assisted reproduction in case of infection in the female partner
- Assisted reproduction with processed sperm in case of infection in the male partner

In several European countries, as well as in the US and Japan (Kato 2006), reproductive assistance for couples affected by HIV has been set up in the past few years. Equal access for HIV-positive women and men is granted in most, but not all of these countries.

The safety of sperm washing

The technique of processing sperm from HIV-positive men prior to the insemination of their HIV-negative partners was first published by Semprini et al. in 1992. The first inseminations with sperm, washed free of HIV, were carried out in Italy and Germany as early as 1989 and 1991, respectively. Up to mid 2003, more than 1,800 couples had been treated in about 4,500 cycles, applying various techniques of assisted reproduction. More than 500 children have been born with no single seroconversion reported in the centers closely following the protocol of washing and testing the sperm prior to assisted reproductive techniques.

Native ejaculate mainly consists of three fractions: spermatozoa, seminal plasma and nuclear concomitant cells. HIV progenome and virus has so far been detected in the seminal plasma, the concomitant cells, and occasionally in immobile spermatozoa. Several studies have indicated that viable, motile spermatozoa are not likely to be a target for HIV infection (Pena 2003, Gilling-Smith 2003).

Motile spermatozoa can be isolated by standardized preparation techniques. After separation of the spermatozoa from plasma fractions and NSC (non-spermatozoa cells), the spermatozoa are washed twice with culture medium and resuspended in fresh culture medium. Incubation for 20–60 minutes allows motile sperm to "swim-up" to the supernatant. To be more certain that it is not contaminated with viral particles, an aliquot of the sample should be tested for HIV nucleic acid using highly sensitive detection methods (Weigel 2001, Gilling-Smith 2003, Pasquier 2006). Depending on the method, the lowest limit of detection is 10cp/ml. After having studied the effectiveness of several methods of sperm processing, Anderson (2005) concluded that the combination of gradient density centrifugation and swim-up allows a 10,000-fold decrease of HIV-1 concentration in sperm. Since HIV could theoretically remain undetected, sperm washing is currently regarded as a very effective risk reduction, but not a risk-free method.

Several studies have shown that sperm washing can also reduce the risk of HCV in couples with male HCV-coinfection (Gilling-Smith 2003, Chu 2006).

Most of the European centers that offer assisted reproduction to HIV-discordant couples are part of the CREATHE-network, which aims to optimize treatment and safety of the methods as well as to compile an extensive database. There are high hopes that soon sufficient clinical cases can be reported to demonstrate the safety and reliability of sperm washing.

Pre-conceptual counseling

The initial counseling of the couple should not only consider extensive information on all reproductive options available, diagnostics and prerequisites for reproductive treatment, but also the psychosocial situation of the couple. Important issues to discuss are the financial situation, current psychosocial problems, the importance of a network of social support from family or friends, and planning and perspectives about the future as a family, including possible disability or death of one of the partners (Nakhuda 2005). A supporting, empathic and accepting mode of counseling is advisable, as many couples feel distressed if their motives for, or entitlement to, parenthood are questioned. The risks of unprotected intercourse or improper condom use, not only during reproductive treatment but at all times, should be discussed (Sauer 2006). In cases where professional psychosocial services are not integrated, co-operation with organizations in the AIDS counseling system or self-help groups is advisable.

Possible stress occurring during the work-up and treatment of the couple should be discussed as well as doubts or fears. Many couples for example are afraid that their test results might indicate that parenthood is impossible.

If the male partner is HIV-infected, the couple need to know that the risk of HIV infection can be minimized, but not excluded. HIV-positive women have to be informed about the risks of vertical transmission and the necessary steps to avoid it. In any case, couples should know that even using state-of-the-art reproductive techniques, achieving a pregnancy cannot be guaranteed.

Table 1: Pre-treatment investigations

General	Comprehensive medical and psycho-social history
Female examination	Gynecological examination, sonography, tubal patency test, basal temperature
	if necessary, endocrine profile, cervical smear (cytology, microbiology)
	(UK: 2-5 FSH/LH and mid-luteal progesterone to evaluate female fertility)
	Serology (rubella, toxoplasmosis, syphilis, CMV, HBV, HCV)
HIV-specific assessments	HIV-associated and accompanying symptoms
	Blood glucose, GOT, GPT, GGT, complete blood count
	Ultra-sensitive HIV-PCR, CD4+/CD8+ T-cell counts
	HIV antibody test of the partner
Male examination	Spermiogram, semen culture
	Serology (HBV, HCV, TPHA)
	Chlamydia PCR

Male HIV infection

Following the decision to conceive with reproductive assistance, the couple should undergo a thorough sexual health and infection screen, including information about the male partner's HIV status. The possibility of HIV infection in the female partner

also has to be excluded. In some cases, it might be necessary to treat genital infections before starting reproductive treatment.

Table 1 shows the investigations as provided in the *German recommendations for assisted reproduction in HIV-discordant couples* (Weigel 2001), revised in 2007 (Tandler-Schneider 2007). There are small differences between the European centers. For the UK recommendations see Gilling-Smith et al. 2003.

After sperm washing and testing for HIV, spermatozoa can be utilized in three different reproductive techniques depending on whether the couples have any additional fertility issues: intra-uterine insemination (IUI), extracorporal fertilization by conventional in-vitro fertilization (IVF) and intracytoplasmic sperm injection followed by embryonic transfer. According to the German recommendations, the choice of method depends on the results of gynecological and andrological investigations and the couple's preference. The success rate using IUI has been shown to be reduced if the sperm is washed and then cryopreserved before use. This is necessary in some centers where PCR testing of the washed sample for HIV cannot be done on the day of insemination. This, together with the fact that semen quality can be impaired in some HIV-infected men (Dulioust 2002, Müller 2003, Nicopoullos 2004, Bujan 2007), results in a number of couples being advised to have IVF or ICSI.

Couples should be informed about three further important aspects:

- Sperm-washing and testing can greatly reduce the risk of infection, but cannot exclude it completely. Following recent study results, this risk seems to be only theoretical and cannot be expressed in percentages.
- During treatment, consistent condom use is of utmost importance. HIV infection of the woman in the early stages of pregnancy can increase the risk of transmission to the child. Sauer (2006) reported a case of seroconversion in a woman already enrolled in a reproductive treatment program, prior to the first treatment, presumably due to condom breakage.
- Most couples attending European centers have to pay for treatment costs themselves. These are dependent on the type of technique applied, and range from about 500 to 5,000 Euro per cycle. An exception is France, where couples have cost-free access to treatment. In Germany, health insurances sometimes cover a part of the costs, but they are not obliged to.
- Even the most sophisticated techniques cannot guarantee successful treatment.
- Following successful treatment, couples are usually monitored for HIV status for 6-12 months after childbirth, depending on the center.

A new approach is the use of PrEP (pre-exposure prophylaxis) to limit the susceptibility of the uninfected woman during timed intercourse. In 2004, a small study was initiated in Switzerland (Vernazza 2006). Couples are advised to have unprotected intercourse only at the time of ovulation. During the 24 hours before having intercourse the female partner takes two doses of Tenofovir. Viral load of the HIV-positive partner should be below detectability to further lower the risk of HIV transmission. The acceptance of this procedure is high. First data indicate a higher pregnacy rate than after insemination with processed sperm (Vernazza 2007): Between 2004 and 2007 21 couplesfollowed the procedure, the pregnancy rate was

70%. No female infection was detected. A similar project was initiated in Germany in 2007.

Female HIV infection

HIV-positive women with unimpaired fertility can conceive by self-insemination. Similar to cases in which the male partner is infected, a fertility screen and further investigations are recommended (see Table 1 for the revised German guidelines , . (Tandler-Schneider 2007)) In some cases, ovarian stimulation may be advisable. Ovarian stimulation, however, requires highly qualified supervision to avoid multiple gestations.

It is important to time ovulation accurately (i.e., by use of computer-based ovulation kits or urine sticks). A simple inexpensive way of determining whether the cycles are ovulatory, which can be helpful in women who have regular cycles, is a basal temperature chart beginning about three months before the first self-insemination.

At the time of ovulation, couples can either have protected intercourse with a spermicide-free condom and introduce the ejaculate into the vaginal cavity afterwards, or the ejaculate can be vaginally injected using a syringe or applied with a portio cap after masturbation. Thus, the conception remains in the private sphere of the couple.

More than two inseminations per cycle are not advisable, as the fraction of motile sperm in the ejaculate can decrease with any additional tries. Furthermore, the couple might experience psychological strain through extensive planning.

After 6–12 months of unsuccessful self-insemination, the couple should have further fertility investigations with a view to assisted conception.

Fertility disorders

Fertility disorders in HIV-positive women seem to have a higher prevalence than in an age-matched HIV-negative population (Ohl 2005), but data still show some conflicting results. The reasons discussed include an increased rate of upper genital tract infections (Sobel 2000), menstrual disorders, and cervical infertility (Gilles 2005). Coll (2006) assumes the possibility of subclinical hypogonadism, potentially due to mitochondrial dysfunction. In some cases, women will only be able to conceive by assisted reproduction. Dependent on the fertility status of both partners, IVF and ICSI can be considered as methods of choice.

Recent data reported from the Strasbourg program indicated infertility problems in most HIV-positive women. IVF and ICSI were far more effective than IUI (Ohl 2005). In the Barcelona program, Coll (2006) observed a decreased pregnancy rate in HIV-positive women after IVF compared to age-matched HIV-negative controls and HIV-positive women who received donated oocytes. Results indicated a decreased ovarian response to hyperstimulation in HIV-positive women. A slightly impaired ovarian response to stimulation during 66 ICSI cycles in 29 HIV-positive women was also described by Terriou (2005). Martinet (2006) found no difference in ovarian response between HIV-positive and HIV-negative women in Brussels.

Although many centers throughout Europe offer assisted reproduction if the male partner is infected, access to treatment for HIV-positive women is currently only possible in Belgium, France, Germany, Great Britain, and Spain. Outside of Europe, some US centers offer reproductive assistance to seropositive women.

HIV infection of both partners

A growing number of HIV-concordant couples now seek reproductive counseling. In some centers, these couples are also accepted for reproductive treatment. One option for couples without fertility disorders might also be timed unprotected intercourse. The discussion pertaining to the transmission of mutated drug-resistant virus between partners, is still ongoing. Up until now, only a very small number of "super infections" have been published, and they only occurred in individuals who were not on a HAART regimen (Marcus 2005).

Couples should be offered the same range of fertility counseling and screening as HIV-discordant couples. The current health of each partner should be carefully evaluated with a full report from their HIV physician.

Psychosocial aspects

- Experiences, from more than a decade of counseling, show the importance of offering professional psychosocial support to couples before, as well as during, and after reproductive treatment.
- Up to one third of the couples decide against the realization of their wish for parenthood after in-depth counseling (Vernazza 2006). Accepting the desire to become parents and dealing with the underlying motives as well as the psychosocial situation in an empathic way enables couples to see obstacles as well as to develop alternative perspectives if this wish cannot be realized for various reasons.
- Frustration and disappointment may accompany failures or strains during treatment (i.e., unsuccessful treatment cycles, premature termination of pregnancy). Left alone with these strains, couples sometimes decide to conceive using unprotected intercourse, to avoid further stress. Depending on the risk perception of the partners, this decision may sometimes be well planned, but other times be born out of despair. These couples might be at risk of infection: in 56 HIV-discordant couples participating in the Milan program who attempted spontaneous conception after failing to conceive with artificial insemination, at least one infection occurred (Semprini 2005).
- Psychiatric co-morbidities in one or both partners (i.e., substance abuse, psychoses) can be reasons to at least postpone treatment. Professional diagnosis and support will be necessary in these cases.
- Often, the central importance of the wish for parenthood of many migrant couples is overlooked in parts of the medical and psychosocial counseling system. Language or communication difficulties on both sides, ignorance of different cultural backgrounds and lack of acceptance of "strange" life-styles can lead to feelings of discrimination, isolation, helplessness or despair in couples.

- Issues concerning the welfare of the child should be openly discussed during reproductive counseling (Frodsham 2004). Many couples are concerned about a potential negative effect of antiretroviral drugs on their offspring. Severe impairment of the health of the prospective parents might lead to concerns for the future well-being of the child.

The future

Following the improvements in morbidity and mortality of men and women living with HIV/AIDS, healthcare professionals encounter a growing number of couples or individuals who are contemplating parenthood. Having a child is the expression of a fulfilled partnership and an important perspective of life. This is no less true in couples afflicted with HIV/AIDS. In the medical and psychosocial care of patients, it is important to create an environment where reproductive aspects and parenting can be discussed on an open and non-judgmental basis.

Future priorities include continued reporting of data pertaining to the applied methodologies as well as to the outcomes, reporting of adverse results and the follow-up of couples (Giles 2005). The first steps towards optimizing semen processing procedures, namely quality control of virus detection in processed sperm and laboratory safety, have already been taken (Politch 2004, Pasquier 2006, Gilling-Smith 2005).

Meikle (2006) criticizes the current state of "fragmented knowledge" regarding infertility service practices for HIV-positive patients. Long-term outcomes in couples that received reproductive assistance, health outcomes among children, both in medical as well as in psychosocial terms, and consensus regarding best practices or surveillance of care provided by clinics have received little notice until now.

A great number of couples cannot afford to pay for the high costs of treatment, or travel long distances, sometimes even to other countries, to reach specialized units. There is an urgent need to develop strategies for the counseling and support of these couples. The use of donated oocytes in reproductive services for HIV-positive women (Coll 2006) is limited in several countries due to legal and ethical considerations. It even enables treatment of women who have reached an age where reproductive assistance is not usually offered anymore due to the high risk of miscarriages and malformation and the low success rate of assisted reproduction techniques.

Medical and technical progress open a wider range of options for couples, but aside from comparing higher or lower success rates, there is an urgent need to discuss psychological and psychosocial issues pertaining to the welfare of parents and child.

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31. Post-Exposure Prophylaxis (PEP)

Thore Lorenzen and Katrin Graefe

Transmission

The risk of HIV transmission is present if an HIV-negative person comes into contact with the blood, semen or vaginal fluids of an HIV-positive source person. But exposure of intact skin to HIV-contaminated body fluids (e.g. blood) is not sufficient to transfer the virus.

Transmission is possible if HIV-containing material enters the body by:

- accidental needlestick injury or incision by surgical instruments
- exposure of damaged skin or mucosal membranes
- unprotected sexual intercourse with an infected person
- IDU sharing needle or equipment
- transfusion of HIV-contaminated blood or blood products

Transmission risk

HIV is not a very contagious pathogen. The transmission rate after contact is about 1:1000 to 1:100. Compared with HIV, the transmission rate for hepatitis C is 10 times higher, and 100 times higher for hepatitis B. Factors for the probability of transmission are the amount of incorporated virus and the exposure time. Contact with body fluids of a patient with a high viral load supposably holds a higher risk of contagion than a similar contact with body fluids of a patient under HAART with a suppressed viral load. Additionally, quick removal of infectious material e.g. from damaged skin or mucosal membrane by washing or disinfection presumably decreases the risk of an HIV infection. For percutaneous contact with HIV-containing blood, an infectiousness of 0.3 % in total is assumed. According to retrospective data, calculations have been established to assess the transmission risks of accidental exposure more precisely (see Table 1).

Table 1: Calculations to assess estimated individual transmission risk after HIV exposure *

Type of Exposure	Relative Risk
Deep needlestick injury or cut	16 : 1
Fresh blood on the penetrating instrument	5 : 1
Penetrating needle previously placed in blood vessel	5 : 1
Source person with high viral load	6 : 1
Exposition of mucosal membrane	1 : 10
Exposition of inflammatory damaged skin	1 : 10

* Source: German-Austrian recommendations for Post-Exposure Prophylaxis against HIV infection 2004

Table 2 provides information about the assumed transmission risk of other types of exposure to HIV, for example unsafe sexual contact. Since only few data exist, these risk estimates vary enormously and should be judged with caution.

Table 2: HIV transmission risk for unprotected sexual contacts *

Type of unprotected contact	Transmission risk per contact
Receptive anal sex with HIV- infected person	0.82 % (0.24 – 2.76)
Receptive anal sex with person of unknown HIV status	0.27 % (0.06 – 0.49)
Insertive anal sex with person of unknown HIV status	0.06 % (0.02 – 0.19)
Receptive vaginal sex	0.05 – 0.15 %
Insertive vaginal sex	0.03 – 5.6 %
Oral sex	Probability unknown, single cases have been reported, particularly with incorporation of semen in the mouth.

* Source: German-Austrian PEP recommendations 2004

In primary HIV infection the establishment of the virus in various tissue reservoirs does not occur immediately after incorporation of the virus. Within a small time frame the establishment of the virus might be prevented by post-expositional intervention.

Simian models show that in mucosal membranes HIV primarily infects the local immunocompetent cells such as Langhans' cells. These cells or their siblings migrate to regional lymph nodes: detection of HIV in the blood occurs days later. The process of local infection and migration of the cells to the lymph nodes takes approximately 24 to 48 hours (Spira 1996, Otten 2000). Theoretically, treatment with appropriate substances may avert a systemic infection.

Effectiveness and limitations of PEP

Early reports on the use of AZT after occupational needlestick injuries date from 1989. An analysis of retrospective case-control studies shows that even prophylaxis with a single substance after exposure reduces the probability of an infection by approximately 80 % (Tokars 1993). The combination of multiple drugs is supposedly even more potent. Unfortunately there have been transmissions despite the use of PEP. Transmission of HIV infection cannot always be prevented. Many of the described cases of PEP failure were treated with AZT mono-prophylaxis. But there are also reports about failures of antiretroviral combination therapies.

With increasing prevalence of resistance under antiretroviral therapy future problems might arise with transmission of resistant virus strains. International surveillance studies report increasing transmissions rates of mutant viruses. But, what to do is still unclear: resistance testing takes days or more. So results would be too late to avoid spread of resistant viruses using appropriate antiretrovirals.

When is PEP indicated?

The indication to provide a PEP should be considered by a physician experienced in HIV treatment. It is important to ascertain whether the source person has a supposed or confirmed HIV infection. Unclear HIV status should be clarified: the source person should be asked for consent to perform HIV testing. But denial of consent has to be respected. If the source person agrees to be tested, it should be performed immediately. For source persons with confirmed HIV infection, the actual HIV viral load, stage of disease, former and current HAART have to be taken into consideration. Optimally, a resistance analysis would also be available (Puro 2003). The affected person should be asked about the first aid procedures that have already been performed.

After clarification of these queries, the exposed person has to be informed about possible risks of pharmaceutical PEP. It should be emphasized that none of the administered substances is approved for use in this special setting. This is also important with regard to the coverage of cost, especially for sexual exposure. The medication cannot be prescribed at the expense of the health insurance. PEP for occupational exposure is usually covered by statutory accident insurance (in Germany).

Table 3 gives an overview of situations in which PEP is recommended according to current guidelines. This serves as an orientation, although deviations may be necessary in individual cases.

Potential risks of PEP

The risks of PEP mainly concern the adverse effects of the antiretroviral substances, most frequently gastrointestinal symptoms such as nausea, vomiting or diarrhea. Changes of hematology, transaminases or creatinine are also possible. Additionally, there have been reports of elevated triglycerides and cholesterol levels, and insulin resistance even in short term use of protease inhibitors (Parkin 2000).

It is unknown whether the temporary use of antiretroviral substances may lead to long term side effects, but this seems to be secondary since the main emphasis is to prevent a chronic and potentially life-threatening disease. For pregnant women particular caution is required since data concerning teratogenicity are lacking.

Table 3: Overview of recommendations for usage of PEP

Occupational Exposure	
• Percutaneous needlestick injury with hollow needle (body fluids with high viral load: blood, liquor, material from biopsies, cultured virus)	Recommended
Deep injury (e.g. cuts), apparently blood stained	Recommended
Needle used before for intravenous injection	Recommended
• Superficial injury (e.g. with surgical needle)	Considered
Where required, exemption, if source person has AIDS or high viral load	Recommended
• Contact of mucosal membrane or damaged skin with fluids with high viral load	Considered
• Percutaneous contact with body fluids other than blood (e.g. urine, saliva)	Not Recommended
• Contact of intact skin with blood (including high viral load)	Not Recommended
• Contact of skin or mucosal membranes with body fluids such as urine or saliva	Not Recommended
Non-occupational Exposure	
• Transfusion of HIV containing blood products (or if HIV contamination is highly probable)	Recommended
• Unprotected receptive sex with an HIV-infected person	Recommended
• IDU sharing contaminated needle or equipment	Recommended
• Unprotected receptive oral sex with ejaculation with an HIV-infected person	Considered
• Kissing and other sexual contacts without semen-/blood-mucosal membrane contact	Not Recommended
• Accidental needlestick injury	Not Recommended

Sources: CDC Guidelines for the management of occupational exposure to HIV 2005; UK guidelines for the use of posr-exposure prophylaxis for HIV following sexual exposure 2006

Initial interventions

According to actual guidelines, depending on the type of exposure, different procedures are recommended following HIV-exposure. Following needlestick or cut injuries with HIV-contaminated instruments, fluid should be expressed by squeezing the tissue surrounding the wound and striking out proximal blood vessels towards the wound. Too intense massage or contusions have to be avoided. The wound should be flushed with an alcoholic, virucidal antiseptic for a minimum of 10 minutes. For skin that has been in contact with blood or body fluids removal of the infectious material and subsequent extensive disinfection with a skin antiseptic appears sufficient. After contamination of an eye, immediate flush with PVP iodine solution 2.5 % is recommended. If such a solution is not available the eye should be washed with water. The oral cavity should be washed several times (about 10-

15 seconds each) with an aqueous solution or preferably 80 % alcohol after contact with potentially infectious material.

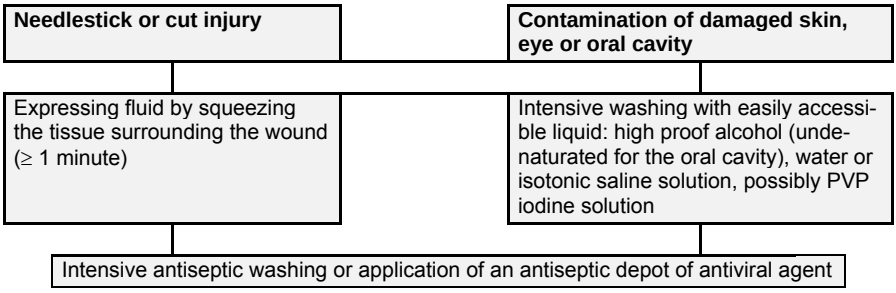

Figure 1: Recommended initial interventions after HIV exposure (Source: German-Austrian recommendations for Post-Exposure Prophylaxis against HIV infection 2004)

Persons, who, through sexual exposure, have contact of anal or genital mucosae to infectious material, should wash the penis with soap and water; genital mucosae should be flushed with water after urination, which might wash contaminated material from the urethra. Intense washing of the vagina or intestines is not recommended due to an elevated risk of injuries.

After these initial interventions, an expert in HIV treatment and antiretroviral therapy should be consulted for the decision whether pharmaceutical PEP needs to be started.

Accurate evaluation and documentation of the course of the accident is very important, especially for occupational exposure. The process of informing the patient about the risks of PEP needs to be documented carefully and the patient should sign an informed consent.

Initiation of PEP

Time is the most important factor for initiation of PEP. The best chance to prevent transmission is within the first 24 hours of exposure. After that time period, the risk of systemic spread of the virus increases. Initiating PEP after more than 72 hours following exposure does not seem reasonable.

PEP should be initiated as soon as possible, preferably within 2 hours of exposure.

If, in this short time frame, consultation with a physician experienced in HIV treatment is not possible, it might be advantageous to just initiate PEP. Interrupting a regimen that isn't indicated is always an option.

Actual recommendations prefer a regimen with a combination of antiretroviral substances given over 4 weeks, preferably consisting of two NRTIs and one PI (see Table 5). NNRTIs, especially nevirapine, should not be used for PEP because of the risk of severe adverse effects (hepatotoxicity) (CDC 2001). For efavirenz such severe adverse effects have not been reported but the impact on the CNS, particularly in the first weeks of intake, limits its use for PEP.

As far as possible, known resistance against antiretroviral substances of the source person should be taken into account; in many cases, this information will not be available. Therefore use of standard regimens for PEP has proven practical. Recommended combinations are shown in Table 5.

To remark: Except Nelfinavir all protease inhibitors are recommended to be used boosted with Ritonavir.

In addition, since 2003, the fusion inhibitor T-20 (Fuzeon™) has been approved for HIV therapy. Other substances, such as attachment inhibitors or coreceptor antagonists are under investigation. These new substances with their mechanism to inhibit viral cell entry might also be interesting with regard to increasing efficiency of PEP. Focusing on enfuvirtide, the subcutaneous route of application and high costs currently prevent its routine use.

Furthermore, difficulties in monitoring a possible seroconversion might occur as development of antibodies against enfuvirtide may lead to cross reaction with gp41 and a positive result in the HIV-ELISA test.

During pregnancy, PEP should only be used after careful consideration of the benefits since there are only limited data on teratogenic effects. In any case, advice of a physician experienced in HIV treatment and pregnancies should be obtained.

After contact with potentially infectious material, not only HIV, but also other diseases might be transmitted. Apart from HIV, testing should be performed for hepatitis B and C. Persons exposed to HBV should receive hepatitis B immunoglobulin and a vaccine series simultaneously if they have no sufficient vaccination status.

Table 4: Recommended antiretroviral combinations for HIV Post-exposure Prophylaxis *

NRTI		PI
1. AZT + 3TC (Combivir™) or 2. TDF + FTC (Truvada™) or 3. TDF + 3TC (Viread™+Epivir™) or 4. d4t + 3TC (Zerit™+ Epivir™)	plus	Lopinavir/r (Kaletra™) or Saquinavir (Invirase™) or Fosamprenavir (Lexiva™ or Telzir™) or Nefinavir (Viracept™)

* Sources: CDC Guidelines for the management of occupational exposure to HIV 2005; UK guidelines for the use of posr-exposure prophylaxis for HIV following sexual exposure 2006

After unprotected sexual contacts, transmissions of other STDs such as syphilis or gonorrhea should be taken into consideration. Testing is recommended at 2 and 4 weeks after exposure.

Management of PEP

After initiation of PEP, the patient should not be discharged without a follow-up consultation. Persons exposed to HIV are under high psychological pressure. It is important to accompany the patiens and to emphasize the generally low risk of transmission but not to dramatize the situation.

Adverse effects generally include gastrointestinal symptoms. Less frequent are changes in hematology, liver enzymes or creatinine. These should be tested after 14 days and at the end of the PEP. Despite close monitoring, different studies report discontinuation rates of 40-50 %. At the end of a completed course or discontinued PEP, HIV testing should be performed after 6 weeks, 3 and 6 months. An HIV PCR only needs to be performed if there is reasonable suspicion of a primary HIV infection.

In any case, the patient has to be advised to practice safer sex until a reliable negative test result is achieved.

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Part 5

Drugs

32. Drug Profiles

Bernd Sebastian Kamps and Christian Hoffmann

3TC – Lamivudine

A well-tolerated cytidine analog. Rapid development of resistance: only one point mutation (M184V) is required, which, however, increases the sensitivity of AZT-resistant viruses and reduces viral fitness. Also effective against hepatitis B virus.

Trade name: Epivir™; component of Combivir™, Trizivir™, and Kivexa™.

Epivir™ tablets: 150 mg or 300 mg; Epivir™ solution 10 mg/ml

Combivir™ tablets: 150 mg 3TC + 300 mg AZT

Trizivir™ tablets: 150 mg 3TC + 300 mg AZT + 300 mg abacavir

Kivexa™ tablets: 300 mg 3TC + 600 mg abacavir

Zeffix™ tablets: 100 mg. Only for HBV, **never** for HIV!!! (dose is too low!).

Drug class: (NRTI)

Manufacturer: GlaxoSmithKline

Indication: HIV infection (also chronic hepatitis B)

Oral dose: 300 mg qd or 150 mg bid. Children receive 4 mg/kg, up to a maximum of 150 mg bid. With poor liver function, in particular reduced creatinine clearance, use just Epivir™ instead of the combined preparations and adjust the dose.

CrCl (ml/min)	**Dose**
30–49	150 mg qd
15–29	150 mg first dose, then 100 mg qd
5–14	150 mg first dose, then 50 mg qd
<5	50 mg first dose, then 25 mg qd

Side effects: rare when using the individual drug. Fatigue, nausea, vomiting, diarrhea, headache, insomnia, myalgia are usually due to AZT and abacavir. Peripheral polyneuropathy, and very rarely pancreatitis, lactic acidosis and anemia.

Internet sources:

USA: Epivir™: http://hiv.net/link.php?id=49

Combivir™: http://hiv.net/link.php?id=50

Trizivir™: http://hiv.net/link.php?id=51

References:

1. Bani-Sadr F, Palmer P, Scieux C, Molina JM. Ninety-six-week efficacy of combination therapy with lamivudine and tenofovir in patients coinfected with HIV-1 and wild-type hepatitis B virus. Clin Infect Dis 2004; 39: 1062-4. http://amedeo.com/lit.php?id=15472862

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Abacavir (ABC

A guanosine analog with good CNS penetration; a component of some combination preparations. The hypersensitivity reaction (HSR) is a substantial problem (see below); otherwise well tolerated, with little mitochondrial toxicity.

Trade name: Ziagen™; component of Kivexa™/ Epzicom™ and Trizivir™

Ziagen™ tablets: 300 mg; Ziagen™ solution 20 mg/ml.

Kivexa/Epzicom™ tablets: 600 mg abacavir + 300 mg 3TC

Trizivir™ tablets: 300 mg abacavir + 150 mg 3TC + 300 mg AZT

Drug class: NRTI

Manufacturer: GlaxoSmithKline

Indications: HIV infection

Oral dose: 300 mg bid or 600 mg qd, with or without food.

Side effects: hypersensitivity reactions (HSR) in 2 to 8 %, usually within the first six weeks. Pruritus and rash are common, but may also be absent. The HSR may present as just fever and slowly developing malaise. Gastrointestinal complaints and fatigue are also possible. Elevated liver function tests, insomnia and dizziness are rare.

Comments/Warnings: contraindicated in cases with abacavir hypersensitivity and after interruption of therapy, if a prior HSR cannot be ruled out in retrospect. Re-exposure can cause acute life-threatening HSR! With only mild symptoms (see below), abacavir should not be stopped too quickly, as an intercurrent infection may simulate the HSR. Often, it is possible to observe the course for one or two days. There is a genetic predisposition (HLA-Typ B5701), and HLA typing may help in the future to reduce the risk of HSR. Patients should consult a doctor **immediately** if at least two of the following symptoms occur:

- fever
- shortness of breath, sore throat or cough
- rash (erythema and/or pruritus)
- nausea or vomiting or diarrhea or abdominal pain
- extreme fatigue, diffuse pain or general malaise

Interactions: 0.7 g/kg ethanol (e.g. 0.5 l wine) increases the AUC of abacavir by 41 % and increases half-life by 26 %.

Internet sources:

USA: http://hiv.net/link.php?id=53

References:

1. Carr A, Workman C, Smith DE, et al. Abacavir substitution for nucleoside analogs in patients with hiv lipoatrophy: a randomized trial. JAMA 2002, 288: 207-15. http://amedeo.com/lit.php?id=12095385
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Acyclovir

Trade name: Zovirax™ (among many others)

Drug class: virostatic

Manufacturer: manufactured by several companies. Generics are generally cheaper than the originally introduced formulation (Zovirax™).

Indications: treatment and prophylaxis of HSV and VZV infections.

Dose: for genital HSV infection: 400 mg po 5x/day for 7 days. In severe cases (ulcerating genital herpes) intravenous treatment with 5-10 mg/kg iv tid. For HSV encephalitis or HSV esophagitis 10 mg/kg iv tid.

For dermatomal herpes zoster 800 mg po 5x/day for 7 days. In cases of disseminated or complicated herpes zoster 10 mg/kg iv tid.

Side effects: rare. Headache, nausea and elevation of creatinine may occur. Phlebitis can occur with intravenous dosing.

Comments/Warnings: Initiation of treatment for HSV should be within the first 24 hours after appearance of symptoms if possible, for VZV within the first 4 days. Adequate fluid intake is important.

Internet sources:

USA: http://hiv.net/link.php?id=55

References:

1. Conant MA, Schacker TW, Murphy RL, et al. Valaciclovir versus aciclovir for herpes simplex virus infection in HIV-infected individuals: two randomized trials. Int J STD AIDS 2002, 13:12-21. http://amedeo.com/lit.php?id=11802924
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Agenerase™ see Amprenavir

Ambisome™ see Amphotericin B

Amphotericin B

Trade names: Amphotericin B™, Ambisome™

Amphotericin B™: 50 mg amphotericin B powder/bottle

Liposomal amphotericin B: 50 mg vials of Ambisome™

Drug class: antimycotic

Manufacturer: Amphotericin B™: Bristol-Myers Squibb; Ambisome™: Gilead

Indications: Fungal infections, including aspergillosis, cryptococcosis, treatment-resistant candidiasis, histoplasmosis, coccidioidomycosis.

Indications for Ambisome™: life-threatening situations with the mycoses listed above. Mainly in cases of pre-existing impaired renal function, elevations in creatinine on amphotericin B (creatinine > 2.0 mg/dl) or poor tolerability of amphotericin B infusions.

Ambisome™ is very expensive!

Dose (per day) of amphotericin B™:

Aspergillosis: 1.0 to 1.5 mg/kg

Candidiasis: 0.2 to 0.8 mg/kg

Coccidioidomycosis: 0.5 to 1.0 mg/kg

Cryptococcosis: 0.7 to 1.0 mg/kg

Histoplasmosis: 0.5 to 1.0 mg/kg

Dose of Ambisome™: initial daily dose of 1 mg/kg, if necessary this may be gradually increased to 3 mg/kg.

Side effects: nephrotoxicity! Hypokalemia! Gastrointestinal complaints. Frequent: fever, chills, and hypotension approx. 10-20 min after starting infusion. Thrombophlebitis. Side effects are generally less severe with Ambisome™.

Comments/Warnings: monitor daily electrolytes (central venous line because of hypokalemia and usually necessary substitutions! Sodium should be kept at normal levels), creatinine, urea, ALT, blood count. Do not combine with other nephrotoxic drugs.

Always prehydrate with 1000 ml 0.9 % NaCl. First test dose always with 5 mg in 250 ml 5 % glucose over 30–60 min under monitoring of blood pressure and pulse for the first hour. If the test dose is tolerated, half of the planned maintenance dose may subsequently be given on the same day. In cases of fever/chills (can be impressive!): 50 mg pethidine iv plus 1 ampule clemastine (Tavegil™), may be repeated after 30 min; steroids if complaints persist (prednisolone 1 mg/kg).

If side effects are severe, switch to Ambisome™, which is probably not more effective (apyrexia, survival) than amphotericin B, but better tolerated and less nephrotoxic (no test dose, no prehydration, no central line necessary). Never mix am-

photericin infusions, and always protect from light. Infuse slowly! The longer the infusion time (>3 hours), the better the tolerability! Always use 5 % glucose as a diluent!

Internet sources:

USA: Ambisome™: http://hiv.net/link.php?id=58

References:

1. Arathoon EG, Gotuzzo E, Noriega LM, et al. Randomized, double-blind, multicenter study of caspofungin versus amphotericin b for treatment of oropharyngeal and esophageal candidiases. Antimicrob Agents Chemother 2002, 46: 451-7. http://amedeo.com/lit.php?id=11796357
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Amprenavir

Amprenavir should be replaced by fosamprenavir (see relevant section). Only the pediatric formulations are still available.

Trade name: Agenerase™

Soft capsules 50 mg.

Solution: 15 mg pro ml.

Drug class: protease inhibitor

Manufacturer: GlaxoSmithKline

Indications: Pediatric HIV patients with previous PI-treatment.

Oral dose: According to body weight: 2 x 20 mg/kg (capsules). 2 x 22.5 mg/kg (solution) – the bioavailability of amprenavir oral solution is about 14 % less.

Side effects: mostly gastrointestinal. Occasional headache, fatigue, and rash in 5-10 %. See also Fosamprenavir.

Comments/Warnings: amprenavir solution contains 50 % propylene glycol. It is therefore contraindicated for concurrent administration with metronidazole.

Internet sources:

USA: Capsules: http://hiv.net/link.php?id=61
Solution: http://hiv.net/link.php?id=62
Combination with ritonavir: http://hiv.net/link.php?id=63

References:

1. Chapman TM, Plosker GL, Perry CM. Fosamprenavir: a review of its use in the management of antiretroviral therapy-naive patients with HIV infection. Drugs 2004; 64: 2101-24. http://amedeo.com/lit.php?id=15341507
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Atazanavir

Relatively well tolerated PI which can be given once daily. Favorable lipid profile in comparison to other PIs. The most important side effects are elevated bilirubin levels, which not unusually manifest as jaundice

Trade name: Reyataz™; abbr. AZV.

Hard capsules: 150 and 200 mg

Drug class: protease inhibitor (PI)

Manufacturer: Bristol-Myers Squibb

Indications: treatment-experienced adults with therapy failure.

Oral dose: 300 mg once daily combined with 100 mg ritonavir once daily, and taken with a meal. Potentially can be given unboosted in cases with ritonavir intolerance: 400 mg once a day (not officially licensed!).

Side effects: very frequent: hyperbilirubinemia (up to 50 %) also with jaundice,; more rarely elevated transaminases. Diarrhea, nausea, vomiting, headache, insomnia, abdominal pain. In contrast to other PIs: No dyslipidemia. The effect on lipodystrophy remains unknown. QT prolongation.

Comments/Warnings: capsules should be swallowed without chewing.

The following are contraindicated: cisapride, pimozide, midazolam, triazolam, simvastatin, lovastatin, ergotamines, and calcium antagonists. Life-threatening interactions are possible with concomitant administration of amiodarone, lidocaine (systemic dosing), tricyclic antidepressants and quinidine (measure plasma levels!).

It should not be given with rifampin (reduces plasma levels of atazanavir by 90 %), St. John's wort, and antacids; caution with sildenafil, vardenafil.

Caution proton pump inhibitors, antacids (see Interactions)!

When combined with efavirenz, the dose of ATV should be increased to 400 mg. With tenofovir, always boost with ritonavir.

Do not combine with indinavir.

Rifabutin: reduce rifabutin dose by 75 % (instead of 300 mg daily, give only 150 mg every other day or three times per week).

Clarithromycin: do not combine with boosted atazanavir.

Caution in liver damage. Contraindicated in liver cirrhosis, Child Pugh B and C.

Contraception: an alternative to the pill is recommended.

Internet sources:

USA: http://hiv.net/link.php?id=224

References:

1. Barreiro P, Rendon A, Rodriguez-Novoa S, Soriano V. Atazanavir: the advent of a new generation of more convenient protease inhibitors. HIV Clin Trials 2005; 6: 50-61. Abstract: http://amedeo.com/lit.php?id=15765311
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4. Colonno R, Rose R, McLaren C, Thiry A, Parkin N, Friborg J. Identification of I50L as the signature atazanavir (ATV)-resistance mutation in treatment-naive HIV-1-infected patients receiving ATV-containing regimens. J Infect Dis 2004; 189: 1802-10. http://amedeo.com/lit.php?id=15122516
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Atovaquone

Trade names: Wellvone™, Mepron™

Suspension with 750 mg/5 ml

Drug class: antibiotic

Manufacturer: GlaxoSmithKline

Indications: PCP prophylaxis in cases of cotrimoxazole hypersensitivity; reserve drug for mild to moderate PCP cases and for cerebral toxoplasmosis.

Dose: for treatment 750-1,500 mg bid (1-2 measuring spoons of 5 ml bid) for 21 days. For prophylaxis 750 mg bid (1 measuring spoon of 5 ml bid) or 1,500 mg qd.

Side effects: gastrointestinal complaints such as nausea, vomiting and diarrhea are frequent (often mild), as are rashes, which occur in approx. 20 %. More rarely headache, insomnia. Elevated liver enzymes, elevated amylase. Anemia, leucopenia (rare).

Comments/Warnings: take atovaquone where possible with fatty dishes, as this improves absorption. In most countries, atovaquone is considerably more expensive than other drugs for PCP prophylaxis.

Rifampin, possibly also rifabutin lower plasma levels of atovaquone by approx. 50 %. The combination with these two drugs is therefore not recommended. Fluconazole probably increases levels.

Lopinavir seems to lower the plasma concentration of atovaquone. Dose adjustment may be necessary.

Internet sources:

UK: http://hiv.net/link.php?id=174

References:

1. Chirgwin K, Hafner R, Leport C, et al. Randomized phase II trial of atovaquone with pyrimethamine or sulfadiazine for treatment of toxoplasmic encephalitis in patients with AIDS: ACTG 237/ANRS 039 Study. Clin Infect Dis 2002, 34:1243-50. http://amedeo.com/lit.php?id=11941551
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Atripla®

Atripla® is the first complete HAART in a single combination tablet (300 mg tenofovir, 200 mg emtricitabin and 600 mg efavirenz), which in addition, ony needs to be taken once daily. Atripla® was licensed in 2006 in the USA; the license in Europe is expected at the end of 2007.

Manufacturer: Gilead, Bristol-Myers Squibb, MSD

Indications: Adult patients with HIV infection.

Dose: 1 tablet in the evening on an empty stomach (half an hour before or 2 hours after eating).

Contra-indications, side effects: see also the sections on Truvada® und Sustiva®.

Internet sources:

UK: http://hiv.net/link.php?id=260

References:

1. Frampton JE, Croom KF. Efavirenz/emtricitabine/tenofovir disoproxil fumarate: triple combination tablet. Drugs 2006; 66: 1501-12 Abstract: http://amedeo.com/lit.php?id=16906786
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Azithromycin

Trade names: Ultreon™, Zithromax™, Azithromycin-CT™, diverse generics

Ultreon™ tablets with 600 mg

Zithromax™ tablets with 250 mg and 500 mg

Zithromax™ powder for suspension with 200 mg per 5 ml

Drug class: macrolide antibiotic

Manufacturer: Pfizer, Mack-Illert, various other companies

Indications: treatment and prophylaxis of MAC infection. Infections of the upper and lower respiratory tract, otitis media. Uncomplicated gonorrhea, uncomplicated genital infections with Chlamydia trachomatis, chancroid.

Dose: primary prophylaxis of MAC infection: 1,200 mg weekly (2 tablets Ultreon™ 600 mg per week). MAC treatment: 1 tablet Ultreon™ 600 mg qd, only in combination with ethambutol and rifabutin.

Uncomplicated gonorrhea: 1,000 mg azithromycin as a single dose.

Uncomplicated genital infections with Chlamydia trachomatis: if an alternative to doxycycline is needed, 1,000 mg azithromycin may be given as a single dose.

Chancroid: 1,000 mg azithromycin as a single dose.

Side effects: mainly gastrointestinal with stomach cramps, nausea, vomiting, diarrhea. Rarely, elevations of transaminases, cholestatic jaundice. Reversible ototoxicity with high doses. Rarely taste disturbances.

Comments/Warnings: caution in cases of known macrolide allergy! Reduced absorption of azithromycin with concurrent dosing of Mg- and Al-containing antacids. These drugs should be taken one hour before or two hours after azithromycin.

Internet sources:

USA: http://hiv.net/link.php?id=176

References:

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4. Phillips P, Chan K, Hogg R, et al. Azithromycin prophylaxis for Mycobacterium avium complex during the era of HAART: evaluation of a provincial program. Clin Infect Dis 2002, 34: 371-8. http://amedeo.com/lit.php?id=11774085
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AZT – Zidovudine

AZT, a thymidine analog and the oldest HIV drug, continues to be a component of many HAART regimens and transmission prophylaxis. Extensive data, good CNS penetration. The most important side effect is myelotoxicity which may cause severe anemia. Unfortunately, once daily dosing is not possible.

Trade name: Retrovir™; component of Combivir™ and Trizivir™

Retrovir™ capsules: 100 mg or 250 mg

Retrovir™ tablets: 300 mg

Retrovir™ syrup: 10 mg/ml

Retrovir™ infusion bottles: 200 ml (10 mg/ml)

Combivir™ tablets: 300 mg AZT + 150 mg 3TC

Trizivir™ tablets: 300 mg AZT + 150 mg 3TC + 300 mg abacavir

Manufacturer: GlaxoSmithKline

Indications: HIV infection. Prevention of maternal-fetal HIV transmission.

Dose: 250 mg bid. In Combivir™ and Trizivir™ 300 mg bid.

Creatinine clearance below 20 ml/min: 300 to 400 mg daily.

Hemodialysis: 300 mg daily. Hepatic failure: 100 mg tid.

Side effects: nausea, vomiting, abdominal discomfort, headache, myalgia, and dizziness. Macrocytic anemia (MCV almost always elevated), rarely neutropenia. Also elevations in LDH, CPK, transaminases. Rarely lactic acidosis.

Comments/Warnings: do not combine with d4T! There is increased myelotoxicity if used with other myelosuppressive drugs, especially ganciclovir, but also cotrimoxazole, dapsone, pyrimethamine, interferon, sulfadiazine, amphotericin B, ribavirin and various other chemotherapeutic agents. Anemia can develop even after months on AZT.

As ribavirin antagonizes the antiviral activity of AZT in vitro, concurrent use of AZT and ribavirin should be avoided.

Initially monthly monitoring of blood count, transaminases, CPK and bilirubin. Gastrointestinal complaints can be treated symptomatically and usually subside after a few weeks.

AZT should always be a component of transmission prophylaxis!

Internet sources:

USA: Retrovir™ tablets: http://hiv.net/link.php?id=66

Retrovir™ IV infusion: http://hiv.net/link.php?id=67

Combivir™: http://hiv.net/link.php?id=68

Trizivir™: http://hiv.net/link.php?id=69

References:

1. Antoniou T, Gough K, Yoong D, Arbess G. Severe anemia secondary to a probable drug interaction between zidovudine and valproic acid. Clin Infect Dis 2004; 38: e38-40. Epub 2004 Feb 11. http://amedeo.com/lit.php?id=14986271
2. Burger DM, Meenhorst PL, Koks CHW, Beijnen JH. Drug interactions with Zidovudine. AIDS 1993, 7:445-60.
3. Dunn D. Short-term risk of disease progression in HIV-1-infected children receiving no antiretroviral therapy or zidovudine monotherapy: a meta-analysis. Lancet 2003; 362: 1605-11. http://amedeo.com/lit.php?id=14630440
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Caelyx™ see Doxorubicin, liposomal

Cidofovir

Trade name: Vistide™

Vials with 375 mg in 5 ml

Drug class: virostatic

Manufacturer: Gilead

Indications: CMV retinitis in HIV-infected patients without renal dysfunction, mainly in cases of resistance/contraindications to ganciclovir or foscavir. As an adjunctive treatment to HAART for PML patients, although efficacy is uncertain.

Dose: induction 5 mg/kg iv weekly, by day 21 maintenance therapy with 5 mg/kg iv every two weeks. A treatment plan (comedication, hydration, etc.) is necessary!

Side effects: renal failure! Isolated cases of acute renal failure after single dose. Less frequent: neutropenia, dyspnea, alopecia, decreased intraocular pressure, iritis, uveitis.

Fever, chills, headache, rash, nausea/vomiting tend to be due to probenecid, usually subside within 12 hours and are lessened with food intake, antipyretics, antiemetics.

Comments/Warnings: with normal renal function, the following scheme is recommended (protocol):

–3 h	2 g probenecid (4 tbl. of 500 mg)
–3 to –1 h	1000-2000 ml 0.9 % NaCl
0 to + 2 h	Cidofovir in 500 ml 0.9 % NaCl over 1-2 h. 1000 ml 0.9 % NaCl in parallel
+4 h	1 g probenecid (2 tbl. of 500 mg)
+10 h	1 g probenecid (2 tbl. of 500 mg)

Check renal function (serum creatinine, electrolytes, proteinuria) before **each** dose. If serum creatinine increases by more than 0.3 mg/dl: reduce dose to 3 mg/kg. If serum creatinine increases by more than 0.5 mg/dl above levels prior to treatment: **discontinue**. Cidofovir is contraindicated at serum creatinine levels > 1.5 mg/dl or creatinine clearance ≤ 55 ml/min or proteinuria > 100 mg/dl. Always ensure adequate hydration!

Discontinue nephrotoxic drugs such as aminoglycosides, amphotericin B, foscarnet, iv pentamidine or vancomycin at least 7 days prior to treatment.

Probenecid is necessary to reduce nephrotoxicity.

Interactions with acetaminophen, acyclovir, ACE inhibitors, ASA, barbiturates, benzodiazepines, bumetanide, clofibrate, methotrexate, famotidine, furosemide, and theophylline.

Internet sources:

USA: http://hiv.net/link.php?id=71

References:

1. Cundy KC, Petty BG, Flaherty J, et al. Clinical pharmacokinetics of cidofovir in HIV-infected patients. Antimicrob Agents Chemother 1995, 39:1247-52. http://amedeo.com/lit.php?id=7574510
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3. Plosker GL, Noble S. Cidofovir: a review of its use in cytomegalovirus retinitis in patients with AIDS. Drugs 1999, 58:325-45. http://amedeo.com/lit.php?id=10473024

Clarithromycin

Trade names: Klacid™, Mavid™, Clarithromycin-CT™, diverse generics

Mavid™ tablets with 500 mg

Klacid™ tablets with 250 mg

Drug class: antibiotic

Manufacturer: Abbott, various other companies

Indications: prophylaxis and treatment of MAC disease. Infections of respiratory tract, ENT, and the skin.

Dose: 500 mg bid, both for primary prophylaxis and for maintenance therapy. 50 % dose reduction and good hydration if creatinine clearance is ≤ 30 ml/min.

Side effects: mainly gastrointestinal complaints (nausea, vomiting, abdominal discomfort, rarely tenesmus, diarrhea). Allergic reactions, headache, elevated transaminases, alkaline phosphatase and bilirubin.

Comments/Warnings: no concurrent treatment with rifampin, carbamazepine, cisapride, terfenadine, pimozide and other macrolide antibiotics such as erythromycin or azithromycin.

Lopinavir and ritonavir increase clarithromycin levels. Clarithromycin and AZT should be taken 1-2 hours apart.

Internet sources:

USA: http://hiv.net/link.php?id=73 (trade name: Biaxin)

References:

1. Benson CA, Williams PL, Currier JS, et al. A prospective, randomized trial examining the efficacy and safety of clarithromycin in combination with ethambutol, rifabutin, or both for the treatment of disseminated Mycobacterium avium complex disease in persons Clin Infect Dis 2003; 37: 1234-43. http://amedeo.com/lit.php?id=14557969
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3. Dunne M, Fessel J, Kumar P, et al. A randomized, double-blind trial comparing azithromycin and clarithromycin in the treatment of disseminated Mycobacterium avium infection in patients with HIV. Clin Infect Dis 2000, 31:1245-52. http://amedeo.com/lit.php?id=11073759

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5. Shafran SD, Singer J, Zarowny DP, et al. A comparison of two regimens for the treatment of Mycobacterium avium complex bacteremia in AIDS: rifabutin, ethambutol, and clarithromycin versus rifampin, ethambutol, clofazimine, and ciprofloxacin. N Engl J Med 1996, 335:377-83. http://amedeo.com/lit.php?id=8676931

Clindamycin

Trade names: e.g. Aclinda™, Clinabeta™, Clindamycin-ratiopharm™, Sobelin™

Drug class: antibiotic

Manufacturer: Clindamycin is manufactured by several different companies.

Indications: for HIV patients: mainly toxoplasmic encephalitis (TE)

Dose: 600 mg iv every 6 h or 600 mg po every 6 h (always with pyrimethamine for TE therapy). Half dose for (oral) maintenance therapy. In renal failure, reduce dose to a quarter or a third.

Side effects: diarrhea in 10-30 % of patients. Allergies are also frequent and often require discontinuation.

In cases of infection with Clostridium difficile pseudomembranous colitis: the spectrum ranges from mild to severe diarrhea with blood and mucous, leukocytosis, fever and severe abdominal cramps, which may progress to peritonitis, shock and toxic megacolon.

Comments/Warnings: clindamycin is contraindicated in inflammatory bowel disease and antibiotic-induced colitis. Caution with reduced hepatic or renal function and in asthma. No concurrent administration of antiperistaltics!

For diarrheas on clindamycin: discontinue and give vancomycin.

Internet sources:

USA: http://hiv.net/link.php?id=76 (trade name Cleocin™).

References:

1. Dannemann B, McCutchan JA, Israelski D, et al. Treatment of toxoplasmic encephalitis in patients with AIDS. A randomized trial comparing pyrimethamine plus clindamycin to pyrimethamine plus sulfadiazine. Ann Intern Med 1992, 116:33-43. http://amedeo.com/lit.php?id=1727093

2. Katlama C, De Wit S, O'Doherty E, Van Glabeke M, Clumeck N. Pyrimethamine-clindamycin vs. pyrimethamine-sulfadiazine as acute and long-term therapy for toxoplasmic encephalitis in patients with AIDS. Clin Infect Dis 1996, 22:268-75. http://amedeo.com/lit.php?id=8838183

Combivir™

Tablets containing 150 mg 3TC + 300 mg AZT

Drug class: NRTI

Manufacturer: GlaxoSmithKline

Indications: HIV infection

Oral dose: 1 tablet bid

In cases of reduced renal function (creatinine clearance below 50 ml/min) and anemia, Combivir™ should be replaced with the individual drugs to allow for adjustment of 3TC and AZT doses.

Warnings and side effects: see chapters on 3TC and AZT.

Internet sources:

USA: http://hiv.net/link.php?id=68

Co-trimoxazole

Trade names: diverse generics.

Tablets: 80/400 mg and 160/800 mg (forte) trimethoprim/sulfamethoxazole (TMP/SMX)

Syrup: 1 ml with 8/40 mg

Ampules: 80/400 mg

Drug class: antibiotic

Manufacturer: co-trimoxazole is manufactured by several companies

Indications: prophylaxis and treatment of Pneumocystis pneumonia (PCP). Prophylaxis and treatment (reserve drug) of cerebral toxoplasmosis.

Dose: PCP *prophylaxis*: 80/400 mg qd or 160/800 mg TMP/SMX 3 x/week. PCP *therapy*: 5 mg/kg (based on trimethoprim) po or iv every 8 h for 21 days, therefore usually 4 to 5 ampules à 80/400 mg every 8 h. Toxoplasmosis prophylaxis: 1 tablet (160/800 mg) qd.

Reduced renal function: halve dose with creatinine clearance of 15 to 50 ml/min. Co-trimoxazole is contraindicated below 15 ml/min.

Side effects: allergies. In high doses, myelotoxicity (anemia, neutropenia!), nausea, vomiting, headache, raised transaminases. In cases of mild allergy, treatment can often be continued.

Comments/Warnings: caution with sulfonamide allergy! Oral suspension for children can be used for desensitization: increase the dose slowly over six days from 12.5, 25, 37.5, 50 and 75 to 100 % of the 480 mg tablet dose (details in Leoung 2001, see below).

Co-trimoxazole can increase levels of anticoagulants and phenytoin and reduce the efficacy of oral contraceptives.

References:

1. Bozzette SA, Finkelstein DM, Spector SA, et al. A randomized trial of three antipneumocystis agents in patients with advanced HIV. N Engl J Med 1995, 332:693-9. http://amedeo.com/lit.php?id=7854375
2. Duval X, Pajot O, Le Moing V, et al. Maintenance therapy with cotrimoxazole for toxoplasmic encephalitis in the era of highly active antiretroviral therapy. AIDS 2004; 18: 1342-4. http://amedeo.com/lit.php?id=15362670
3. El-Sadr WM, Luskin-Hawk R, Yurik TM, et al. A randomized trial of daily and thrice-weekly trimethoprim-sulfamethoxazole for the prevention of Pneumocystis carinii pneumonia in HIV-infected persons. Clin Infect Dis 1999, 29:775-783. http://amedeo.com/lit.php?id=10589887
4. Leoung GS, Stanford JF, Giordano MF, et al. Trimethoprim-sulfamethoxazole (TMP-SMZ) dose escalation versus direct rechallenge for pneumocystis carinii pneumonia prophylaxis in HIV-infected

patients with previous adverse reaction to TMP-SMZ. J Infect Dis 2001, 184:992-7. http://amedeo.com/lit.php?id=11574913

5. Para MF, Finkelstein D, Becker S, et al. Reduced toxicity with gradual initiation of trimethoprim-sulfamethoxazole as primary prophylaxis for Pneumocystis carinii pneumonia. ACTG 268. J Acquir Immune Defic Syndr 2000, 24:337-43. http://amedeo.com/lit.php?id=11015150

Crixivan™ see Indinavir

d4T – Stavudine

Stavudine is a thymidine analog. Subjective tolerability is good; the drug was long considered an important alternative to AZT. Due to the mitochondrial toxicity (lipoatrophy, lactic acidosis, peripheral neuropathy), particularly in combination with ddI, the (long-term) use of d4T is no longer recommended.

Trade name: Zerit™

Hard capsules: 15, 20, 30, and 40 mg

Solution: 200 mg of 1 mg/ml

Drug class: NRTI

Manufacturer: Bristol-Myers Squibb

Indications: HIV infection

Oral dose: 40 mg bid for body weight > 60 kg, but 30 mg bid for body weight < 60 kg.

In renal failure:

Weight	CrCl 26-50 ml/min	CrCl below 26 ml/min (incl. dialysis patients)*
<60 kg	15 mg bid	15 mg qd
>60 kg	20 mg bid	20 mg qd

*Hemodialysis: take d4T after dialysis, and at the same time on non-dialysis days.

Side effects: more mitochondrial toxicity, and lipoatrophy than other NRTIs. Peripheral neuropathy (PNP), especially in combination with ddI (up to 24 %). Rare: diarrhea, nausea, headache. Hepatic steatosis, pancreatitis. Very rare, but potentially fatal: lactic acidosis, especially in combination with ddI (and in pregnancy!).

Comments/Warnings: d4T should not be combined with AZT. D4T is contraindicated in PNP.

Avoid neurotoxic medication with other neurotoxic drugs (ethambutol, cisplatin, INH, vincristine, etc.).

d4T can be taken on an empty stomach or with a light meal.

References:

1. Domingo P, Labarga P, Palacios R, Guerro MF, Terron JA, Elias MJ et al. Improvement of dyslipidemia in patients switching from stavudine to tenofovir: preliminary results. AIDS 2004; 18: 1475-8. http://amedeo.com/lit.php?id=15199328

2. Gallant JE, Staszewski S, Pozniak AL, et al. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naive patients: a 3-year randomized trial. JAMA 2004; 292: 191-201. http://amedeo.com/lit.php?id=15249568

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4. Llibre JM, Domingo P, Palacios R, et al. Sustained improvement of dyslipidaemia in HAART-treated patients replacing stavudine with tenofovir. AIDS 2006; 20: 1407-14. Abstract: http://amedeo.com/lit.php?id=16791015
5. McComsey GA, Paulsen DM, Lonergan JT, et al. Improvements in lipoatrophy, mitochondrial DNA levels and fat apoptosis after replacing stavudine with abacavir or zidovudine. AIDS 2005; 19: 15-23. Abstract: http://amedeo.com/lit.php?id=15627029
6. Saag MS, Cahn P, Raffi F, et al. Efficacy and safety of emtricitabine vs stavudine in combination therapy in antiretroviral-naive patients: a randomized trial. JAMA 2004; 292: 180-9. http://amedeo.com/lit.php?id=15249567
7. Shah SS, Rodriguez T, McGowan JP. Miller Fisher variant of Guillain-Barre syndrome associated with lactic acidosis and stavudine therapy. Clin Infect Dis 2003; 36: e131-3. http://amedeo.com/lit.php?id=12746793

Dapsone

Trade name: diverse generics.

Tablets: 50 mg

Drug class: antibiotic

Indications: reserve drug for prophylaxis of PCP and toxoplasmosis.

Dose: 100 mg daily. Alternative: 50 mg qd **plus** pyrimethamine 50 mg bid/week **plus** folinic acid 30 mg/week.

Side effects: allergies (pruritus, rash), fever. Frequently hemolytic anemia (with almost obligatory elevation of LDH!), hepatitis.

Comments/Warnings: dapsone is contraindicated in severe anemia and must be used with caution in G-6-PD deficiency. It is contraindicated in Mediterranean G-6-PD deficiency. No simultaneous administration with ddI, antacids and H2 blockers (to be taken at least two hours apart). Development of LDH on dapsone is not useful for diagnostic purposes. Rifabutin, rifampin lower dapsone levels.

References:

1. El-Sadr WM, Murphy RL, Yurik TM, et al. Atovaquone compared with dapsone for the prevention of Pneumocystis carinii pneumonia in patients with HIV infection who cannot tolerate trimethoprim, sulfonamides, or both. N Engl J Med 1998, 339:1889-95. http://amedeo.com/lit.php?id=9862944
2. Girard PM, Landman R, Gaudebout C, et al. Dapsone-pyrimethamine compared with aerosolized pentamidine as primary prophylaxis against Pneumocystis carinii pneumonia and toxoplasmosis in HIV infection. N Engl J Med 1993, 328:1514-20. http://amedeo.com/lit.php?id=8479488
3. Torres RA, Barr M, Thorn M, et al. Randomized trial of dapsone and aerosolized pentamidine for the prophylaxis of pneumocystis carinii pneumonia and toxoplasmic encephalitis. Am J Med 1993, 95:573-83. http://amedeo.com/lit.php?id=8018144

Daraprim™ see pyrimethamine

Darunavir (TMC-114)

Darunavir is a new, well-tolerated PI with considerable activity against PI-resistant viruses, and was recently licensed in Europe and the USA. Darunavir is boosted with ritonavir.

Trade name: Prezista™

Tablets: 300 mg

Drug class: Protease inhibitor

Manufacturer: Tibotec

Indications: intensively pre-treated patients with treatment failure (for example strains resistant to two or more PIs).

Dose: 600 mg bid (2 tablets each time) plus 100 mg ritonavir bid.

Side effects: moderate gastrointestinal complaints and dyslipidemia, although the dyslipidemia is not as pronounced as with other PIs. Rash (7 %) in the first 2 weeks.

Interactions: relevant interactions occur with lopinavir – the plasma levels of darunavir fall, and the combination should be avoided. Because darunavir is metabolized via the cytochrome P450 system, numerous other interactions should be considered. The following drugs should therefore not be used in combination:

St. John's wort, astemizole, terfenadine, cisapride, pimozide, midazolam, triazolam, ergotamine derivatives, rifapin, phenobarbital, phenytoin, carbamazepine. For example:

- In combination with efavirenz, there is the possibility of reduced darunavir and increased efavirenz levels.
- Instead of pravastatin, atorvastatin can be used in the lowest doses (10 mg). The dose of rifabutin has to be reduced to 150 mg every two days. Darunavir raises the levels of calcium antagaonists; reduces methadone levels; interferes with birth control pills.
- Maximum doses of PDE5 inhibitors with darunavir administration: 10 mg Cialis™ in 72 hours; 2,5 mg Levitra™ in 72 hours; 25 mg Viagra™ in 48 hours.

For further information (itraconazole, voriconazole, ketoconazole, cyclosporine, SSRIs, etc) see product information.

Comments/warnings: darunavir should be taken at mealtimes. Caution with sulfonamide allergy.

References:

1. Arasteh K, Clumeck N, Pozniak A, et al. TMC114/ritonavir substitution for protease inhibitor(s) in a non-suppressive antiretroviral regimen: a 14-day proof-of-principle trial. AIDS 2005; 19: 943-7. Abstract: http://amedeo.com/lit.php?id=15905675
2. De Meyer S, Azijn H, Surleraux D, et al. TMC114, a novel HIV type 1 protease inhibitor active against protease inhibitor-resistant viruses, including a broad range of clinical isolates. Antimicrob Agents Chemother 2005; 49: 2314-21. http://amedeo.com/lit.php?id=15917527
3. Kovalevsky AY, Tie Y, Liu F, et al. Effectiveness of nonpeptide clinical inhibitor TMC-114 on HIV-1 protease with highly drug resistant mutations D30N, I50V, and L90M. J Med Chem 2006; 49: 1379-87. Abstract: http://amedeo.com/lit.php?id=16480273
4. Poveda E, Blanco F, Garcia-Gasco P, et al. Successful rescue therapy with darunavir (TMC114) in HIV-infected patients who have failed several ritonavir-boosted protease inhibitors. AIDS 2006; 20: 1558-60. Abstract: http://amedeo.com/lit.php?id=16847414
5. Sekar VJ, Lefebvre E, De Paepe E, et al. Pharmacokinetic interaction between TMC114/r and omeprazole or ranitidine in HIV-negative healthy volunteers. Antimicrob Agents Chemother 2007; Abstract: http://amedeo.com/lit.php?id=17210768
6. Surleraux DL, Tahri A, Verschueren WG, et al. Discovery and selection of TMC114, a next generation HIV-1 protease inhibitor. J Med Chem 2005; 48: 1813-22. Abstract: http://amedeo.com/lit.php?id=15771427

Daunorubicin, liposomal

Trade name: DaunoXome™

50 mg vials of liposomal daunorubicin

Drug class: cytostatic

Manufacturer: Gilead

Indications: Kaposi's sarcoma in patients with CD4 cells < 200/µl and in cases of severe mucocutaneous or visceral KS.

Dose: 40 mg/m^2 i.v. over 30-60 minutes, every 2-3 wks.

Side effects: during infusion: back pain, flushing. Symptoms usually resolve when the infusion is slowed or stopped. Fatigue, headaches, chills. Pancytopenia, elevated transaminases and alkaline phosphatase.

In myelosuppression (neutrophils < 1,000/µl): delay the next dose and treat with G-CSF if necessary. Caution cardiotoxicity – cardiomyopathy!

Comments/Warnings: contraindicated if there is hypersensitivity to anthracyclines. Caution with pre-existing cardiovascular disease, previous treatment with anthracyclines.

LVEF should be evaluated before initiation of treatment. Afterwards, echocardiography before each cycle when the cumulative dose is 240 mg/m^2 .

Internet sources:

USA: http://hiv.net/link.php?id=82 (2.3 MB)

References:

1. Gill PS, Wernz J, Scadden DT, et al. Randomized phase III trial of liposomal daunorubicin versus doxorubicin, bleomycin, and vincristine in AIDS-related Kaposi's sarcoma. J Clin Oncol 1996; 14: 2353-64. http://amedeo.com/lit.php?id=8708728
2. Fumagalli L, Zucchetti M, Parisi I, et al. The pharmacokinetics of liposomal encapsulated daunorubicin are not modified by HAART in patients with HIV-associated Kaposi's sarcoma. Cancer Chemother Pharmacol 2000, 45: 495-501. http://amedeo.com/lit.php?id=10854138
3. Hjortsberg C, Persson U, Lidbrink E, Bennett C. Cost-effectiveness analysis of pegylated-liposomal doxorubicin and liposomal daunorubicin treatments in patients with Kaposi's sarcoma. Acta Oncol 1999, 38:1063-7. http://amedeo.com/lit.php?id=10665764
4. Rosenthal E, Poizot-Martin I, Saint-Marc T, Spano JP, Cacoub P. Phase IV study of liposomal daunorubicin (DaunoXome) in AIDS-related Kaposi sarcoma. Am J Clin Oncol 2002, 25:57-9. http://amedeo.com/lit.php?id=11823698

DaunoXome™ see Daunorubicin, liposomal

ddC – Zalcitabine

The distribution of ddC (HIVID™) was stopped in 2006 due to the complicated dosing, moderate efficacy, side effects and cross-resistances.

ddI – Didanosine

ddI was one of the first NRTIs, which today, because of its side effects (pancreatitis 10 %) and mitochondrial toxicity, is only used in certain resistence situations. The dose has to be adjusted according to body weight.

Combination with tenofovir and d4T should be avoided.

Trade name: Videx™

Enteric coated capsules: 125 mg, 200 mg, 250 mg, 400 mg.

Powder: 4 g per bottle.

Drug class: NRTI

Manufacturer: Bristol-Myers Squibb

Indications: HIV infection

Oral dose: 400 mg qd (body weight > 60 kg) or 250 mg qd (body weight < 60 kg). ddI must be taken on an empty stomach, at least 2 hours after or at the latest 1 hour before meals.

Side effects: diarrhea, nausea, headache. ddI specific: pancreatitis, even after longer periods on treatment! Peripheral polyneuropathy. Rarely: episodes of lactic acidosis, especially in combination with d4T and ribavirin.

Comments/Warnings: acute and chronic pancreatitis are contraindications, as is treatment with ribavirin! Caution with d4T, ethambutol, cisplatin, disulfiram, INH, vincristine, etc. (PNP).

Concurrent dosing with tenofovir increases the C_{max} and AUC of ddI by 28 % and 44 %, respectively. The ddI dose should therefore be reduced to 250 mg. Tenofovir is taken two hours before or one hour after ddI; the two should not be combined at all if possible (see HAART chapter).

With indinavir, dapsone, ketoconazole, itraconazole, or tetracyclines there should be a two-hour interval.

Initially, monthly monitoring of amylase, blood count, transaminases and bilirubin. Patients should be informed about the risk and signs of pancreatitis. ddI should be discontinued if there is clinical suspicion; avoid rechallenge.

Internet sources:

USA: http://hiv.net/link.php?id=86

References:

1. Leon A, Mallolas J, Martinez E, et al. High rate of virological failure in maintenance antiretroviral therapy with didanosine and tenofovir. AIDS 2005; 19: 1695-7. Abstract: http://amedeo.com/lit.php?id=16184042
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Diflucan™ see Fluconazole

Delavirdine

Delavirdine is rarely used, due to high dosing and drug interactions. Delaviridine is not licensed in Europe.

Trade name: Rescriptor™; abbr. DLV.

Tablets: 100 mg and 200 mg (can also be dissolved in water!).

Drug class: NNRTI

Manufacturer: Pfizer

Indications: HIV infection.

Oral dose: 400 mg tid

Side effects: rash, usually occurring within the first six weeks of treatment. In mild cases, give antihistamines; discontinue DLV if systemic effects (fever, conjunctivitis, myalgia and arthralgia) occur. Nausea, elevated transaminases.

Comments/Warnings: delavirdine is contraindicated for concurrent treatment with rifabutin, rifampin, carbamazepine, phenytoin, alprazolam, astemizole, phenobarbital, cisapride, midazolam, terfenadine and triazolam.

Delavirdine interacts with numerous drugs via reduction of CYP3A-activity. It increases the AUC of some PIs (saquinavir, nelfinavir), sildenafil, dapsone, clarithromycin, quinidine and warfarin. Delavirdine levels are lowered by ddI, H_2 blockers, carbamazepine, phenytoin and antacids.

Internet sources:

USA: http://hiv.net/link.php?id=178

References:

1. Conway B. Initial therapy with protease inhibitor-sparing regimens: evaluation of nevirapine and delavirdine. Clin Infect Dis 2000, Suppl 2:S130-4. http://amedeo.com/lit.php?id=10860897
2. Harris M, Alexander C, O'Shaughnessy M, Montaner JS. Delavirdine increases drug exposure of ritonavir-boosted protease inhibitors. AIDS 2002; 16: 798-9.
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Doxorubicin (liposomal)

Trade name: Caelyx™

10 ml (20 mg) and 25 ml (50 mg) vials

Drug class: anthracycline

Manufacturer: Schering-Plough, Ortho Biotech (USA)

Indications: Kaposi's sarcoma in AIDS patients with < 200 CD4 cells/µl and severe mucocutaneous or visceral involvement.

Dose: 20 mg/m^2 i.v. in 250 ml 5 % glucose over 30 minutes every 2-3 weeks.

Side effects: cardiomyopathy, myelosuppression, stomatitis (rarely severe), hand-foot syndrome (painful erythema). Treatment: cool affected areas. Beware extravascularisation (never s.c. or i.m., no bolus administration!).

Comments/Warnings: contraindicated in cardiomyopathy, severe myelosuppression (neutrophils < 1,000/µl, platelets < 50,000/µl).

Contraindicated in cardiomyopathy, previous treatment with anthracyclines above the cumulative dose.

ECG and echocardiography (left ventricular ejection fraction?) before and during treatment and at periodic intervals during treatment above the cumulative dose of 450 mg/m^2 before each cycle.

Hand-foot syndrome is induced by sweating, pressure, friction – therefore no tight gloves, no sun, or long showers. Cool drinks are beneficial!

This drug is expensive (in Germany, two 20 mg vials cost approximately 1,343 Euro).

References:

1. Martin-Carbonero L, Barrios A, Saballs P, et al. Pegylated liposomal doxorubicin plus highly active antiretroviral therapy versus highly active antiretroviral therapy alone in HIV patients with Kaposi's sarcoma. AIDS 2004; 18: 1737-40. http://amedeo.com/lit.php?id=15280789
2. Nunez M, Saballs P, Valencia ME, et al. Response to liposomal doxorubicin and clinical outcome of HIV-1-infected patients with Kaposi's sarcoma receiving HAART. HIV Clin Trials 2001; 2: 429-37. http://amedeo.com/lit.php?id=11673818

Efavirenz

Efavirenz is a frequently used NNRTI. Diverse CNS side effects are a substantial problem (disturbances of sleep architecture, morning dizziness, somnolence). Further disadvantages include drug interactions and cross-resistance, as with the other members of this drug class.

Efavirenz is also available in the fixed combination Atripla™.

Trade name: Sustiva™, or Stocrin™. Also a component of Atripla™

Sustiva™ tablets: 600 mg. Capsules: 50 mg, 100 mg, 200 mg

Atripla™ tablets (600 mg plus 200 mg emtricitabine + 300 mg tenofovir)

Drug class: NNRTI

Manufacturer: Bristol-Myers Squibb, MSD

Indications: HIV infection

Oral dose: 600 mg daily, at bedtime.

Side effects: CNS symptoms occur frequently: nightmares, confusion, dizziness, somnolence, abnormal thinking, depression, impaired concentration, insomnia, and depersonalization. These symptoms usually resolve after a few weeks. A rash (15 %) in the first weeks, usually mild, and further treatment is normally possible.

Elevation of liver function tests and biliary enzymes (γGT). Dyslipidemia, occasionally very uncomfortable, painful gynecomastia.

Comments/Warnings: contraindicated in pregnancy. Caution in women of child-bearing age; talk about possible wish to have children.

Contraindicated for concurrent administration with ergotamines, astemizole, cisapride, midazolam, terfenadine and triazolam. Should not be combined with contraceptive pills.

Increase dose of lopinavir/r with efavirenz (2 x 3 tablets/day (TDM!), atazanavir/r (400/100 mg), rifabutin (450 mg), methadone (approximately 20-30 %).

Not to be taken with fatty meals (poorer absorption).

Internet sources:

USA: http://hiv.net/link.php?id=88

References:

1. Boffito M, Rossati A, Reynolds HE, et al. Undefined duration of opiate withdrawal induced by efavirenz in drug users with hiv infection and undergoing chronic methadone treatment. AIDS Res Hum Retroviruses 2002; 18: 341-2.
2. Clifford DB, Evans S, Yang Y, et al. Impact of efavirenz on neuropsychological performance and symptoms in HIV-infected individuals. Ann Intern Med 2005; 143: 714-21. Abstract: http://amedeo.com/lit.php?id=16287792
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Emtricitabine (FTC)

Emtricitabine (FTC) is a well-tolerated cytidine analog, comparable to 3TC both biochemically and in its resistance profile, but has a longer half-life.

Trade name: Emtriva™. Also in Truvada™ and Atripla™.

Emtriva™ hard capsules with 200 mg; solution: 170 ml (1 mg = 10 mg/ml).

Truvada™ (emtricitabine 200 mg + tenofovir 300 mg).

Drug class: NRTI

Manufacturer: Gilead

Indications: HIV infection

Dose: 1 x 200 mg daily (solution: 240 mg = 24 ml).

Use single-drug preparations instead of combination preparations with reduced creatinine clearance (see respective section for dose). Emtricitabine is adjusted as follows:

CrCl (ml/min)	**Dose**
30–49	200 mg every 2 days
15–29	200 mg every 3 days
Below 14 or dialysis	200 mg every 4 days

Side effects: rare. Most commonly, headache, nausea, diarrhea, rash. Possibly hyperpigmentation.

Comments/Warnings: danger of hepatitis rebound with HBV coinfection after stopping FTC. Do not stop therapy if possible, check liver function.

Internet sources:

USA: http://hiv.net/link.php?id=223

References:

1. Dando TM, Wagstaff AJ. Emtricitabine/tenofovir disoproxil fumarate. Drugs 2004; 64: 2075-82 http://amedeo.com/lit.php?id=15341498
2. Frampton JE, Croom KF. Efavirenz/emtricitabine/tenofovir disoproxil fumarate: triple combination tablet. Drugs 2006; 66: 1501-12 Abstract: http://amedeo.com/lit.php?id=16906786
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Emtriva™ see Emtricitabine

Enfuvirtide see T-20

Epivir™ see 3TC (at the beginning of this chapter)

Epzicom™ see Kivexa

Erypo™ see Erythropoetin

Erythropoietin

Trade name: Erypo™

Including vials with 2,000, 4,000 or 10,000 I.U./ml

Drug class: anti-anemic

Manufacturer: Janssen-Cilag among other companies

Indications: anemia in chronic renal failure, reduction of the need for transfusion in patients with solid tumours and malignant lymphomas, who are receiving chemotherapy and are at risk of transfusion. Asymptomatic when hemoglobin is at the

earliest below 10-11 g/dl, if endogenous erythropoietin levels are below 500 mU/ml.

Dose: According to the indication 3 x 50-100 I.U./kg/week s.c. until a hematocrit of 30-35 % is reached. If there is no response, increase dose; if there is no response after a further 6 weeks: discontinue. If there is a response, a weekly maintenance dose of 100-200 I.U./kg body weight is sufficient. At hematocrit values > 40 % or Hb > 13 g/dl: discontinue.

Side effects: in particular at the start, flu-like symptoms, such as headache, arthralgia, asthenia, dizziness, fatigue.

Comments/Warnings: erythropoietin is contraindicated with uncontrolled hypertension. It is expensive and should be used sparingly. Before initiating treatment, other causes of anemia should be excluded. These include:

- Vitamin B12 or folic acid deficiency, iron deficiency, occult blood loss, hematological disorders such as thalassemia and myelodysplasia.
- AIDS-defining illnesses with bone marrow involvement such as MAC infection, tuberculosis, CMV infection, lymphoma, Kaposi's sarcoma.

Strict monitoring of blood pressure initially!

Subcutaneous administration of Erypo™ is **contraindicated** in patients with chronic renal insufficiency due to the risk of antibody-induced erythroblastopenia (Pure Red Cell Aplasia).

Store Erypo™ at 2-8° Celsius in the original package. Do not freeze!

Drug interactions: erythropoietin can diminish the efficacy of concurrently administered antihypertensives. Concurrent treatment with anticonvulsive drugs may increase seizure susceptibility.

Ethambutol

Drug class: tuberculostatic

Manufacturer: Ethambutol is manufactured by several different companies.

Indications: tuberculosis, MAC infection

Dose: 15 to 25 mg/kg (maximum 2 g) daily, usually 3 tablets à 400 mg qd. Ethambutol should only be given as combination therapy.

Dose reduction in renal failure:

CrCl	Dose
Above 75 ml/min	25 mg/kg
40-75 ml/min	15 mg/kg
30-40 ml/min	15 mg/kg every second day
<30 ml/min	Measurement of serum levels required *

*Serum levels should be within the range of the minimal inhibitory concentration 2-5 µg/ml after 2-4 hours.

Side effects: ethambutol can lead to optical neuritis with impaired vision (decreased acuity, restricted fields, loss of red-green color discrimination). It is usually reversible if ethambutol is discontinued immediately.

Other side effects: nausea, vomiting, abdominal pain, headache, dizziness, pruritus, arthralgia, elevated serum uric acid (acute gout attacks possible!), abnormal liver function tests.

Comments/Warnings: ethambutol is contraindicated with pre-existing optical nerve damage.

Ophthalmologic examination before initiation of treatment and subsequently at 4-week intervals (color discrimination, field of vision, acuity). Immediate discontinuation to prevent optical atrophy if drug-related impairment of vision occurs.

Patients should be informed that impairment of vision may occur and to immediately report this to the treating physician.

Aluminum hydroxide reduces absorption of ethambutol; ethambutol should therefore be taken at least one hour before antacids.

Monitor liver values and uric acid levels at monthly intervals.

References:

1. Shafran SD, Singer J, Zarowny DP, et al. A comparison of two regimens for the treatment of Mycobacterium avium complex bacteremia in AIDS: rifabutin, ethambutol, and clarithromycin versus rifampin, ethambutol, clofazimine, and ciprofloxacin. N Engl J Med 1996, 335:377-83. http://amedeo.com/lit.php?id=8676931
2. Ward TT, Rimland D, Kauffman C, Huycke M, Evans TG, Heifets L. Randomized, open-label trial of azithromycin plus ethambutol vs. clarithromycin plus ethambutol as therapy for Mycobacterium avium complex bacteremia in patients with HIV infection. Clin Infect Dis 1998, 27:1278-85. http://amedeo.com/lit.php?id=9827282

Etravirin (TMC-125)

Etravirin is a NNRTI, which is also effective against NNRTI-resistant HIV strains. Since February 2007, etravirin has been available in an Expanded Access Program. Requirements for participation include limited treatment options following previous treatment (NNRTI + NRTI + at least 2 previous therapy regimes with a PI basis).

Trade name: not yet known

Drug class: NNRTI

Manufacturer: Tibotec

Dose: 200 mg bid (2 tablets bid)

Side effects: headache, diarrhea, rash.

Interactions: tipranavir/r, nevirapine and efavirenz reduce etravirin exposure and should therefore not be combined.

Etravirin increases fosamprenavir/r levels (+ 69 %), and the dose may need adjusting. Etravirin can be used with rifabutin und clarithromycin in most situations without dose adjustments; however, in MAC treatment, clarithromycin is not recommended.

Etravirin reduces sildenafil levels by 69 %.

Dose adjustment is not necessary with proton pump inhibitors, H2-blockers, methadone and contraceptives.

Literatur:

1. Andries K, Azijn H, Thielemans T, et al. TMC125, a novel next-generation nonnucleoside reverse transcriptase inhibitor active against nonnucleoside reverse transcriptase inhibitor-resistant human immunodeficiency virus type 1. Antimicrob Agents Chemother 2004; 48: 4680-6. Abstract: http://amedeo.com/lit.php?id=15561844
2. Gruzdev B, Rskhmanova A, Doubovskaya E, et al. A randomized, double-blind, placebo-controlled trial of TMC125 as 7-day monotherapy in antiretroviral naive, HIV-1 infected subjects. AIDS 2003; 17: 2487-94. http://amedeo.com/lit.php?id14600520
3. Sankatsing SU, Weverling GJ, Peeters M, et al. TMC125 exerts similar initial antiviral potency as a five-drug, triple class antiretroviral regimen. AIDS 2003; 17:2623-7. http://amedeo.com/lit.php?id=14685056

Filgrastim see G-CSF

Fluconazole

Fluconazole is an antifungal azole and the drug of choice for treatment of candidiasis in HIV infection and for secondary prophylaxis of cryptococcosis. It is also a component of acute therapy for cryptococcosis.

Trade name: Diflucan™, several generics

50 mg, 100 mg and 200 mg capsules

Oral solution with 50 mg per 10 ml. Powder for suspension with 50 mg per 5 ml

Bottles for infusion with 100 mg, 200 mg and 400 mg

Drug class: antimycotic

Manufacturer: Pfizer and several other companies

Indications: Candidiasis, cryptococcal infections, a few rare mycoses.

Dose: for oropharyngeal candidiasis: 100 mg qd po; for Candida esophagitis 200 mg qd for 7-10 days. Double the dose on the first day. An attempt may be made with a higher dose if there is persistance after 10 days (up to 800 mg daily).

Cryptococcal meningitis: Initially, 400-800 mg daily, combined with flucytosine and amphotericin B if possible. After completion of acute therapy – usually after 6 weeks – maintenance therapy with 200 mg fluconazole daily.

Renal insufficiency: halve dose with creatinine clearance of 50 to 10 ml/min; reduce to 25 % below 10 ml/min.

Side effects: rarely gastrointestinal complaints and elevated transaminases. Reversible alopecia in approximately 10 % of cases with more than 400 mg daily.

Comments/warnings: azole-resistant Candida strains on long-term treatment. No effect on C. krusei or Aspergillus. In cases of C. glabrata infection, higher doses are required (sensitivity dose-dependent).

Fluconazole levels are reduced by rifabutin/rifampin. Fluconazole increases serum concentrations of rifabutin, atovaquone, clarithromycin, theophylline, opiates, coumarins, benzodiazepines, phenytoin, and anti-convulsive drugs as well as AZT.

The tablets have good absorption, and infusions (2-3 times more expensive) are only required in cases of non-adherence, mucositis or problems with absorption.

Internet sources:

USA: http://hiv.net/link.php?id=94

References:

1. Chapman TM, Plosker GL, Perry CM. Fosamprenavir: a review of its use in the management of antiretroviral therapy-naive patients with HIV infection. Drugs 2004; 64: 2101-24. http://amedeo.com/lit.php?id=15341507
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3. Gathe JC Jr, Ive P, Wood R, et al. SOLO: 48-week efficacy and safety comparison of once-daily fosamprenavir/ritonavir versus twice-daily nelfinavir in naive HIV-1-infected patients. AIDS 2004; 18: 1529-37. http://amedeo.com/lit.php?id=15238771

Fosamprenavir

Fosamprenavir is a calcium phosphate ester of amprenavir, which is more soluble and is better absorbed than amprenavir. Overall tolerability is fairly good. Fosamprenavir has an interesting resistance profile and a variety of possibilities for dosing (see below).

Trade name: USA: Lexiva™, Europe: Telzir™

Film-coated tablets with 700 mg (60 = N3). Suspension 50 mg/ml (225 ml = N1)

Drug class: protease inhibitor

Manufacturer: GlaxoSmithKline

Indications: HIV infection, both treatment-naïve and -experienced patients

Dose: varies for **treatment-naïve** patients:

- 700 mg bid + 100 mg ritonavir bid (2 x 2 pills, is the usual dose).
- 1,400 mg bid (without ritonavir - not licensed in Europe!).
- 1,400 mg qd + 200 mg ritonavir qd (4 pills qd, not in Europe).

The once-daily version is not recommended for PI-experienced patients. **PI-experienced** patients should therefore only receive the following dose:

- 700 mg bid + 100 mg ritonavir bid (2 pills bid).

Fosamprenavir may be taken with or without food.

Side effects: most common: diarrhea; less frequent: nausea, vomiting, rash (up to 20 %). Rarely: Stevens-Johnson syndrome (< 1 %).

Comments/warnings: contraindicated: cisapride, pimozide, midazolam, triazolam, ergotamines. Flecainide and propafenone are contraindicated when fosamprenavir is boosted with ritonavir. There may be life-threatening interactions with amiodarone, lidocaine (systemic), tricyclic anti-depressants and quinidine.

Do not administer together with rifampin (this reduces amprenavir plasma levels by 90 %), delavirdine or St. John's wort; use cautiously with simvastatin, lovastatin, sildenafil, vardenafil.

Carbamazepine, phenobarbital, phenytoin and dexamethasone can lower plasma levels of amprenavir. Rifabutin: dose reduction of rifabutin by approximately 50 %; 75% if fosamprenavir is boosted with ritonavir (instead of 300 mg daily, only 150 mg every other day, or 150 mg 3 x/week).

Efavirenz seems to lower plasma levels significantly (probably to an extent that is clinically relevant). However, this is not the case if fosamprenavir is boosted. But: on once daily fosamprenavir/r, the ritonavir dose should be increased to 1 x 300 mg. Caution in combination with lopinavir (plasma levels of both drugs are reduced)!

Ketoconazole, itraconazole: if dosed > 400 mg daily, possibly dose reduction of ketoconazole/itraconazole. If fosamprenavir is boosted with ritonavir, ketoconazole and itraconazole doses above 200 mg daily are not recommended.

Caution in patients with sulfonamide allergy, reduced liver function (possibly dose reduction). Possibly, an increase in the methadone dose might be required.

Internet sources:

USA: http://hiv.net/link.php?id=222

References:

1. Bicanic T, Harrison T, Niepieklo A, Dyakopu N, Meintjes G. Symptomatic relapse of HIV-associated cryptococcal meningitis after initial fluconazole monotherapy: the role of fluconazole resistance and immune reconstitution. Clin Infect Dis 2006; 43: 1069-73. http://amedeo.com/lit.php?id=16983622
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Foscarnet

Trade name: Foscavir™

250 ml bottles with 24 mg/ml

Drug class: virostatic

Manufacturer: AstraZeneca

Indications: reserve drug for induction and maintenance therapy of CMV retinitis. Severe acyclovir-resistant herpes or varicella zoster infections.

Dose: 90 mg/kg iv over at least 2 hours twice daily for induction therapy (2-3 weeks) of CMV retinitis. 90-120 mg/kg over 2 hours once daily for maintenance therapy. HSV and VZV: 60 mg/kg iv bid for 2 weeks.

Side effects: nephrotoxicity! Usually reversible after discontinuation of foscarnet. Electrolyte changes (hypocalcemia, hypokalemia) are also common. More rarely: anemia, neutropenia, fever, rash, headache, nausea, vomiting, diarrhea. Often painful penile ulcers (wash after every urination!).

Comments/Warnings: good hydration! At least 2.5 l fluids daily. To prevent hypocalcemia give one ampule of 10 % calcium solution in 100 ml 5 % glucose immediately prior to infusion of foscarnet. Give 500-1,000 ml 5 % glucose before or after foscarnet dose. Do not mix infusions.

Initial monitoring of Na, K, Ca, creatinine, blood count 3x/week.

No concurrent treatment with other nephrotoxic drugs.

Adjust dose in renal insufficiency. See prescribing information.

References:

1. Breton G, Fillet AM, Katlama C, Bricaire F, Caumes E. Acyclovir-resistant herpes zoster in HIV-infected patients: results of foscarnet therapy. Clin Infect Dis 1998, 27: 1525-7. http://amedeo.com/lit.php?id=9868672
2. Cheung TW, Jayaweera DT, Pearce D, et al. Safety of oral versus intravenous hydration during induction therapy with intravenous foscarnet in AIDS patients with cytomegalovirus infections. Int J STD AIDS 2000, 11: 640-7. http://amedeo.com/lit.php?id=11057934
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Foscavir™ see Foscarnet

Fuzeon™ see T-20

Ganciclovir

Trade name: Cymeven™

Bottles for injection with 500 mg. Orally, valganciclovir should be used instead of ganciclovir (see Valganciclovir).

Drug class: virostatic

Manufacturer: Hoffmann-La Roche

Indications: CMV retinitis. Since the approval of valganciclovir: only for use in patients for whom oral treatment is not possible.

Dose: initial treatment with normal renal function: 5 mg/kg bid as an iv infusion over one hour, for at least 14-21 days. Maintenance: 6 mg/kg iv qd, 5 x/week.

Side effects: leukopenia, anemia and thrombocytopenia are dose limiting. Less frequent: nausea, vomiting, diarrhea or CNS symptoms such as confusion or headache.

Comments/Warnings: monitor blood count every two days. Reduce dose by 30 % to 50 % for neutrophil counts between 500 and 800/µl; discontinue drug when below 500/µl (G-CSF if necessary!). Contraindicated in neutropenia < 500/µl, thrombocytopenia < 25,000/µl and concurrent chemotherapy.

Caution if administering with AZT and ddI (increased toxicity!).

Ganciclovir is a potential teratogen and carcinogen. Dose adjustment is necessary in renal insufficiency (see link below).

Internet sources:

USA: http://hiv.net/link.php?id=97

References:

1. Casper C, Nichols WG, Huang ML, Corey L, Wald A. Remission of HHV-8 and HIV-associated multicentric Castleman's disease with ganciclovir treatment. Blood 2003; : Blood 2003 Nov 13 http://amedeo.com/lit.php?id=14615380
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3. Imai Y, Shum C, Martin DF, Kuppermann BD, Drew WL, Margolis TP. Emergence of drug-resistant cytomegalovirus retinitis in the contralateral eyes of patients with AIDS treated with ganciclovir. J Infect Dis 2004; 189: 611-5. Epub 2004 Jan 28. http://amedeo.com/lit.php?id=14767813

G-CSF

Trade names: Neupogen™ (Filgrastim), Granocyte™ (Lenograstim)

Granocyte™: Vials with 13.4 million I.U. and 33.6 million I.U.

Neupogen™: prefilled syringes with 300 µg and 480 µg

Neupogen™: vials with 300 µg in 1 ml and 480 µg in 1.6 ml

Drug class: cytokine

Manufacturer: Amgen, Chugai Pharma

Indications: neutropenia, especially drug-induced (AZT, ganciclovir, interferon, myelosuppressive chemotherapy), rarely HIV-related.

Dose: with chemotherapy, usually approx. 5 µg/kg Neupogen™ daily on fixed days. Outside of chemotherapy protocols, 1-5 µg/kg Neupogen™ 1-3x/week, titrate dose down. The goal is usually at least 1,000 neutrophil granulocytes/µl. For Granocyte™ doses see product information.

Side effects: bone, back or muscle pain in 10 to 20 % of patients, sometimes severe (requiring generous analgesia). Irritation at the injection site.

Comments/Warnings: G-CSF is expensive. Long-term treatment should be avoided (change the drug causing neutropenia if possible). Remainders of individual ampules should be kept refrigerated in a syringe.

Monitoring: blood count twice weekly.

Internet sources:

USA, Neupogen™: http://hiv.net/link.php?id=100

References:

1. Campbell TB, Rapaport E, Schooley RT, Kuritzkes DR. Increased replication of HIV-1 minor variants during hematopoietic stem-cell mobilization with filgrastim. J Infect Dis 2004; 190: 257-66. Epub 2004 Jun 22. http://amedeo.com/lit.php?id=15216459
2. Davidson M, Min YI, Holbrook JT, et al. Use of filgrastim as adjuvant therapy in patients with AIDS-related cytomegalovirus retinitis. AIDS 2002, 16:757-65. http://amedeo.com/lit.php?id=11964532
3. Davidson M, Min YI, Holbrook JT, et al. Influence of filgrastim (granulocyte colony-stimulating factor) on HIV type 1 RNA in patients with cytomegalovirus retinitis. J Infect Dis 2002, 186: 1013-8. http://amedeo.com/lit.php?id=12232843

Hivid™ see ddC – no longer on the market.

Indinavir

Indinavir was, in 1996, one of the first PIs. Today, however, its use is limited due to side effects, especially skin and renal problems. Ritonavir boosting is recommended.

Trade name: Crixivan™.

Hard capsules of 200 mg, 333 mg and 400 mg

Drug class: protease inhibitor

Manufacturer: Merck/MSD

Indications: HIV infection

Dose: two current dosing regimens:

Boosted: 800 mg bid (two 400 mg capsules bid) plus 100 mg ritonavir bid (one 100 mg capsule bid). 400 mg bid (one 400 mg capsule bid) plus 400 mg ritonavir bid (four 100 mg capsules bid). Dose reduction often possible on TDM.

Unboosted dose (uncommon!): 800 mg tid (two 400 mg capsules tid) one hour before/two hours after eating.

Side effects: nephrolithiasis (in up to 25 %); less frequently: nephrotoxicity with elevated serum creatinine. Diarrhea, nausea/vomiting, hyperbilirubinemia.

Frequently: sicca syndrome (dry skin, dry mouth, dry eyes); alopecia, ingrown toenails and paronychia; rarely hair loss.

Lipodystrophy ("Crixbelly"), dyslipidemia, disorders of glucose metabolism.

Comments/Warnings: At least 1.5 l of fluid should be consumed daily to prevent nephrolithiasis. Nephrolithiasis and also probably skin problems, correlate with plasma levels. No concurrent administration of ddI.

In combination with ritonavir, indinavir can be taken twice daily and with meals.

Concurrent use of rifampin, astemizole, terfenadine, cisapride, triazolam, ergotamines, simvastatin, lovastatin, or St. John's wort is contraindicated.

The following dose adjustments are necessary:

- Rifabutin: boosting with ritonavir: 150 mg rifabutin every 2 days or three times a week.
- Ketoconazole and itraconazole: 600 mg indinavir tid.
- Sildenafil: maximum 25 mg sildenafil/48h.

Internet sources:

USA: http://hiv.net/link.php?id=102

References:

1. Acosta EP, Wu H, Hammer SM, et al. comparison of two indinavir/ritonavir regimens in the treatment of HIV-infected individuals. J Acquir Immune Defic Syndr 2004; 37: 1358-1366. http://amedeo.com/lit.php?id=15483465
2. Elzi L, Hirsch HH, Battegay M. Once-daily directly observed therapy lopinavir/ritonavir plus indinavir as a protease inhibitor-only salvage therapy in heavily pretreated HIV-1-infected patients: a pilot study. AIDS 2006; 20: 129-31. Abstract: http://amedeo.com/lit.php?id=16327333
3. Ghosn J, Lamotte C, Ait-Mohand H, et al. Efficacy of a twice-daily antiretroviral regimen containing 100 mg ritonavir/400 mg indinavir in HIV-infected patients. AIDS 2003; 17: 209-14. http://amedeo.com/lit.php?id=12545081
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Interferon alfa 2a/2b

Trade names: 2a: Roferon™, Pegasys™; 2b: Intron A™, PegIntron™

Pegasys™ (pegylated interferon α-2a): vials with 135 and 180 µg

PegIntron™ (pegylated interferon α-2b): vials with 50, 80, 100, 120 and 150 µg

Roferon-A™: prefilled syringes with 3, 4.5, 6 or 9 mill I.U. Alternatively, vials with 3 or 18 mill I.U. or cartridges with 18 mill I.U.

Intron A™ (Interferon alfa-2b): either in pen devices with 18, 30 or 60 mill I.U. or in vials with corresponding syringes and cannulas with 18 or 25 mill I.U.

Drug class: cytokine

Manufacturer: Roche (Roferon™, Pegasys™); Schering-Plough (Intron A™, Peg-Intron™)

Indications: severe Kaposi's sarcoma in patients with good immune status (> 300 CD4 cells/µl; always try HAART first). Chronic hepatitis C, possibly also for hepatitis B.

Dose: Peg-Intron™: 1.5 µg/kg 1 x/week

Pegasys™: 180 µg 1 x/week

Standard interferons: 6 mil I.U. 3 x/week

Duration is dependent on success of treatment of KS, on HCV genotype and success of treatment for hepatitis C. Interferon is injected subcutaneously.

Side effects: Frequent influenza-like symptoms such as fever, and myalgia. Depression (even suicidality), fatigue, sleeping disorders, personality changes. Anemia, thrombocytopenia and leukopenia. Autoimmune thyroiditis. Reversible hair loss. Possibly also impaired vision.

Comments/Warnings: influenza-like symptoms usually occur a few hours after dosing and can be reduced with Paracetamol (1,000 mg in advance!).

All side effects are usually reversible.

Contraindications are severe heart, liver or renal dysfunction, bone marrow disorders, CNS disorders (e.g. epilepsy, severe depression), uncompensated thyroid disorders.

Monitor blood count every two weeks initially, later monthly. TSH every three months.

Interferons must be kept refrigerated.

References:

1. Chung RT, Andersen J, Volberding P, et al. Peginterferon Alfa-2a plus ribavirin versus interferon alfa-2a plus ribavirin for chronic hepatitis C in HIV-coinfected persons. N Engl J Med 2004; 351: 451-9. http://amedeo.com/lit.php?id=15282352
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Interleukin-2

Interleukin-2 is not licensed for HIV; justified as a therapy attempt in individual cases (contact health insurance) with failed immune reconstitution (< 100 CD4 cells despite several months of viral suppression). Otherwise only in studies.

Trade name: Proleukin™ (Aldesleukin). Bottles for injection with 18×10^6 I.E.

Drug class: cytokine

Manufacturer: Chiron

Dose: 4.5-9 Mill I.E. sc bid for 5 days, every 6-8 weeks.

Side effects: almost obligatory fever, chills. Fatigue, malaise, nausea/vomiting, myalgia. Rarely hypotension (caution with antihypertensives).

Comments/warnings: counseling! The clinician must be experienced! Generous administration of paracetamol. Side effects usually subside 1-2 days after the last dose. Contraindicated in individuals with severe coronary disease, infections or pO2 < 60 mm; it is also contraindicated in pregnancy.

Internet sources:

USA: http://hiv.net/link.php?id=112

References:

1. Levy Y, Gahery-Segard H, Durier C, et al. Immunological and virological efficacy of a therapeutic immunization combined with interleukin-2 in chronically HIV-1 infected patients. AIDS 2005; 19: 279-86. Abstract: http://amedeo.com/lit.php?id=15718838
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Intron A™ see Interferon

Invirase™ see Saquinavir

Isoniazid (INH)

Drug class: tuberculostatic

Manufacturer: isoniazid is offered by different manufacturers

Indications: combination therapy of tuberculosis.

Prophylactic treatment after tuberculin conversion.

Dose: 200 to 300 mg qd (4 to 5 mg/kg, maximum 300 mg) po, iv only in severe cases during the first two weeks of therapy. For prophylaxis of neuropathy, INH should always be combined with 100 mg pyridoxine po qd.

Pediatric dose: 6 (to 10) mg/kg qd, maximum 300 mg.

Side effects: toxic hepatitis, more frequent in older patients, with liver disease and alcohol abuse.

Peripheral neuropathy! Discontinue INH in severe cases and treat for several weeks with pyridoxine and vitamin B12. Psychosis, CNS symptoms. Fever, rash, nausea, vomiting, anemia, leukopenia, thrombocytopenia.

Comments/Warnings: contraindications are acute hepatitis and history of INH-associated hepatopathy or severe febrile reactions, peripheral neuropathy, macrohematuria.

Patients on treatment with carbamazepine or an hydantoin derivative might require dose adjustment of these drugs.

Interactions with barbiturates, cycloserine, theophylline, phenytoin and rifampin; doses of these drugs should be reduced due to CNS disorders.

Reduced absorption if taken concurrently with aluminum-based antacids.

Do not combine with d4T, ddI (PNP risk), and caution with alcohol.

Initially, biweekly monitoring of blood count, transaminases, bilirubin, and renal function. Discontinue INH with elevated transaminases to more than 3-fold initial levels and symptoms; or with a 5-fold elevation even in the absence of symptoms.

References:

1. Benator D, Bhattacharya M, Bozeman L, et al. Rifapentine and isoniazid once a week versus rifampicin and isoniazid twice a week for treatment of drug-susceptible pulmonary tuberculosis in HIV-

negative patients: a randomised clinical trial. Lancet 2002, 360: 528. http://amedeo.com/lit.php?id=12241657

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4. Scholten JN, Driver CR, Munsiff SS, Kaye K, Rubino MA, Gourevitch MN et al. Effectiveness of isoniazid treatment for latent tuberculosis infection among human immunodeficiency virus (HIV)-infected and HIV-uninfected injection drug users in methadone programs. Clin Infect Dis 2003; 37: 1686-92. Epub 2003 Nov 17. http://amedeo.com/lit.php?id=14689352

Itraconazole

Trade name: Sempera™

100 mg capsules

Oral solution (Sempera Liquid™) with 10 mg/ml (150 ml)

Drug class: antimycotic

Manufacturer: Janssen-Cilag / GlaxoSmithKline

Indications: histoplasmosis, aspergillosis, treatment-resistant Candida infections (second choice).

Dose: histoplasmosis, aspergillosis 200 mg bid.

Fluconazole-resistant Candida infections: 100 mg qd to 100 mg bid (up to 200 mg bid), ideally as itraconazole oral solution.

Side effects: nausea, vomiting, rash, dizziness. Toxic hepatitis.

Comments/Warnings: due to numerous interactions and unreliable plasma levels, oral dosing of itraconazole is problematic. However, in contrast to fluconazole, it is effective for many non-albicans strains, aspergillosis, and histoplasmosis.

No concurrent administration of itraconazole capsules with ddI, H2 blockers, omeprazole, antacids. No concurrent administration (of capsules or oral solution) with rifampin, rifabutin, carbamazepine, phenytoin, phenobarbital, simvastatin, lovastatin and isoniazid (these lower the bioavailability of itraconazole).

Itraconazole increases serum levels of cyclosporine, calcium antagonists, digoxin, lovastatin, simvastatin and indinavir. Dose adjustment of indinavir: 600 mg tid.

Itraconazole has a negative inotropic effect and should not be given to patients with heart failure.

To achieve maximum absorption:

- the capsules should be taken immediately after a full meal. Acidic drinks such as coke and orange juice may increase absorption;
- the oral solution should be taken between meals, and not together with grapefruit juice.

Internet sources:

USA: http://hiv.net/link.php?id=114

References:

1. Caillot D, Bassaris H, McGeer A, et al. Intravenous itraconazole followed by oral itraconazole in the treatment of invasive pulmonary aspergillosis in patients with hematologic malignancies, chronic granulomatous disease, or AIDS. Clin Infect Dis 2001, 33: e83-90. http://amedeo.com/lit.php?id=11550120
2. Chariyalertsak S, Supparatpinyo K, Sirisanthana T, Nelson KE. A controlled trial of itraconazole as primary prophylaxis for systemic fungal infections in patients with advanced HIV infection in thailand. Clin Infect Dis 2002, 34: 277-284. http://amedeo.com/lit.php?id=11740718
3. Crommentuyn KM, Mulder JW, Sparidans RW, Huitema AD, Schellens JH, Beijnen JH. Drug-drug interaction between itraconazole and the antiretroviral drug lopinavir/ritonavir in an HIV-1-infected patient with disseminated histoplasmosis. Clin Infect Dis 2004; 38: e73-5. http://amedeo.com/lit.php?id=15095234
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Kaletra™ see Lopinavir

Kivexa™ (USA: Epzicom™)

Tablets: with 3TC (300 mg) and abacavir (600 mg).

As with Ziagen™, watch for hypersensitivity syndrome.

Drug class: nucleoside reverse transcriptase inhibitors (NRTI)

Manufacturer: GlaxoSmithKline

Indications: HIV infection

Dose: 1 tablet daily. Replace Kivexa™ with the individual drugs if kidney function is impaired (creatinine clearance below 50 ml/min), in order to adjust the 3TC dose.

Side effects: hypersensitivity syndrome with abacavir (see abacavir section!).

Comments/Warnings: abacavir hypersensitivity syndrome (2-6 %) can be life-threatening. For further information, see 3TC and abacavir.

Internet sources:

http://hiv.net/link.php?id=240

Reference:

1. DeJesus E, Herrera G, Teofilo E, et al. Abacavir versus zidovudine combined with lamivudine and efavirenz, for the treatment of antiretroviral-naive HIV-infected adults. Clin Infect Dis 2004; 39 :1038-46. http://amedeo.com/lit.php?id=15472858

Klacid™ see Clarithromycin

Lamivudine see 3TC (at the beginning of this chapter)

Lexiva™ see Fosamprenavir

Lopinavir

Effective PI in treatment-naïve as well as treatment-experienced patients. Disadvantages include gastrointestinal side effects (diarrhea) and the often significant dyslipidemia, which is more extreme than with some other PIs. As with all PIs, lipodystrophy and various drug interactions should be considered.

Trade name: Kaletra™

Tablets with 200 mg lopinavir + 50 mg ritonavir.

Solution with 80 mg lopinavir + 20 mg ritonavir per ml; bottles of 160 ml.

Keep the solution refrigerated, maximum of 4-6 weeks at up to 25°C.

Drug class: protease inhibitor (PI)

Manufacturer: Abbott

Indications: HIV infection

Oral dose: 2 tablets bid or 5 ml solution bid with meals. In the USA: 4 tablets qd.

In combination with efavirenz or nevirapine, the lopinavir dose should probably be increased to 3 tablets bid or 6.5 ml solution bid. Measure plasma levels!

Side effects: mainly diarrhea, nausea, dyslipidemia, and lipodystrophy. Also: headaches, and elevated transaminases.

Comments/Warnings: drug interactions are numerous. All drugs metabolized by the CYP3A or CYP2D6 enzyme systems are contraindicated: flecainide, propafenone, astemizole, terfenadine, ergotamines, cisapride, pimozide, midazolam, triazolam. Rifampin and St. John's wort reduce the efficacy of lopinavir.

Caution with: lovastatin, simvastatin (myopathy, rhabdomyolysis), carbamazepine, phenobarbital, phenytoin or sildenafil (hypotension), amiodarone, warfarin, lidocaine, tricyclic antidepressants, quinidine, cyclosporine, tacrolimus. Measure plasma levels in patients with reduced liver function tests.

If lopinavir is combined with ddI, ddI must be taken one hour before or two hours after lopinavir. Lopinavir solution contains alcohol, therefore no comedication with disulfiram or metronidazole. Caution with the pill (contraception not safe).

When used with rifabutin, the rifabutin dose should be reduced by 75 %, i.e. to 150 mg qd every two days. Increasing the methadone dose may be necessary.

Capsules (not tablets) should be kept refrigerated for a maximum of 4-6 weeks at a maximum temperature of 25°C.

Internet sources:

USA: http://hiv.net/link.php?id=116

References:

1. Eron JJ, Feinberg J, Kessler HA, et al. Once-daily versus twice-daily lopinavir/ritonavir in antiretroviral-naive HIV-positive patients: a 48-week randomized clinical trial. J Infect Dis 2004; 189: 265-72. http://amedeo.com/lit.php?id=14722892
2. Eyer-Silva WA, Neves-Motta R, Pinto JF, Morais-De-Sa CA. Inflammatory oedema associated with lopinavir-including HAART regimens in advanced HIV-1 infection: report of 3 cases. AIDS 2002, 16: 673-4.
3. Hicks C, King MS, Gulick RM, et al. Long-term safety and durable antiretroviral activity of lopinavir/ritonavir in treatment-naive patients: 4 year follow-up study. AIDS 2004; 18: 775-9. http://amedeo.com/lit.php?id=15075512

4. Kempf DJ, King MS, Bernstein B, et al. Incidence of resistance in a double-blind study comparing lopinavir/ritonavir plus stavudine and lamivudine to nelfinavir plus stavudine and lamivudine. J Infect Dis 2004; 189: 51-60. http://amedeo.com/lit.php?id=14702153

5. Martinez E, Domingo P, Galindo MJ, et al. Risk of metabolic abnormalities in patients infected with HIV receiving antiretroviral therapy that contains lopinavir-ritonavir. Clin Infect Dis 2004; 38: 1017-23. http://amedeo.com/lit.php?id=15034836

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7. Johnson MA, Gathe JC Jr, Podzamczer D, et al. A once-daily lopinavir/ritonavir-based regimen provides noninferior antiviral activity compared with a twice-daily regimen. J Acquir Immune Defic Syndr 2006; 43: 153-60. Abstract: http://amedeo.com/lit.php?id=16951643

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9. van der Lee M, Verweel G, de Groot R, Burger D. Pharmacokinetics of a once-daily regimen of lopinavir/ritonavir in HIV-1-infected children. Antivir Ther 2006; 11: 439-45. Abstract: http://amedeo.com/lit.php?id=16856617

10. Oldfield V, Plosker GL. Lopinavir/ritonavir: a review of its use in the management of HIV infection. Drugs 2006; 66: 1275-99. Abstract: http://amedeo.com/lit.php?id=16827606

11. Johnson M, Grinsztejn B, Rodriguez C, et al. 96-week comparison of once-daily atazanavir/ritonavir and twice-daily lopinavir/ritonavir in patients with multiple virologic failures. AIDS 2006; 20: 711-8. Abstract: http://amedeo.com/lit.php?id=16514301

Maraviroc

Maraviroc (abbr.: MVC; earlier UK-427,857) is the first and currently the most promising CCR5-antagonist.

Because maraviroc only inhibits R5-trope viruses, the recpeptor tropism has to be determined before treatment with maraviroc is started.

The studies conducted so far have shown excellent tolerability. Since April 2007, maraviroc has been available in several countries through an expanded access program for treatment-experienced patients with R5-trope viruses and limited therapy options.

Trade name: Celsentri®, Selzentry®.

Tablets with 150 mg and 300 mg.

Drug class: CCR5 inhibitor.

Manufacturer: Pfizer.

Indication: treatment-experienced adult patients with CCR5-trope HIV strains.

Dose: 300 mg bid, before or after a meal.

Dose adjustment with concurrent administration of the following drugs:

Drug	Maraviroc Dose (recommended)
Protease inhibitor (exception: Tipranavir)	2 x 150 mg
Itraconazole, Ketoconazole	2 x 150 mg
Clarithromycin, Telithromycin	2 x 150 mg
Efavirenz	2 x 600 mg
Rifampin, Rifabutin	2 x 600 mg

Interactions: In combination with some PIs such as lopinavir, saquinavir or atazanavir, the maraviroc dose probably has to be halved; possibly raised in combination with efavirenz (Abel 2005). Interactions with tipranavir seem to be irrelevant (Abel 2006).

Halve the dose in combination mit PIs (except tipranavir), ketoconazole, itraconazole.

Double the dose in combination mit efavirenz, rifampin, carbamazepine, phenobarbital und phenytoin.

Simultaneous administration of INH is contraindicated (hepatotoxicity).

Side effects: well-tolerated so far; rarely headache, dizziness, fatigue, loss of appetite, nausea, muscle pain. Data on long-term effects are not available.

Literatur:

1. Abel S, Russell D, Ridgway C, Muirhead G. Overview of the drug-drug interaction data for maraviroc. Abstract 76, 7th IWCPHT 2005, Quebec.
2. Abel S, Taylor-Worth R, Ridgway C, Weissgerber G, Kraft M. Effect of boosted tipranavir on the pharmacokinetics of maraviroc (UK427,857) in healthy volunteers. Abstract 77, 7th IWCPHT 2006, Lissabon, Portugal.
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4. Coakley E, Petropoulos CJ, Whitcomb JM. Assessing chemokine co-receptor usage in HIV. Curr Opin Infect Dis 2005; 18: 9-15. Abstract: http://amedeo.com/lit.php?id=15647694
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Mavid™ see Clarithromycin

Mycobutin™ see Rifabutin

Nelfinavir

Nelfinavir is a well-tolerated PI, but is slightly less potent than boosted PIs or NNRTIs. The main problems include frequent diarrhea and the high pill burden. Administration was simplified with the introduction of the 625 mg capsule (dose: 2 capsules bid).

Trade name: Viracept™, abbr. NFV

250 mg film-coated tablets (N2: 270); 50 mg/g oral powder (N1: 144 g). Film-coated tablets with 625 mg, in Europe not available.

Drug class: protease inhibitor

Manufacturer: Hoffmann-La Roche, Pfizer

Indications: HIV infection

Oral dose: 1,250 mg bid or 750 mg tid with meals. Boosting with ritonavir is not useful.

Side effects: diarrhea! Meteorism, and nausea also occur. Lipodystrophy, dyslipidemia, reduced glucose tolerance.

Comments/Warnings: contraindicated for comedication with rifampin, the "pill", astemizole, terfenadine, cisapride, triazolam, ergotamines, simvastatin, lovastatin, and St. John's wort.

In combination with rifabutin: 150 mg rifabutin qd and increase nelfinavir dose to 1,250 mg bid or 1,000 mg tid.

Methadone: possibly increase dose.

Sildenafil: maximum 25 mg/48 h.

Diarrhea can often be controlled with loperamide (maximum 16 mg/day).

Internet sources:

USA: http://hiv.net/link.php?id=118

References:

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Neupogen™ see G-CSF

Nevirapine

Nevirapine is a frequently prescribed NNRTI, which is also used successfully for the prevention of mother-to-child transmission. As with all NNRTIs, a single point mutation is sufficient to develop high-level resistance. With very good long-term tolerability (favorable lipid profile!), hepatotoxicity within the first months of treatment (see below) is a problem. Dose should always be increased gradually.

Trade name: Viramune™, abbr. NVP

Tablets: 200 mg.

Suspension: 10 mg/ml

Drug class: NNRTI

Manufacturer: Boehringer Ingelheim

Indications: HIV infection. According to the FDA, patients with a good immune status (women > 250, men > 400 CD cells/µl) should not receive nevirapine as a component of primary therapy due to the increased risk of hepatotoxicity.

Oral dose: 1 tablet bid with or without meals. Always start with lead-in dosing! The initial lead-in dose (1 tablet/day over two weeks) reduces the frequency of rash. For resumption of treatment after treatment interruption, lead-in dosing is generally not necessary if the drug was well tolerated.

Side effects: hepatotoxicity, rash. Less frequently: fever, nausea, drowsiness, headache, myalgia. These side effects may occur with or without hepatotoxicity and/or rash. γGT elevation on nevirapine is almost the rule.

To detect **hepatotoxicity** (up to 15 %; defined as an increase in transaminases to at least three times the upper limit of normal), liver function tests should be monitored biweekly for the first two months. Thereafter, monthly tests are necessary, as more than half of the hepatotoxic episodes occur after the first quarter of treatment. In such cases, treatment must be interrupted until liver function tests have returned to initial levels. Treatment is restarted with 200 mg qd. The dose may be increased to 200 mg bid only after a prolonged period of observation. If liver enzymes increase again, nevirapine should be permanently discontinued. The website of the EMEA provides detailed guidelines: **Fehler! Hyperlink-Referenz ungültig.**. The risk is greater with a good immune status (women > 250 CD4 cells/µl: 12-fold ; men > 400 CD4 cells/µl: 5-fold).

A **rash**, often pruritic and usually occurring within the first six weeks, can generally be treated with antihistamines if mucous membranes are not involved and transaminases are normal. Topical formulations are effective against pruritus. Nevirapine must be discontinued if a severe rash occurs; in these cases, steroids may be used (e.g. prednisolone 1 mg/kg for 3-5 days). Nevirapine should also be discontinued if other symptoms occur (such as fever, conjunctivitis, myalgia, arthralgia, malaise). If the rash occurs during the first two weeks, the dose should not be increased until the rash has resolved completely. Prophylactic treatment with steroids or antihistamines is not advised.

Comments/Warnings: cautious use in hepatic dysfunction (TDM).

Contraindicated for comedication with rifampin, ketoconazole, St. John's wort and the "pill".

Azole derivatives: fluconazole should be used for antimycotic treatment.

Dose adjustment in combination with

- Lopinavir: possibly increase Kaletra™ (measure plasma levels!)
- Indinavir: increase indinavir dose to 1,000 mg tid.
- Methadone: if withdrawal symptoms occur, dose may need to be increased.

Nevirapine has a favorable long-term profile. In particular, lipid levels are usually positively influenced. γGT is almost always increased during long-term treatment. Values of up to 150 U/l can be tolerated. Nevirapine should not be given for post-exposure prophylaxis.

Internet sources:

USA: http://hiv.net/link.php?id=121

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Norvir™ see Ritonavir

Pegasys™ see Interferon

PegIntron™ see Interferon

Pentacarinat™ see Pentamidine

Pentamidine

Trade name: Pentacarinat™

Vials: 300 mg

Drug class: antibiotic

Manufacturer: Aventis, GlaxoSmithKline

Indications: treatment and secondary prophylaxis of Pneumocystis pneumonia if co-trimoxazole is contraindicated (hypersensitivity, resistance to treatment).

Dose: treatment: 200-300 mg Pentacarinat™ iv for five days (4 mg/kg), then halve the dose. In very mild cases, daily inhalations with 300 mg.

In renal failure and creatinine clearance of 50-10 ml/min: 4 mg/kg q 24-36 h; < 10 ml/min: 4 mg/kg q 48 h.

Prophylaxis: inhalation of 300 mg 1-2 x/month.

Side effects: frequent with intravenous dosing! Nausea, vomiting, metallic taste; nephrotoxicity (increased creatinine in the second week of treatment) up to renal failure. Hypo- or hyperglycemia (possible even months after end of treatment), hypotension, arrhythmia, pancreatitis.

Leukopenia and thrombocytopenia. Inhalation may induce cough, rarely asthma attacks.

Comments/Warnings:

Inhalation: pentamidine as an aerosol is contraindicated in asthma and treatment with beta-blockers. Inhalation may be ineffective with pulmonary disease. Prior inhalation of a ß-mimetic may be desirable.

Infusions: caution in liver or renal failure, hyper- or hypotension, hyperglycemia, cytopenia. Always ensure sufficient intake of electrolytes and fluids. No concurrent administration of other nephrotoxic drugs (e.g. aminoglycosides, amphotericin B, foscarnet). Patient should remain in supine position before, during and after infusions of pentamidine (caution: hypotension!). Pentamidine should be infused slowly over at least 2 hours! Daily monitoring of BUN, serum creatinine, blood count, fasting blood glucose, urinalysis and serum electrolytes, weekly monitoring of bilirubin, alkaline phosphatase, transaminases.

References:

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Prezista™ see Darunavir

Proleukin™ see Interleukin-2

Pyrimethamine

Trade name: Daraprim™

Tablets: 25 mg

Manufacturer: GlaxoSmithKline

Indications: prophylaxis and treatment of cerebral toxoplasmosis. Prophylaxis of pneumocystis pneumonia.

Dose: treatment of toxoplasmosis: Daraprim™ 2 tbl. à 25 mg bid (for 3 days, then halve the dose) **plus** Leucovorin™ 1 tbl. à 15 mg every other day **plus either** sulfadiazine or clindamycin.

PCP prophylaxis in combination with dapsone: Daraprim™ 2 tbl. à 25 mg per week **plus** Dapsone™ 1 tbl. à 50 mg qd **plus** Leucovorin™ 2 tbl. à 15 mg per week.

Side effects: Myelosuppressive! Most important side effect is anemia. Thrombocytopenia and leukopenia. Nausea, colics, vomiting, diarrhea. Rarely seizures, tremor or ataxia.

Comments/Warnings: pyrimethamine is contraindicated in megaloblastic anemia resulting from folic acid deficiency. Caution in patients with seizures, renal failure, asthma or G6PD deficiency. All patients on pyrimethamine should receive folinic acid to decrease myelosuppression. Initial weekly monitoring of blood counts.

Product information UK: http://hiv.net/link.php?id=124

References:

1. Chene G, Morlat P, Leport C, et al. Intention-to-treat vs. on-treatment analyses of clinical trial data: experience from a study of pyrimethamine in the primary prophylaxis of toxoplasmosis in HIV-infected patients. Control Clin Trials 1998, 19: 233-48. http://amedeo.com/lit.php?id=9620807
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Raltegravir (MK-0518)

Raltegravir is an integrase inhibitor, which should be available in 2007 through an expanded-access program for patients with viruses that are resistant to at least one of the drug classes: NRTIs, NNRTIs and PIs. So far a well-tolerated, promising drug in therapy-naïve as well as treatment-experienced patients. No long-term experience.

Trade name: Isentress®; Abk.: RGV

Drug class: Integrase inhibitor

Manufacturer: Merck

Dose: the current Phase-III studies are investigating MK-0518 in a twice daily dose of 400 mg. Boosting with ritonavir is not useful.

Side effects: so far well tolerated, rarely nausea, dizziness, headaches. No long-term data.

Interactions: Not yet known. The simultaneous intake of food has no influence on the bioavailability of MK-0518.

References:

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Rebetol™ see Ribavirin

Ribavirin

Trade names: Copegus™, 200 mg film-coated tablets. Rebetol™, 200 mg hard capsules or solution (40 mg/ml)

Drug class: virostatic

Manufacturer: Roche (Copegus™), Schering Plough (Rebetol™)

Indication: chronic Hepatitis C, only in combination with interferon

Dose: daily dose 800 mg for body weight < 65 kg, 1,000 mg for 65-85 kg, 1,200 mg for > 85 kg. Daily dose should be divided into two daily applications. Ribavirin should be taken with meals. Treatment duration depends on genotype and other factors. Lower doses yield a lower treatment response (see below)!

Side effects: the most important side effect is reversible hemolytic anemia; gastrointestinal complaints, headache and fatigue may also occur. Rarely lactic acidosis, pancreatitis in combination with NRTIs.

Comments/Warnings: ribavirin is contraindicated in severe coronary disease, renal failure, decompensated liver cirrhosis, and hemoglobinopathy. It is also contraindicated in pregnancy and reliable contraception is required due to ribavirin's potential teratogenicity.

Dose reduction (600-800 mg/day) may be necessary in cases of severe anemia (hemoglobin < 10 g/dl). However, always consider erythropoietin before dose reduction as there is a linear correlation between mg/kg ribavirin dose and treatment success. Discontinuation of ribavirin may be necessary at hemoglobin values < 8.5 g/dl.

Avoid concurrent administration of other myelosuppressive medications (AZT!).

Ribavirin can lead to lactic acidosis in combination with other NRTIs. Most importantly, ddI should be avoided but care should be taken with d4T and other NRTIs!

Efavirenz-induced depression may worsen on ribavirin.

Monitoring of blood count, AST, ALT, lipase initially at weekly intervals, later monthly. Lactate measurement if unspecific symptoms occur!

Internet sources:

USA: Copegus™: http://hiv.net/link.php?id=197, Rebetol™: http://hiv.net/link.php?id=126

References:

1. Bani-Sadr F, Carrat F, Pol S, et al. Risk factors for symptomatic mitochondrial toxicity in HIV/hepatitis C virus-coinfected patients during interferon plus ribavirin-based therapy. J Acquir Immune Defic Syndr 2005; 40: 47-52. Abstract: http://amedeo.com/lit.php?id=16123681
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Rescriptor™ see Delavirdine

Retrovir™ see AZT

Reyataz™ see Atazanavir

Rifabutin

Trade name: Mycobutin™, Alfacid™

150 mg capsules

Drug class: antibiotic, tuberculostatic

Manufacturer: Pharmacia and other companies

Indications: infections with Mycobacterium avium complex (MAC), always in combination with other drugs (usually ethambutol and azithromycin). Also for treatment of tuberculosis, when rifampicin is not possible.

Dose: 300 mg rifabutin daily (+ azithromycin + ethambutol).

Renal failure: dose reduction by 50 % for creatinine clearance < 30 ml/min.

Dose adjustments for concurrent dosing with antiretroviral drugs:

Drug	Recommendation
Atazanavir/r*, Darunavir/r*, Fosamprenavir/r*, Indinavir/r*, Lopinavir/r*, Saquinavir/r*, Tiprana-vir/r*	Rifabutin: 150 mg every other day or three times per week (see product information)
Nelfinavir	Nelfinavir 1,250 mg bid + rifabutin 150 mg/day
Delavirdine	Rifabutin is contraindicated
Efavirenz	Rifabutin 450 mg/day or 600 mg three times weekly
Nevirapine	Standard dose

* /r = boosted with ritonavir

Side effects: Nausea, vomiting, elevation of liver enzymes, jaundice. Uveitis usually only with daily doses > 300 mg and concurrent treatment with clarithromycin or fluconazole. Red discoloration of urine, skin and body secretions (patients should be informed about this!).

Comments/Warnings: contraindicated in cases of known hypersensitivity to rifabutin and rifampin; also in thrombocytopenia and severe hepatic dysfunction. Monitor blood count and liver enzymes twice monthly initially, later monthly.

Numerous interactions: rifabutin can decrease the efficacy of the following drugs:

analgesics, anticoagulants, corticosteroids, cyclosporine, digitalis (except digoxin), dapsone, oral antidiabetics, oral contraceptives, narcotic analgesics, phenytoin and quinidine.

Erythromycin, ketoconazole, itraconazole, fluconazole and clarithromycin can increase plasma levels of rifabutin.

Take antacids at least three hours after rifabutin.

Internet sources:

USA: http://hiv.net/link.php?id=129

References:

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Rifampin (or rifampicin)

Trade names: various generics.

Tablets with 150 mg and 300 mg, 450 mg and 600 mg

Solution: 100 mg/ml

Vials: 300 mg and 600 mg

Drug class: tuberculostatic

Indications: tuberculosis. Only in combination therapies!

Dose: 600 mg daily (body weight > 50 kg) or 450 mg (body weight < 50 kg). Ideally taken in the morning on an empty stomach!

Side effects: toxic hepatitis (up to 20 %), cholestatic changes. Red discoloration of urine and other body fluids (inform patients!). Soft contact lenses may permanently stain red. Allergies are frequent. Gastrointestinal complaints such as nausea, vomiting, diarrhea.

Comments/Warnings: caution in liver disease. Discontinue rifampin if ALT > 100 U/l or with elevated bilirubin (careful re-exposure with gradually increasing doses is possible after normalization of values), and in patients with severe and persistent diarrhea (pseudomembranous colitis!).

If possible, rifampin should not be combined with NNRTIs or PIs.

Rifampin increases metabolism of numerous drugs, reducing their efficacy if administered concurrently. These drugs include atovaquone, warfarin, barbiturates, benzodiazepines, beta-blockers, clarithromycin, contraceptives, steroids, oral antidiabetics, cyclosporine, dapsone, digitalis, doxycycline, erythromycin, haloperidol, ketoconazole, methadone, phenytoin, theophylline, trimethoprim, verapamil. Combination with ketoconazole or voriconazole is contraindicated.

Antacids, opiates and anticholinergics reduce the bioavailability of orally administered rifampin if given simultaneously. To avoid this interaction, rifampin should be given several hours before these drugs.

Not for use in pregnancy.

Blood count and liver values should be monitored fortnightly.

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Ritonavir

Due to its gastrointestinal side effects, the therapeutic dose of ritonavir is rarely prescribed. However, at lower doses it is frequently used for boosting and is better tolerated. Numerous interactions.

Trade name: Norvir™, but also included in Kaletra™

100 mg soft capsules

80 mg/ml oral solution

Drug class: protease inhibitor

Manufacturer: Abbott

Indications: HIV infection

Oral dose: used as a single PI in very rare cases: 600 mg bid (increase as: 300 mg bid on day 1-2, 400 mg bid on day 3-5, 500 mg bid on day 6-13).

Better: for boosting of other PIs! Daily doses:

- Atazanavir (300 mg Reyataz™ qd): 100 mg ritonavir qd.
- Darunavir (600 mg Prezista™ bid): 100 mg ritonavir bid.
- Fosamprenavir (700 mg Telzir™ bid): 100 mg ritonavir bid, or possibly 200 mg qd + 1,400 mg fosamprenavir qd (only in treatment-naïve patients, and only in the USA).
- Indinavir (800 mg Crixivan™ bid): 100 mg ritonavir bid, or possibly 400 mg ritonavir bid + 400 mg indinavir bid.
- Lopinavir (Kaletra™): Fixed combination, see lopinavir.
- Saquinavir (1,000 mg Invirase™ bid): 100 mg ritonavir bid.
- Tipranavir (Aptivus™) + 200 mg ritonavir bid.

Side effects: dose dependent; frequently, nausea, vomiting, diarrhea, perioral paresthesias (tingling), electric sensations on arms/legs. Elevated transaminases and γGT, dyslipidemia, lipodystrophy, rarely, diabetes mellitus.

Comments/Warnings: even the low boosting doses used in combination with other PIs have multiple drug interactions! The following are contraindicated: rifampin, amiodarone, astemizole, bepridil, terfenadine, encainide, flecainide, cisapride, triazolam, ergotamine, simvastatin, lovastatin, quinidine, and St. John's wort. Sildenafil should be avoided.

Caution should be taken and plasma levels measured if possible with: methadone, immunosuppressants (cyclosporine, tacrolimus), macrolides (erythromycin, clarithromycin), steroids, calcium antagonists, tricyclics and other antidepressants, neuroleptics (haloperidol, risperidone, thioridazine), antimycotic drugs (ketoconazole, itraconazole), carbamazepine, tolbutamide, rifabutin, theophylline, and warfarin.

Internet sources:

USA: http://hiv.net/link.php?id=31

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Roferon see Interferon

Saquinavir

Saquinavir was the first PI to be licensed for HIV therapy in 1995. Apart from gastrointestinal problems, saquinavir is well tolerated. Today, it is only used boosted with ritonavir. Since the introduction of the 500 mg capsule, the number of tablets taken has been significantly reduced.

Trade name: Invirase 500™, abbr. SQV.

Film-coated tablets. The earlier soft gel capsules (200 mg Fortovase™) and hard gel capsules (200 mg Invirase™) have been taken off the market.

Drug class: protease inhibitor

Manufacturer: Hoffmann-La Roche

Indications: HIV infection

Oral dose: Combination with ritonavir is standard: 1,000 mg saquinavir bid + 100 mg ritonavir bid.

Side effects: Usually well tolerated. Side effects mainly gastrointestinal with diarrhea, nausea, abdominal discomfort, meteorism. Rarely elevation of transaminases or γGT, headache. As with other PIs, lipodystrophy, dyslipidemia and reduced glucose tolerance may occur with long-term treatment.

Comments/Warnings: contraindicated for comedication with rifampin, astemizole, terfenadine, cisapride, triazolam, ergotamine, simvastatin, lovastatin, and St. John's wort.

If saquinavir is not combined with other PIs it must be taken with meals.

Internet sources:

USA: http://hiv.net/link.php?id=132

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Sempera™ see Itraconazole

Sobelin™ see Clindamycin

Stavudine see d4T

Sulfadiazine

Drug class: sulfonamide antibiotic

Indications: treatment and prophylaxis of cerebral toxoplasmosis, only in combination with pyrimethamine.

Dose: For treatment 2-3 500 mg tablets qid (daily dose 4-6 g). For prophylaxis halve the dose (500 mg qid)!

Renal insufficiency: creatinine clearance 50-10 ml/min: halve dose. At values below 10 ml/min: administer one third of the dose.

Side effects: very frequently, allergies with pruritus, fever and urticaria, often treatment-limiting. Rare: Stevens-Johnson syndrome. Gastrointestinal complaints such as nausea, vomiting, diarrhea. Renal problems with renal failure, crystalluria, nephrolithiasis in up to 7 %. Anemia, leukopenia, thrombocytopenia. Elevated liver enzymes.

Comments/Warnings: sulfadiazine is contraindicated in sulfonamide hypersensitivity and allergies to sulfonylurea antidiabetics, acetazolamide or thiazide diuretics; also in G6PD deficiency, renal failure and severe hepatic disease or dysfunction (e.g. acute hepatitis); and during pregnancy and breastfeeding.

Sulfadiazine can increase levels of sulfonyl urea (oral antidiabetics), anticoagulants, diphenylhydantoin.

Concurrent dosing with antacids reduces absorption of sulfadiazine (separate administration 1-2 hours apart). Ensure sufficient intake of fluids (at least 2 l daily).

Monitor blood count, ALT, creatinine, and BUN at least weekly initially.

Monitor urine! In case of crystalluria: alkalize urine.

References:

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Stocrin™ see Efavirenz

Sustiva™ see Efavirenz

T-20 (Enfuvirtide)

T-20 is an entry inhibitor, which is used for salvage in treatment-experienced patients. T-20 has to be injected subcutaneously twice daily, but apart from local skin reactions it is otherwise well tolerated.

Trade name: Fuzeon™

90 mg/ml powder and solvent. Each bottle contains 108 mg T-20.

1 ml of the reconstituted solution contains 90 mg T-20.

Drug class: fusion inhibitor (or entry inhibitor)

Manufacturer: Hoffmann-La Roche

Indications: treatment of HIV-1 infection in patients with evidence of HIV-1 replication despite ongoing HAART.

Dose: 90 mg subcutaneously bid.

Side effects: generally well tolerated. However, almost all patients have local injection site reactions: erythema, inflammation, induration, rash. In the licensing studies, approximately 10 % of patients required intermittent use of analgesics or were temporarily affected in their daily activities.

Patients on T-20 possibly have an increased risk of contracting bacterial pneumonia. Therefore, it is important to be particularly vigilant in patients with risk factors for pneumonia (low baseline CD4 cell count, high viral load, iv drug users, smokers, history of pulmonary disease).

Hypersensitivity reactions with rash, fever, nausea, chills, hypotension or elevated transaminases are rare (< 1 %).

Comments/warnings: interactions not known.

Injection sites: upper arm, ventral hip, and abdomen. Change injection sites! Possibly less irritation on the back. Do not inject at sites with inflammatory signs from previous injections, sites with naevi, scars or disrupted skin integrity.

Internet sources:

USA: http://hiv.net/link.php?id=225

References:

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Tenofovir

Tenofovir DF is the prodrug of the acyclic **nucleotide** analog tenofovir, and has good oral bioavailability. Well tolerated, low mitochondrial toxicity. However, potential nephrotoxicity and a few interactions must be considered (ddI, atazanavir). Good efficacy against hepatitis B virus.

Trade name: Viread™. Abbr.: TDF

Film-coated tablets 300 mg tenofovir disoproxilfumarate or 245 mg tenofovir disoproxil.

Also in Truvada™ in combination with emtricitabin (see Emtricitabin), and in Atripla™ in combination with emtricitabin and efavirenz (see Efavirenz).

Drug class: nucleo**t**ide reverse transcriptase inhibitor

Manufacturer: Gilead

Indications: HIV infection

Oral dose: 300 mg qd, with a meal. Dose adjustments:

Viread™, adjust dose in renal insufficiency

	Creatinine clearance (ml/min)		Hemodialysis patients
	30 - 49	10 - 29	
Recommended dose interval	Every 48 hours	Every 72 to 96 hours	Every 7 days following the completion of a hemodialysis*

*See leaflet in packet for more information

Side effects: usually well tolerated. There is a potential risk of nephrotoxicity, although in most cases, disturbance of renal function is mild. Severe renal side effects are rare (renal failure, Fanconi's syndrome, nephrogenic diabetes insipidus). Patients with renal disease should either not receive tenofovir or reduce the dose (see above). Control creatinine clearance and serum phosphate before starting tenofovir, then every four weeks during the first year, and every three months thereafter. More frequent controls are useful if there is disturbance of renal function (actual or in the medical history) or renal insufficiency.

It is not currently known whether long-term treatment can lead to bone density changes (seen in animal studies).

Comments/Warnings: when serum phosphate is < 1.5 mg/dl (0.48 mmol/l) or creatinine clearance < 50 ml/min: check renal function within one week. Simultaneous determination of glucose and potassium in blood, as well as glucose in the urine. Interruption of therapy may be necessary if creatinine clearance is < 50 ml/min or serum phosphate is < 1.0 mg/dl (0.32 mmol/l).

Creatinine clearance in ml/min is calculated as follows:

Women: (1.04 x (140 – age) x kg) / creatinine (µmol/l)

Men: (1.23 x (140 – age) x kg) / creatinine (µmol/l)

Concurrent administration of drugs that are also eliminated via active tubular secretion can lead to increased serum concentrations of both drugs: cidofovir, acyclovir, valacyclovir, ganciclovir, valganciclovir.

Use with caution in combination with ddI: co-medication with tenofovir increases the Cmax and AUC of ddI by 28 % and 44 %, respectively. The combination should be avoided (if necessary, reduce the dose of ddI to 250 mg). Atazanavir and lopinavir increase the plasma levels of tenofovir. Tenofovir reduces the plasma level of atazanavir (always boost with 100 mg ritonavir).

Larger controlled studies on use in pregnancy are yet to come.

Internet sources:

USA: http://hiv.net/link.php?id=134

References:

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Tipranavir

Tipranavir is the first nonpeptidic protease inhibitor (PI), which was superior to other boosted PIs in two large studies on intensively PI-treatment-experienced patients. Important salvage drug, moderately hepatotoxic, has to be boosted with increased ritonavir doses.

Trade name: Aptivus™. Abbr.: TPV

250 mg soft capsules

Drug class: non-peptide protease inhibitor (NPPI)

Manufacturer: Boehringer Ingelheim

Indications: HIV-infected adult patients who are either highly treatment-experienced or who have multiple PI resistances.

Oral dose: 500 mg bid tipranavir + 200 mg bid ritonavir with meals.

Side effects: Mainly gastrointestinal with diarrhea and nausea.

Increased transaminases (sometimes severe) have been observed in at least 6 % of patients, with clinical hepatitis and liver failure in rare cases. Dyslipidemia (20 %) occurs more frequently than with other PIs. Relatively rare: rash (urticarial or maculopapular).

Interactions: combination of tipranavir and ritonavir inhibits the activity of CYP3A and induces p-glycoprotein. Therefore, elevated serum drug levels have to be expected for those drugs that are primarily metabolized by CYP3A (see following table). Further information in the US product description at http://hiv.net/link.php?id=256

Drugs that are contraindicated on tipranavir therapy

Antiarrhythmics	Amiodarone, bepridil, flecainide, propafenone, quinidine
Antihistamines	Astemizole, terfenadine
Ergotamine derivatives	(Dihydro)-ergotamine, (methyl)-ergonovine
Prokinetics	Cisapride
Neuroleptics	Pimozide
Sedatives/hypnotics	Midazolam, triazolam

Tipranavir reduces the serum level of lopinavir, saquinavir and amprenavir, so that a combination is not recommended.

Fluconazole and clarithromycin increase the serum level of tipranavir. Careful monitoring is required on concurrent therapy.

Antacids reduce tipranavir levels by 30 %: stagger doses.

Rifampicin reduces tipranavir levels by 80 %: avoid.

Tipranavir/r increases the serum level of atorvastatin, therefore, begin with the smallest dose of atorvastatin, or – better still – change to another substance.

The same applies to rifabutin. Consequently: rifabutin 150 mg every two days or three times a week.

Tipranavir reduces the plasma level of abacavir and retrovir by 35 to 40%. Theoretically it may be necessary to increase the dose of abacavir and retrovir, but there are no recommendations.

ddI should only be taken at a two-hour interval to tipranavir.

Comments/Warnings: contraindicated in liver cirrhosis (Child-Pugh B and C). Caution in chronic hepatitis B or C. Determine transaminases (monthly initially), cholesterol, and triglycerides before and during treatment.

Women who take an estrogen-based contraceptive appear to have a higher incidence of rash.

Internet sources:

US: http://hiv.net/link.php?id=256

References:

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Trizivir™

The combination AZT+3TC+abacavir is virologically not as effective as "divergent" combinations, and is today only an option for patients with compliance problems and with co-medications that have many interactions (tuberculostatics). Further disadvantages: mitochondrial toxicity, abacavir HSR, once daily dosing not possible.

Trade name: Trizivir

Film-coated tablets with 150 mg 3TC **and** 300 mg AZT **and** 300 mg abacavir

Drug class: Nucleoside reverse transcriptase inhibitor (NRTI)

Manufacturer: GlaxoSmithKline

Indications: HIV infection

Oral dose: 1 tablet bid. In cases of impaired renal function (creatinine clearance less than 50 ml/min), the individual drugs should be given separately to allow for dose adjustment of 3TC and AZT.

Side effects: mostly gastrointestinal, see the individual drugs. Hypersensitivity reaction with abacavir (see under abacavir!). There are possibly additive effects with regard to mitochondrial toxicity.

Comments/Warnings: watch closely for hypersensitivity reactions (see Abacavir). See individual drugs.

Internet sources: USA: http://hiv.net/link.php?id=51

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Truvada™

Truvada™ is a much-used combination preparation, containing tenofovir and emtricitabine. Overall good tolerability, but monitoring of renal function is needed (see Tenofovir).

Film-coated tablets with 200 mg emtricitabine plus 300 mg tenofovir disoproxil fumarate or 245 mg tenofovir disoproxil.

Drug class: nucleoside and nucleotide reverse transcriptase inhibitor (NRTI).

Manufacturer: Gilead

Indications: HIV infection

Oral dose: 1 film-coated tablet daily

With reduced creatinine clearance of 30-49 ml/min, dose should be reduced to 1 tablet every two days. Truvada should not be prescribed at values lower than this.

Side effects: see Tenofovir

Comments/Warnings: refer to information in Tenofovir section.

In HIV patients with chronic hepatitis B coinfection, exacerbation of hepatitis may occur after discontinuing Truvada™. In such cases, clinical and laboratory monitoring is recommended for several months.

Absorption of Truvada™ is not affected by food intake.

Internet sources:

USA: http://hiv.net/link.php?id=241

References:

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Valcyte™ see Valganciclovir

Valganciclovir

Valganciclovir is the first CMV drug with good efficacy that can be administered orally, and to a large extent overshadows all other substances. Valganciclovir is a prodrug of ganciclovir and therefore has a similar toxicity profile: neutropenia, anemia and thrombocytopenia.

Trade name: Valcyte™

Tablets: 450 mg

Drug class: virostatic

Manufacturer: Hoffmann-La Roche

Indications: oral induction and maintenance therapy of CMV retinitis.

Dose: for induction 900 mg bid for 3 weeks (or until scar formation of CMV lesions), then suppressive therapy 900 mg daily.

The following doses should be used for renal failure:

CrCl (ml/min)	Induction therapy	Suppressive therapy
≥ 60	900 mg bid	900 mg daily
40 – 59	450 mg bid	450 mg daily
25 – 39	450 mg daily	450 mg q 48 h
10 – 24	450 mg q 48 h	450 mg 2 x/week

Side effects: frequently leukopenia, but also thrombocytopenia, anemia. Gastrointestinal complaints such as nausea, vomiting and diarrhea are more frequent than with intravenously-administered ganciclovir.

Comments/Warnings: monitoring of blood count at least 2-3 x/week during induction. Discontinuation if neutrophils below 500/µl (G-CSF if needed!). Contraindicated in neutropenia < 500/µl, thrombocytopenia < 25,000/µl and concurrent chemotherapy. Caution when concurrent dosing with ddI, as valganciclovir can double levels of ddI (increased toxicity!).

Valganciclovir is potentially teratogenic; reliable contraception is required.

Valganciclovir must be taken with meals.

The drug is very expensive! It should be discontinued when sufficient immune reconstitution has been reached (see OI chapter).

Internet sources:

USA: http://hiv.net/link.php?id=135

References:

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Vfend™ see Voriconazole

Videx™ see ddI

Viracept™ see Nelfinavir

Viramune™ see Nevirapine

Viread™ see Tenofovir

Vistide™ see Cidofovir

Voriconazole

Voriconazole is an orally available azole antimycotic, which is the therapy of choice for invasive aspergillosis. It is also active against invasive Candida infections.

Trade name: Vfend™

Tablets: 50 mg and 200 mg

Powder for reconsitution: 40 mg/ml

Bottles for injection: 200 mg

Drug class: azole antimycotic

Manufacturer: Pfizer

Indications: invasive aspergillosis; candidemia in non-neutropenic patients; fluconazole-resistant, severe invasive Candida infections (including C. krusei); treatment of severe infections caused by Scedosporium spp and Fusarium spp.

Dose:

Intravenous administration: initial dose on day 1: 6 mg/kg every 12 h; then 4 mg/kg every 12 h.

Oral administration: initial dose on day 1: 400 mg every 12 h; then 200 mg every 12 h. Halve the oral dose if under 40 kg.

Safety and effectiveness in pediatric patients below the age of 12 years have not been established.

Side effects: most commonly, elevated transaminases, rash and impairment of vision (overly bright images, blurred vision, light sensitivity or altered color vision) in approximately 30 %, usually appearing within 30 minutes of taking voriconazole, and lasting approximately 30 minutes.

More rarely fever, nausea, vomiting, diarrhea, headache, abdominal pain.

Comments/warnings: voriconazole is metabolized via the cytochrome 450 enzymatic pathway. Serum levels of voriconazole are so significantly reduced by some drugs that co-administration is contraindicated: rifampin, rifabutin, carbamazepine, long-acting barbiturates.

Serum levels of several drugs are significantly elevated by voriconazole, and therefore comedication is contraindicated: sirolimus, ergotamine derivatives, terfenadine, astemizole, cisapride, pimozide, quinidine.

Concurrent administration of rifabutin is also contraindicated.

Co-administration with NNRTIs or PIs (exception: indinavir) may require dose modifications, as is the case with a number of other drugs: cyclosporine, tacrolimus, anticoagulants, digoxin, statins, calcium antagonists, vincristine, vinblastine, phenytoin, omeprazole (see product information).

Voriconazole tablets should be taken one hour before or two hours after a meal.

Avoid strong sun exposure. Do not drive at night (due to potential visual impairment).

References:

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Zerit™ see d4T

Ziagen™ see Abacavir

Zidovudine see AZT

Zovirax™ see Acyclovir

33. Drug-Drug Interactions

Leonie Meemken and Laura Dickinson

In the field of the HIV-therapy, the most important interactions can occur during efflux/influx transport of drugs via transporters such as P-glycoprotein (P-gp) and metabolism by the cytochrome P450 enzyme system in the liver.

The cytochrome-P450 system consists of an array of various isoenzymes. Like many other drugs, protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) are primarily metabolized by the isoenzyme CYP-3A4, mainly found in the liver and enterocytes of the gastrointestinal tract; therefore partial metabolism already starts in the intestine. The rate of drug metabolism can depend on genetic polymorphism of the isoenzymes involved. Thus, absence or reduced activity of the concerned enzymes can result in prolonged retention of a drug in the body.

Drugs that are metabolized by the cytochrome-P450 system can act in three different ways: as (1) a substrate, (2) an inhibitor or as (3) an inducer of the corresponding enzymes. Some drugs such as ritonavir (RTV), efavirenz (EFV) and nelfinavir (NFV) can show a combination of the three. The specific drug combination determines the predominant characteristic.

To evaluate possible drug interactions, a complete medication history including herbal extracts and recreational drugs is necessary. In particular, the use of drugs characterized by an increased potential for interactions, e. g. protease inhibitors, rifabutin, azole-antimycotics and anticonvulsants should be carefully observed. Due to the potential for increased risks of toxicity or virological failure, the possibility of drug interactions should always be taken into account. For more information about often complex drug interactions and for individual consultation refer to “www.ifi-interaction-hotline.com”. Furthermore, a more comprehensive summary of interaction data can be found at “www.hiv-druginteractions.org”.

Drug plasma concentrations depend on many different factors such as age, sex, liver and renal diseases and ethnic population. Thus, drug interactions are often difficult to predict. In many cases, dose adjustments in combination with therapeutic drug monitoring (TDM) can be very useful.

Abbreviations used in the following tables:

AUC = Area Under the Curve,
Cmin = Minimum concentration / trough concentration,
QD = Once daily,
BID = Twice daily,
TID = Three times daily,
↓↑ = AUC (if no other parameter is specified) decreases or increases,
TDM = Therapeutic Drug Monitoring.

Part One: ART + ART

Abacavir - ABC, Ziagen® (component of Kivexa®, Trizivir®)

Metabolism: alcohol dehydrogenase and glucuronyltransferase

Approved dose: ABC 300 mg BID or 600 mg QD

Drugs	Interactions	Comments
NRTIs	No clinically significant interaction	
NNRTIs [1,2]	No clinically significant interaction	Caution when starting concomitant therapy (NNRTI-allergy/ABC-HSR).
PIs		
TPV/r [3]	ABC: 40 % ↓	**Avoid combination, if possible.** Mechanism unclear.
LPV/r [4]	ABC: 32 % ↓	Moderate decrease.
ATV/r [4]	ABC: 17 % ↓	Small decrease.

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Amprenavir - APV, Agenerase®

see fosamprenavir

Atazanavir - ATV, Reyataz®

Metabolism: atazanavir (ATV) is primarily metabolized by CYP-3A4 and is an inhibitor of CYP-3A4, CYP-2C9, CYP-1A2, and the UDP-glucuronosyltransferase (UGT)-1A1 [19].

Approved dose: ATV/r 300/100 mg QD

Drugs	Interactions	Comments
CCR5-Inhibitors		

Drugs	Interactions	Comments
Maraviroc [20]	ATV: maraviroc ↑ 360 %, ATV/r: maraviroc ↑ 490 %	Dose reduction: maraviroc 150 BID.
NRTIs		
TDF [1,3]	ATV 400 + TDF 300 QD [1]: ATV ↓ 25 % (Cmin 40 % ↓) ATV/r 300/100 + TDF 300 QD: ATV ↓ 11 % (Cmin 20 % ↓), TDF ↑ 37 %	Boost ATV. Take ATV/r 300/100 QD with a meal [1,2].
ABC [18]	ATV/r 300/100 + ABC 600 QD: ABC ↓ 17 %	Small decrease.
NNRTIs		
EFV [2,4,5]	ATV 400 + EFV 600 QD: ATV ↓ up to 74 % [4,5]	Boost ATV. Take ATV/r 400/100 QD with a meal [2].
NVP [6]	Theoretically: NVP ↓	No data.
PIs		
IDV/r [2]	ATV and IDV: risk of additive hyperbilirubinemia	**Avoid combination.**
SQV/r [7-9,21]	ATV 300 + SQV/r 1600/100 QD: SQV ↑ 60 %, RTV ↑ 41 % [8] ATV 300 + SQV/r 1000/100 BID: QD: SQV, ATV, RTV ↑ [7]	Invirase 500/r: 1500/100 QD probably sufficient: TDM [9]. Safe: 2000/100 QD. SQV-BID regime has a higher forgiveness rate [21].
NFV [10]	ATV 400 QD + NFV 1250 BID: Cmin NFV: 57 % ↑, M8: 124 % ↑	TDM.
FPV/r [11,12]	ATV 300 QD + FPV/r 700/100 BID: [11]: ATV ↓ 22 % (Cmin 24 % ↓) [12]: Adequate levels of both drugs	Controversial data => TDM.
LPV/r [13-15]	ATV 400 QD + LPV/r 400/100 BID: 1. LPV ↓ 16 % (Cmin 35 % ↓) [13] 2. ATV (Cmin 45 % ↑) [14] 3. ATV ↓ 38 % (Cmin 38 %↓) [15]	Controversial data => TDM. 1. HIV-patients. 2. Healthy subjects. 3. HIV-patients.
TPV/r [16]	ATV 300 QD + TPV/r 500/100 BID: ATV ↓ 68 % (Cmin 81 % ↓) TPV (Cmin 75 % ↑)	**Avoid combination.**
DRV/r [17]	ATV 300 QD + DRV/r 400/100 BID: ATV (Cmin 50 % ↑) RTV ↑ 50 - 59 %	Increased occurrence of hyperbilirubinemia, ocular icterus.

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Darunavir - DRV (TMC-114), Prezista®

Metabolism: DRV is primarily metabolized by CYP-3A4 [1]. By means of boosting with RTV, DRV is an inhibitor of CYP-3A4.

Approved dose: DRV/r 600/100 mg BID taken with a meal [1]

Drugs	Interactions	Comments
CCR5-Inhibitors		
Maraviroc [4]	DRV/r: maraviroc ↑ 400 %	Dose reduction: maraviroc 150 BID.

Drugs	Interactions	Comments
NRTIs		
ddI [1]		ddI 1h before or 2h after intake of DRV/r.
TDF [2]	TDF 300 QD + DRV/r 300/100 BID: TDF ↑ 22 %	No dose adjustment.
NNRTIs		
EFV [1]	EFV 600 QD + DRV/r 300/100 BID: DRV ↓ 13 % (Cmin 31 % ↓) EFV ↑ 21 %	Clinical significance unclear, combine with caution.
NVP [1]	NVP 200 BID + DRV/r 400/100 BID: NVP ↑ 27 %	Combination possible.
PIs		
ATV [3]	ATV 300 QD + DRV/r 400/100 BID: ATV ↑, RTV ↑ 50 - 59 %	Increased incidence of hyperbilirubinemia and ocular icterus.
IDV [1]	IDV 800 BID + DRV/r 400/100 BID: IDV 23 % ↑, DRV 24 % ↑	Combination possible, if clinically necessary.
LPV/r [1]	LPV/r 400/100 + DRV/r 300/100 BID: DRV ↓ 53 %, LPV/r 37 % ↑	**Avoid combination.** No appropriate dosages known as yet.
SQV [1]	SQV 1000 BID + DRV/r 400/100 BID: DRV ↓ 26 %	**Avoid combination**.

References

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Didanosine - ddI, Videx®

Metabolism: hypoxanthine-oxidase.

Elimination: 30 - 50 % renal

Approved dose: ddI 250 mg QD < 60 kg, 400 mg QD ≥ 60 kg

Drugs	Interactions	Comments
NRTIs		
d4T [1-3]	Risk of lactic acidosis, pancreatitis, neuropathy ↑	Only for patients with a specific resistance profile.
TDF [3-5]	In combination of ddI and TDF: dosage according to weight: ≥ 60 / < 60 kg: ddI 250/200 mg. Caution: despite dose reduction, probably risk of lactic acidosis and pancreatitis ↑	**Unfavourable combination. Avoid combination, if possible.** If clinically necessary, monitor lipase and lactate.
PIs		
ATV [1,3]	ddI-tablets: ATV ↓ 87 %, ddI-EC: no data	Take ddI 2h apart from ATV.

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Efavirenz - EFV, Sustiva®

Metabolism: efavirenz is primarily metabolized by CYP-2B6 and by CYP-3A4 as a minor route. EFV can either induce or inhibit CYP-3A4 and is also a poor inhibitor of CYP-2C9 and -2C19 [1,2]. 20 % of Africans and 3 % of Caucasians are slow EFV metabolizers and could receive increased EFV side-effects.

Approved dose: EFV 600 mg QD

Note: wrong positive cannabinoid test in urine with CEDIA DAU multilevel THC assay [2].

Drugs	Interactions	Comments
CCR5-Inhibitors		
Maraviroc [16]	Maraviroc ↓ 50 %	Increase dose: maraviroc 600 BID.
NRTIs		
TDF [14]	No significant interactions known [1]. Perhaps neuropsychiatric manifestations in slow EFV metabolizers.	No clear evidence.
NNRTIs		
NVP [3,4]	NVP 400 QD + EFV [3]: EFV ↓ 22 % (Cmin 36 % ↓)	**Unfavourable combination.** Efficacy ↓, toxicity ↑ [4].

Drugs	Interactions	Comments
PIs		
ATV [5,6]	ATV 400 QD + EFV: ATV ↓ up to 74 %	Boost ATV. Take ATV/r 400/100 QD with a meal.
FPV/r [7]	FPV/r 700/100 BID + EFV: no clinically significant interactions	Off label use: FPV/r QD => 300 RTV QD [7].
IDV/r [2,8,9]	IDV/r 800/100 BID + EFV: IDV ↓ 19 % (Cmin 48 % ↓) [9]	IDV/r: 800/100 BID [9], probably increase dose [10].
LPV/r [10]	Tablets: LPV/r 600/150 BID + EFV: LPV ↑ 35 %, RTV ↑ 56 - 92 %	Tablets, recommendations: LPV/r 400/100 BID for ART-naive patients. LPV/r 600/150 BID for pre-treated patients [1].
SQV [13,15]	SQV 1600/200 or 1200/100 QD or 1000/100 BID + EFV: adequate levels	SQV-BID regime has a higher forgiveness rate [15].
NFV [2]	NFV 1250 BID + EFV: NFV ↓ 38 %	TDM.
TPV/r [11]	EFV ↓ 1 - 31 %, TPV ↓	Limited data.
DRV/r [12]	DRV/r 300/100 BID + EFV: DRV ↓ 13 %, EFV ↑ 21 %	Limited data. Use combination with caution.

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Emtricitabine - FTC, Emtriva® (component of Truvada®)

Elimination: renal

Approved dose: FTC 200 mg QD

Drugs	Interactions	Comments
NRTIs		
3TC [1,2]	Antagonism	**Avoid combination.**
NNRTIs, PIs	No significant interactions known	

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Enfuvirtide - T-20, Fuzeon®

No clinically significant interactions known.

Fosamprenavir - FPV, Lexiva®/Telzir®

Metabolism: fosamprenavir (FPV) is a prodrug of amprenavir (APV). APV is metabolized by CYP-3A4 and is also an inhibitor of CYP-3A4 (as potent as indinavir and nelfinavir). Additionally, there are reports suggesting that APV is an inducer of CYP-3A4.

Approved dose: FPV/r: 700/100 BID

Drugs	Interactions	Comments
NRTIs [2,3,4]	No interactions with: AZT, 3TC, ABC, ddI, TDF [3,4]	
NNRTIs		
EFV [5]	EFV 600 QD + FPV/r: no clinical significance	Off label use: FPV/r QD => RTV: 300 QD [5].
NVP [6]	NVP 200 BID + FPV/r: no clinical significance	In this study, no dose adjustment was necessary.
PIs		
ATV [7,8]	ATV 300 QD + FPV/r: [7]: ATV ↓ 22 % or [8]: adequate levels	Controversial data => TDM.

Drugs	Interactions	Comments
IDV [9]	IDV 800 + APV 800 TID: APV ↑ 33 %, IDV ↓ 38 %	Probably no dose adjustment necessary.
LPV/r [10-15]	1. LPV/r 400/100 BID + FPV/r: APV ↓ 63 %, LPV ↑ 37 % [11]	**Unfavourable combination, avoid combination** or TDM.
	2. LPV/r 400/100 + FPV 700 BID: APV ↓ 64 %, LPV ↓ 48 % [10]	Dose separation corrects LPV-, but not APV-levels [12].
	3. LPV/r 533/133 + FPV 1400 BID: APV ↓ 26 % LPV: adequate [11]	
NFV [9]	NFV 750 + APV 800 TID: APV ↑ 300 %, NFV ↑ 15 %	Probably, no dose adjustment necessary.
SQV/r [16]	SQV/r 1000/100 or 1000/200 + FPV 700 BID: no effect on FPV, but SQV: RTV 100: SQV ↓ 24 % RTV 200: SQV ↑ 12 %	RTV 100: FPV + SQV => TDM of SQV. RTV 200: FPV + SQV => Safe.
TPV/r [17]	TPV/r 500/200 + APV 600 BID: APV ↓ 44 % (Cmin ↓ 56 %)	**Avoid combination.**

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Indinavir - IDV, Crixivan®

Metabolism: indinavir (IDV) is primarily metabolized by CYP-3A4 and can also inhibit CYP-3A4. For optimal adsorption, an acidic gut pH is necessary; therefore IDV should be taken with a light meal [1].

Approved dose: IDV 800 mg TID, IDV/r 800/100 BID

Drugs	Interactions	Comments
NRTIs		
ddI [2-4]	No interactions between ddI EC + IDV [4]	However, take ddI 1h apart from IDV [2]
NNRTIs		
EFV [2,5-7]	IDV/r 800/100 BID + EFV 600 QD: IDV ↓ 19 % (Cmin 48 % ↓, but > 0.1 mg/L) [6]	IDV/r: 800/100 BID, probably higher doses may be necessary [6]. No IDV QD in combination with EFV [7].
NVP [2,8,9]	IDV/r 800/100 + NVP 200 BID: IDV: Cmin 57 % ↓, but IDV > 0.1 mg/L [8]	IDV/r: 800/100 BID [8], probably higher doses of IDV may be necessary [8]. NVP QD decreases IDV/r more than NVP BID [9].
PIs		
ATV [10]	IDV + ATV: bilirubin levels ↑	**Avoid combination.**
APV [11]	IDV 800 + APV 800 TID: APV ↑ 33 %**,** IDV ↓ 38 %	In this study, no dose adjustment was necessary.
LPV/r [12-15]	IDV 800 + LPV/r 400/100 BID: LPV ↓ [12]	TDM.
NFV [16]	IDV 1200 + NFV 1250 BID: no clinically significant interactions	In this study, no dose adjustment was necessary.
SQV [17]	IDV 800 TID + single dose SQV: SQV ↑ 500 - 800 % [17]	Lower doses: synergistic effect. Higher doses: antagonistic effect [1].
TPV/r	No data	**Avoid combination.**

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Lamivudine - 3TC, Epivir® (component of Combivir®, Kivexa®, Trizivir®)

Elimination: renal.

Approved dose: 3TC 150 mg BID or 300 mg QD

Drugs	Interactions	Comments
CCR5-Inhibitors		
Maraviroc [4]	Maraviroc 300 BID + 3TC: no effect on 3TC	

Drugs	Interactions	Comments
NRTIs		
FTC [1-3]	Antagonism	**Avoid combination.**
NNRTIs	No clinically significant interaction	
PIs	No clinically significant interaction	

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Lopinavir - LPV/r, Kaletra®

Metabolism: Kaletra® is primarily metabolized by CYP-3A4. It is also a strong inhibitor of CYP-3A4 and induces glucuronyltransferase [1].

Approved dose for the Meltrex® tablet: 400/100 mg BID

Drugs	Interactions	Comments
CCR5-Inhibitors		
Maraviroc [30]	Maraviroc ↑ 270 %	Dose reduction: maraviroc 150 BID.
NRTIs		
ddI [2]	No data	ddI + LPV/r: 2h time interval.
TDF [3,4]	1. Healthy subjects: TDF ↑ 32 %, LPV/r ↑ 32 % [4] 2. Heavily pre-treated patients: LPV (Cmin 34 % ↓) [3]	Probably no increase in renal side-effects. TDM of LPV/r.
ABC [29]	ABC ↓ 32 %	Moderate decrease.
NNRTIs		
EFV [2,5,6]	Tablets: EFV 600 QD + LPV/r 600/150 BID: LPV ↑ 35 %, RTV ↑ 56 - 92 % [6]	Tablets: LPV/r 400/100 BID in ART-naive patients. LPV/r 600/150 BID in pre-treated patients [6].
NVP [2,7,8]	NVP 200 BID + LPV/r-tablet: 1. 23 pre-treated patients: LPV/r ↓ 27 % (Cmin 51 % ↓) 2. 31 patients with VL < 80 c/ml: adequate levels of both drugs	Tablets: LPV/r 400/100 BID in ART-naive patients. LPV/r 600/150 BID in pre-treated patients [2].

Drugs	Interactions	Comments
PIs		
ATV [9-11]	ATV 400 QD + LPV/r-tablet: 1. LPV ↓ 16 % (Cmin 35 % ↓) [9] 2. ATV (Cmin 45 % ↑) [11] 3. ATV ↓ 38 % (Cmin 38 % ↓) [10]	Controversial data => TDM. 1. HIV-patients. 2. Healthy subjects. 3. HIV-patients.
FPV/r [12-15]	1. FPV 700 BID + LPV/r-capsules: APV ↓ 63 % (Cmin 65 % ↓) LPV ↑ 37 % [12] 2. FPV 700 BID + LPV/r: APV ↓ 64 % (Cmin 69 % ↓) LPV ↓ 48 % (Cmin 61 % ↓) [13] 3. FPV 1400 + LPV/r 533/133 BID: APV ↓ 26 % (Cmin 42 % ↓) LPV: adequate levels [14]	**Unfavourable combination.** Dose separation corrects LPV-, but not APV-levels [15].
IDV [16-21]	IDV 800 BID + LPV/r-capsules: PK-values of LPV slightly lower	IDV + LPV/r: TDM.
NFV [22]	NFV 1000 + LPV/r 400/100 BID: LPV/r ↓ 27 % (Cmin 33 % ↓)	LPV/r 600/150 BID is recommended for strongly pretreated patients.
SQV [23-26]	SQV 1000 BID + LPV/r 400/100 BID: adequate SQV-, LPV-levels	Synergistic effect, favourable combination: TDM.
TPV [27]	TPV 500 BID + LPV/r: LPV ↓ 55 % (Cmin 52 - 70 % ↓)	**Avoid combination.**
DRV/r [28]	DRV/r 300/100 BID + LPV/r: DRV ↓ 53 %, LPV/r ↑	**Avoid combination.**

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Maraviroc

Metabolism: Maraviroc is metabolized by isoenzyme CYP-3A4 and is a substrate of the P-glycoprotein.

Approved dose: 300 mg BID

Drugs	Interactions	Comments
NRTIs		
3TC, AZT [1]	Maraviroc 300 BID + 3TC, AZT: no effect on 3TC, AZT	
TDF [2]	No effect on maraviroc	
NNRTIs		
EFV [3]	Maraviroc ↓ 50 %	Increase dose: maraviroc 600 BID.
NVP [3]	Adequate level of maraviroc compared to historical data.	Pfizer recommends maraviroc 600 BID because NVP is an enzyme inducer.
PIs		
ATV, ATV/r [4]	Maraviroc ↑ 360 %, ↑ 490 %	Dose reduction for all PIs except for TPV/r: maraviroc 150 BID (no data for FPV/r).
DRV/r [5]	Maraviroc ↑ 400 %	
LPV/r [3]	Maraviroc ↑ 270 %	
SQV/r [6]	Maraviroc ↑ 980 %	
TPV/r [7]	No effect on maraviroc	No dose adjustement.
NNRTI + PIs		
LPV/r + EFV [8]	Maraviroc ↑ 250 %	Dose reduction: maraviroc 150 BID.
SQV/r + EFV [8[	Maraviroc ↑ 500 %	

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Nelfinavir - NFV, Viracept®

Metabolism: nelfinavir (NFV) is primarily metabolized by CYP-2C19 and futher by CYP-3A4, CYP-2D6 and CYP-2C9. NFV is an inhibitor of CYP-3A4 [1,2].
Approved dose: NFV 1250 mg BID

Drugs	Interactions	Comments
NRTIs		
ddI [1,2]	No data.	Take ddI 2h before or 1h after intake of NFV.
TDF [3]	No significant interactions known	
NNRTIs		
EFV [4]	NFV 1250 BID + EFV 600 QD: NFV ↓ 38 % (Cmin 65 % ↓)	Clinical significance unknown, possibly TDM.
NVP [5]	NFV 750 TID + NVP 200 BID	In this study, no dose adjustment was necessary.
PIs		
ATV [6,7]	NFV 1250 BID + ATV 400 QD: NFV: Cmin 57.4 % ↑, M8: 124 % ↑, no effect on AUC, Cmax and Tmax	TDM.
APV [8]	NFV 750 + APV 800 TID: APV: (Cmin 290 % ↑) NFV ↑ 15 %	TDM.
IDV [9]	NFV 1250 + IDV 1200 BID	In this study, no dose adjustment was necessary.
LPV/r [10]	NFV 1000 + LPV/r 400/100 BID: (healthy subjects) LPV/r ↓ 27 % (Cmin 33 % ↓)	LPV/r 600/150 BID: recommended for strongly pre-treated patients.
SQV/r [11,12]	NFV 1250 + SQV/r 1000/100 BID: M8 (NFV-metabolite) ↑ 270 %	Probably no dose adjustment necessary. Low potential for interactions.
TPV/r	No data	**Avoid combination.**

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Nevirapine - NVP, Viramune®

Metabolism: nevirapine (NVP) is primarily metabolized by CYP-3A4 and is an inducer of CYP-3A4 and -2B6 [1,2].

Approved dose: NVP 200 mg BID

Drugs	Interactions	Comments
CCR5-Inhibitors		
Maraviroc [17]	Adequate level of maraviroc compared to historical data	Pfizer recommends maraviroc 600 BID because NVP is an enzyme inducer.
NRTIs	No significant interactions known [1]	
NNRTIs		
EFV [2,3,4]	EFV 600 QD + NVP 400 QD [3]: EFV ↓ 22 % (Cmin 36 % ↓)	**Avoid combination.** Efficacy ↓, toxicity ↑ [4].
PIs		
ATV [2,5]	Theoretically: ATV ↓	No data.
FPV/r [6]	FPV/r 700/100 BID + NVP: no clinical significance	Probably no dose adjustment necessary.
IDV/r [7,8]	IDV/r 800/100 BID + NVP: IDV: Cmin 57 % ↓, RTV: Cmin 59 % ↓, but IDV > 0.1 mg/L [7]	IDV/r 800/100 BID: probably higher dosages in pre-treated patients [7]. NVP QD possibly more decreases IDV levels than NVP BID [8].
LPV/r [9-11]	NVP 200 BID + LPV/r 400/100 BID: 1. 23 pre-treated patients: LPV/r ↓ 27 % (Cmin 51 % ↓) 2. 31 patients with VL < 80 c/ml: adequate levels of both drugs [11]	Tablets: LPV/r 400/100 BID suitable for ART-naive patients. LPV/r 600/150 BID: recommended for strongly pre-treated patients.
NFV [12,13]	NFV 750 TID + NVP: NFV ↑ 4 %, Cmax 14 % ↑	Probably no dose adjustment.
SQV/r [2,14]	SQV ↓ 24 %	Clinical significance unknown.
TPV/r [15,16]	NVP ↓ 3 - 24 %	Limited data, no dose adjustment known as yet.

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Saquinavir - SQV, Invirase 500®

Metabolism: 90 % of saquinavir (SQV) is metabolized by CYP-3A4. Further, SQV is a weak inhibitor of CYP-3A4. In-vitro studies have shown that SQV is also a substrate of P-glycoprotein (P-gp) [1,2].

Approved dose: SQV/r 1000/100 mg BID [3]

Drugs	Interactions	Comments
CCR5-Inhibitors		
Maraviroc [18]	Maraviroc ↑ 980 %	Dose reduction: maraviroc 150 BID.
NRTIs		
ddI [1]		Take ddI 1h before or 2h after intake of SQV.
TDF [4,5]	No clinically significant interactions	
NNRTIs		
EFV [2]	SQV 1600/200 or 1200/100 QD or 1000/100 BID + EFV: adequate levels	SQV-BID regime has a higher forgiveness rate.
NVP [6,7]	SQV ↓ 24 %	Clinical significance unknown.
PIs		
ATV [8-11]	SQV 1600 QD + ATV/r 300/100 QD: SQV ↑ 60 %, RTV ↑ 41 % [8] SQV 1000 BID + ATV/r 300/100 QD: SQV, ATV, RTV ↑ [11]	Invirase 500/r: 1500/100 QD probably sufficient: TDM [10]. Safe: 2000/100 QD. SQV-BID regime has a higher forgiveness rate.
FPV/r [12]	SQV 1000 + FPV/r 700/100 or 700/200 BID: no effect on FPV, but on SQV RTV 100: SQV ↓ 14 % RTV 200: SQV ↑ 12 %	RTV 100: FPV + SQV => unsafe: TDM. RTV 200: FPV + SQV => safe.
IDV [13,14]	IDV 800 TID + single dose SQV: SQV ↑ 500 - 800 % [13,14]	Insufficient data.
LPV/r [3,15-17]	SQV 1000 + LPV/r 400/100 BID: adequate SQV- and LPV-levels	Synergistic effect.
NFV [19,20]	SQV/r 1000/100 + NFV 1250 BID: NFV-M8 ↑ 270 %	In this study, no dose adjustment was necessary.
TPV/r [21]	SQV 1000 + TPV/r 500/200 BID: SQV↓ 70 % (Cmin 81 % ↓)	**Avoid combination.**
DRV/r [22]	SQV 1000 + DRV/r 400/100 BID DRV ↓ 26 %	**Avoid combination.**

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Stavudine - d4T, Zerit®

Elimination: 34 - 43 % renal

Approved dose: d4T 40 mg BID > 60 kg, 30 mg BID < 60 kg

Drugs	Interactions	Comments
NRTIs		
AZT [1,2]	Antagonism	**Avoid combination.**
ddI [1,2]	Risk of lactic acidosis, pancreatitis, neuropathy ↑	**Avoid combination, if possible.**

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Tenofovir - TDF, Viread® (component of Truvada®)

Elimination: renal, TDF is excreted either by glomerular filtration or by active renal tubular secretion.

Approved dose: TDF 300 mg QD

Drugs	Interactions	Comments
CCR5-Inhibitors		
Maraviroc [3]	No effect on maraviroc	
NRTIs		
ddI [1,2,4,5]	See ddI	**Unfavourable combination! Avoid combination, if possible.** If clinically necessary, monitor lipase and lactate.
ABC [6], FTC [7], d4T [8], 3TC [9]	No significant interactions known	
NNRTIs		
EFV [9,24]	No significant interactions known. Perhaps neuropsychiatric manifestations in slow EFV metabolizers	No clear evidence.
PIs		
ATV/r [10-14]	ATV 400 QD + TDF: ATV ↓ 25 % (Cmin 40 % ↓) TDF ↑ 24 % [11]	ATV/r 300/100 QD: administer with food. Boost ATV. (Otherwise risk of subtherapeutic drug levels).
	ATV/r 300/100 + TDF [10]: ATV ↓ 25 % (Cmin 23 % ↓, not significant [12])	Boosted ATV-levels are 2 to 4-fold higher than unboosted ATV without TDF [13].
DRV/r [23]	Healthy subjects: TDF ↑ 22 % (Cmax 24 % ↑)	
FPV/r [15,16]	No significant interactions known	
IDV [9]	No significant interactions known	
LPV/r [17,18]	1. Healthy subjects: TDF: 32 % ↑ (Cmax 15 % ↑), LPV/r: unchanged 2. Pre-treated patients: Cmin LPV 34 % ↓, Cmin RTV 44 % ↓	In clinical studies, no increased appearance of renal side-effects. TDM of LPV/r.
NFV [19]	No significant interactions known	
RTV [17]	No significant interactions known	
SQV/r [20,21]	No significant interactions known	
TPV/r [22]	TPV/r 500/100 or 750/200 BID + TDF [4]: TDF (depending on TPV dose): 11 % ↓ and 17 % ↓	**Avoid combination.**

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Tipranavir - TPV/r, Aptivus®

Metabolism: TPV is metabolized by isoenzyme CYP-3A4 and is also a substrate of P-glycoprotein (P-gp). Further, TPV is an inducer of CYP-3A4, glucuronyltransferase, and P-glycoprotein [1,2]. TPV is an inhibitor of CYP-3A4 when boosted with RTV. Thus, interactions between TPV/r and drugs that are both metabolized by CYP-3A4 and transported by P-glycoprotein are difficult to predict.

Approved dose: TPV/r 500/200 mg BID taken with a meal [1,2]

Drugs	Interactions	Comments
CCR5-Inhibitors		
Maraviroc [9]	TPV/r: no effect on maraviroc	No dose adjustment.
NRTIs		
ABC [2,3]	ABC ↓ 40 %	**Avoid combination.** Clinical significance has not been firmed yet.
AZT [1-4]	AZT ↓ 35 % (Cmax ↓ 46 - 61 %) TPV (Cmin ↓ 34 %) [4]	**Avoid combination.** Clinical significance has not been firmed yet.
ddI [1-4]	ddI ↓	ddI 2h before or after intake of TPV/r.
TDF [1,2,4]	TPV/r 500/100 or 750/200 + TDF 300 QD [4]: TDF (depending on TPV dose): Cmax ↓ 23 - 38 %, TPV ↓ 11 - 17 %	No dose adjustment known as yet.
NNRTIs		
EFV [2-4]	EFV ↓ 1 - 31 % [4] TPV ↓ (Cmin ↓)	Limited data. No dose adjustment known as yet.
NVP [5]	NVP ↓ 3 - 24 %	Limited data. No dose adjustment known as yet.
PIs		
APV [6]	TPV/r 500/200 + APV 600 BID: APV ↓ 44 % (Cmin 56 % ↓)	**Avoid combination.**
ATV [8]	ATV 300 QD + TPV/r 500/100 BID: ATV ↓ 68 % (Cmin 81 % ↓) TPV (Cmin 75 % ↑)	**Avoid combination.**
IDV [2,7]	Limited data	**Avoid combination.**
LPV/r [6]	TPV 500 + LPV/r 400/100 BID: LPV ↓ 55 % (Cmin 52 - 70 % ↓)	**Avoid combination.**
NFV [2]	No data	**Avoid combination.**
SQV [2,6]	TPV/r 500/200 + SQV 1000 BID: SQV ↓ 76 % (Cmin 81 % ↓)	**Avoid combination.**

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Zalcitabine - ddC, HIVID® (phased out in 2006)

Zidovudine - AZT, Retrovir® (component of Combivir®, Trizivir®)

Metabolism: hepatic by glucuronosyltransferase

Elimination: renal

Approved dose: AZT 250 mg or 300 mg BID

Drugs	Interactions	Comments
CCR5-Inhibitors		
Maraviroc [3]	Maraviroc 300 BID + AZT: no effect on AZT	
NRTIs		
d4T [1]	Antagonism	**Avoid combination.**
NNRTIs	No significant interactions known	
PIs		
TPV/r [2]	AZT ↓ 35 %	**Avoid combination, if possible.**

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Part 2: ART + co-medication

Antibiotics

Drugs	Interactions	Comments
PIs		
Clarithromycin	Theoretically: clarithromycin ↑, PIs ↑ Side-effects: e.g. diarrhoea, metallic taste, QT-prolongation with ATV [4]	Theoretical alternative [1,7]: azithromycin (exception: NFV). Dose reduction of clarithromycin in hepatic and renal failure.
	ATV/r, TPV/r: clarithromycin ↑, active metabolite of clarithromycin ↓, ATV ↑ 30 %, TPV ↑ 66 %	ATV: **avoid combination** or 50 % dose reduction of clarithromycin. ATV, TPV: **avoid combination** in H.-influenza-infections as the active clarithromycin-metabolite is primarily effective.
Erythromycin	Theoretically: PIs ↑, erythromycin ↑	Theoretical alternative: azithromycin [1,7] (exception: NFV).
Azithromycin	NFV 750 TID [2,6]: azithromycin ↑ > 100 %, NFV ↓ 28 %	**Caution:** side-effects of azithromycin.
NNRTIs		
Clarithromycin [1,2,8,9]	EFV, NVP: clarithromycin ↓, active clarithromycin-metabolite ↑, EFV ?, NVP ↑ 26 %, skin rashes, exanthemas ↑	NVP: monitor liver function. EFV, NVP: theoretical alternative: azithromycin [1].
Erythromycin [1,5]	Theoretically: EFV, NVP ↑	**Caution:** possibly side-effects of EFV and NVP. Theoretical alternative: azithromycin [4].
NRTIs		
Aminoglycosides	TDF: additive nephrotoxicity	**Avoid combination.**
Atovaquone	AZT ↑ 35 % ± 23 %	Monitor side-effects of AZT.
Clarithromycin	AZT ↓ 10 - 25 % [10]	Take 2 - 4h apart, monitor efficacy of AZT.
Cotrimoxazole [3]	AZT: possibly haematotoxicity ↑	**Avoid combination.**
Dapsone [2,11]	AZT: possibly haematotoxicity ↑ d4T, ddI: risk of neuropathy ↑	AZT, d4T, ddI: **avoid combination.**
Isoniazid [2]	d4T, ddI: risk of neuropathy ↑	ddI: **avoid combination.**
Pentamidine (i. v.)	d4T, ddI: pancreas toxicity ↑ TDF: possibly additive nephrotoxicity	D4T, ddI: **avoid combination.** Start with d4T after one week. TDF: monitor creatinine.
CCR5-Inhibitors		
Clarithromycin [12]	Maraviroc ↑	Dose reduction: maraviroc 150 BID.

References

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Antidepressants

Drugs	Interactions	Comments
PIs		
Tricyclic antidepressants	Theoretically: possibly PIs ↑, tricyclic antidepressants ↑ [1,2]	Monitor anticholinergic effects, possibly reduce tricyclic antidepressants dose. Theoretical alternative: citalopram.
St. John's Wort	Theoretically: PIs ↓ [1,4]	**Avoid combination.** Theoretical alternative: citalopram.
SSRI: citalopram	No significant interaction known	
SSRI: fluvoxamine	Theoretically: PIs ↑	Monitor side-effects of PIs.
SSRI: fluoxetine [3]	Theoretically: fluoxetine ↑, PIs ↑ RTV (100 - 600 BID): serotonin syndrome: fever, psychic changes, myoclonus, diarrhoea, vormitus	Probably higher potential for interactions. Long half-life: 4 days. Monitor toxicities.
SSRI: paroxetine	FPV/r: paroxetine ↓ 60 % [6], DRV/r: paroxetine ↓ 30 - 40 % [1,11]	**Caution**. Monitor paroxetin efficacy, possibly adjust paroxetine dose.
SSRI: sertraline	TPV/r: sertraline ↑ [1] DRV/r: sertraline (50 QD) ↓ 30 - 40 % [11]	High therapeutic range: possibly adjust sertraline dose.

Trazodone	IDV, DRV/r, RTV: theoretically: trazodone ↑ [5,7] symptoms: syncope, sickness, vomiting, hypotension	Possibly reduce dose of trazodone.
Venlafaxine	Theoretically: venlafaxine ↑, PIs ↑ Study: IDV ↓ 28 %, venlafaxine unchanged [9]	Controversial data for IDV. Monitor efficacy of venlafaxine, IDV: TDM.
Bupropion	Theoretically: bupropion ↑ Bupropion (150 - 300 QD) + NFV or EFV or RTV 100 mg: no epileptic seizures [10]	Monitor side-effects of bupropion.
NNRTIs		
St. John's Wort	Theoretically: EFV ↓, NVP ↓ [1,8]	**Avoid combination.**

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Oral Antidiabetics

Drugs	Interactions	Comments
PIs		
Pioglitazone Glimepiride, glipizide, repaglinide, rosiglitzone, tolbutamide	Theoretically: PIs ↓, pioglitazone ↑ [2] TPV/r: drug level fluctuations since all drugs are metabolized by CYP-2C8, CYP-2C9 and -3A4 [1]	**Avoid combination.** Theoretical alternative: rosiglitazone. Closely monitor glucose.

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Antihistamines

Drugs	Interactions	Comments
PIs		
Astemizole, loratadine (> 20 mg), terfenadine	Theoretically: antihistamines ↑ Risk of QT-prolongation ↑ [1,3,4]	**Avoid combination:** terfenadine, astemizole [3,4]. Caution: loratadine > 20 mg. Theoretical alternatives: cetirizine [3,4].
NNRTIs		
Astemizole, loratadine (> 20 mg), terfenadine	Theoretically: antihistamines ↓↑ Risk of QT-prolongation (EFV [1-3], NVP [2])	See above.

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Anticonvulsants

Drugs	Interactions	Comments
PIs		
Carbamazepine, phenytoin, primidone	Theoretically: PIs ↓ Carbamazepine ↑, phenytoin ↑, primidone ↑ [1-5] Case report: LPV/r: carbamazepine ↑ 46 %. Carbamazepine toxicity: vertigo, drowsiness, disorientation, ataxia, vomiting occurred within 12 hours. Resolved with carbamazepine dose reduction [7]	**Avoid combination:** carbamazepine, phenytoin, primidone. Theoretical alternative: gabapentin, levetiracetam.

Lamotrigine	LPV/r: lamotrigine ↓ 56 % TPV/r, NFV: theoretically: lamotrigine ↓	LPV/r: possibly increase dose of lamotrigine by 200 % [5].
Valproic acid	Possibly LPV/r ↑ [4] Case report: LPV/r + valproic acid 250 TID: after 21 days exacerbated mania resolved by increasing valproic acid dose: 1500 [8].	Monitor closely decreased valproic acid levels when giving ritonavir-boosted PI regimes.
Phenytoin	NFV: phenyotin ↓	TDM of anticonvulsants [1,6].
NNRTIs		
Carbamazepine, phenytoin, primidone	Theoretically: EFV ↓, NVP ↓ Anticonvulsants ↓ [1]	**Avoid combination** or TDM. Theoretical alternatives: gabapentin, levetiracetam, valproic acid, lamotrigine.
Oxcarbazepine	Theoretically: EFV ↓, NVP ↓ Anticonvulsants ↓ [1] Study: adequate EFV levels [9]	No clear evidence.
Valproic acid	Case report: after EFV initiation valproic acid ↓ 50 % [10]	Mechanism unclear.
NRTIs		
Fosphenytoin, phenytoin, valproic acid	AZT clearance ↓ 30 % phenytoin ↑↓, AZT ↑ 79 % [3]	TDM of phenytoin. Monitor side-effects of AZT.

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Antimycotics

Drugs	Interactions	Comments
PIs		
Itraconazole Ketoconazole [1-5,7,8]	Theoretically: PIs ↑ Ketoconazole, itraconazole ↑	Monitor PIs and azole side-effects. ATV/r, DRV/r, LPV/r, TPV/r: ketoconazole and itraconazole doses: < 200 mg/d. Theoretical alternative: fluconazole (exception: TPV/r). NFV, SQV: no dose adjustment.
Voriconazole	RTV 100 BID + voriconazole: voriconazole ↓ 39 % TPV/r: voriconazole ↑↓ [1,8]	**Avoid combination**.
Fluconazole [1,8]	No significant interactions (except for TPV: fluconazole ↑ 56 %)	TPV/r: **caution,** fluconazole not > 200 mg/d.
Caspofungin [1]	No significant interactions (except for NFV)	NFV: possibly increase caspofungin (50 mg) to 70 mg QD.
NNRTIs		
Itraconazole Ketoconazole [10]	Theoretically: EFV ↑, ketoconazole, itraconazole ↓ NVP ↑ 28 %, ketoconazole ↓ 63 %	Theoretical alternative: fluconazole [2].
Fluconazole	NVP ↑ 100 %, transaminases ↑ by 500 % in 25 % of patients [3].	TDM of NVP.
Voriconazole	EFV: voriconazole 77 % ↓, EFV ↑ 44 % [1,9]	NNRTIs: **avoid combination.** NVP: no data.
NRTIs		
Fluconazole	AZT ↑ 74 % [4]	Monitor side-effects of AZT.
Amphotericin B [2]	TDF: possibly additive nephrotoxicity	**Avoid combination,** especially with pre-damaged kidney**.**
CCR5-Inhibitors		
Ketoconazole, itraconazole [11]	Ketoconazole 400 QD: maraviroc ↑ 500 %	Ketoconazole, itraconazole: maraviroc 150 BID.

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Ergotamines and ergotamine derivates (Antimigraines)

Drugs	Interactions	Comments
PIs		
Ergotamines, ergotamine derivates	Theoretically: ergotamines ↑ [1] Life-threatening ergotism ↑	**Avoid combination.** Theoretical alternative: triptans.

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Herbal extracts, vitamins and food

Few data are available on interactions between antiretrovirals and herbal prepartions. Furthermore, interactions can be difficult to predict as the routes of metabolism of active constituants are rarely known. In many cases, theoretical investigations have to be taken into account. Therefore, caution must be excerised when considering coadministration of ART and herbal remedies. In the following table, the most widely studied interactions are shown.

Drugs	Interactions	Comments
PIs / NNRTIs		
Grapefruit juice [1]	IDV: 26 % ↓, APV ↓, SQV ↑	**Avoid combination** [1].
Vitamin C (1 g)	IDV 800 TID: Cmin IDV 32 % ↓ (not significant) [2]	**Avoid** high doses of vitamin C (> 1 g/d) over a long period.
Garlic capsules: allicin 300 mg QD	SQV 1200 TID: SQV ↓ 51 % [3]	**Avoid combination.**
Ginseng	Theoretically: PIs, NNRTIs ↓ [4]	**Avoid combination.**
St. John's Wort	PIs, NNRTIs ↓	**Avoid combination**.

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Cardiovascular drugs

Drugs	Interactions	Comments
PIs		
Calcium antagonists [1-3,6]	Theoretically: calcium antagonists ↑ Case report: LPV/r + nifedipine 30 mg BID: nifedipine toxicity: malaise, severe hypotension, oliguria, oedemas, creatinine increase	**Avoid combination** or reduce dose of calcium antagonists.
Diltiazem	ATV: diltiazem ↑ 200 %	Reduce diltiazem by 50 %.
Bosentan	Theoretically: PIs ↓	**Avoid combination** or TDM. Possible alternative: sildenafil (see PDE) [4,5].
Antiarrhythmics [1-3]	Theoretically: antiarrhythmics ↑ TPV/r: potential for severe, life-threatening arrhythmia	**Avoid combination** or possibly reduce dose of antiarrhythmics and monitor closely.
NNRTIs		
Calcium antagonists	Theoretically: calcium antagonists ↓↑	**See above.**
Bosentan	Theoretically: NNRTIs ↓	**See above.**
Antiarrhythmics	Theoretically: antiarrhythmics ↓↑	**Avoid combination** or start with low antiarrhythmics dose.

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Hypnotics

Drugs	Interactions	Comments
PIs		
Barbexaclone, phenobarbital	Theoretically: PIs ↓	**Avoid combination** or TDM.
Benzodiazepines (among others alprazolam, diazepam, midazolam, triazolam)	Theoretically: benzodiazepines ↑ Prolonged sedation, disorientation [1-4]	**Avoid combination:** alprazolam, midazolam, triazolam. Theoretical alternatives: oxaze-

		pam, lorazepam, temazepam.
NNRTIs		
Barbexaclone, phenobarbital	Theoretically: EFV ↓, NVP ↓, benzodiazepines ↓	See above.
Benzodiazepines [1,5]	Theoretically: benzodiazepines ↓	See above.
CCR5-Inhibitors		
Midazolam [6]	Maraviroc: no relevant clinical interactions	

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Immunosuppressants

Drugs	Interactions	Comments
PIs		
Cyclosporine, sirolimus, tacrolimus	Theoretically: immunosuppressants ↑ [1,2]	Dose adjustment of immunosuppressants: TDM.
Tacrolimus [1,2,4,5]	LPV/r: tacrolimus ↑ 2000 %	See above.
	NFV: tacrolimus levels on average 16-fold lower than in the HIV-negative control group [2,6]	See above.
Cyclosporine	SQV: cyclosporine 300 % ↑ [2,3]	See above.
NNRTIs		
Cyclosporine, sirolimus, tacrolimus	EFV: possibly immunosuppressants ↑ ↓ [7] NVP: theoretically immunosuppressants ↓	See above.
NRTIs		
Cyclosporine, tacrolimus	No data, possibly additive nephrotoxicity	**Avoid combination**, especially with pre-damaged kidney.

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Substitution (methadone, buprenorphine)

Drugs	Interactions	Comments
PIs		
Methadone [2,4-8, 15]	ATV/r, FPV/r, SQV/r: no clinically significant interaction	
	LPV/r: methadone ↓ 36 % [3] TPV/r: methadone ↓ 50 % [13] DRV/r: R/S-methadone ↓ 16/24 %, 25 % patients withdrawals [14]	LPV/r, NFV, TPV/r, DRV/r: monitor opiate withdrawals. If necessary, adjust dose of methadone.
Buprenorphine [17,18]	Case report: ATV/r + buprenorphine 8, 12, 14 mg: Buprenorphine ↑ toxicity: sedation, drowsiness, deficiency in concentration, reduced mental performance [16]	ATV/r: dose reduction of buprenorphine perhaps necessary.
	LPV/r + sustained-release bupropione 100 mg: buprenorphine ↓ 57 % active metabolite ↓ 50 % [17]	LPV/r: controversial data. Monitor for withdrawals. Dose increase of buprenophine perhaps necessary [18].
NNRTIs		
Methadone [3]	EFV: methadone ↓ 60 %	Increase dose of methadone. Dose reduction of methadone when stopping EFV therapy.
	NVP: methadone ↓, after 4 - 10 days: opiate withdrawals [1,9,10]	Increase methadone dose in 10 mg steps.
Buprenophine [19]	EFV: buprenorphine ↓ 49 % No withdrawals within 15 days	Withdrawals could also start after 15 days: monitoring.
NRTIs		
Methadone	AZT ↑ 41 % [3]	Monitor side-effects of AZT.
	ddI ↓ 41 % [11]	Clinical significance unclear.
	TDF: no interaction known [12]	

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Neuroleptics

Drugs	Interactions	Comments
PIs		
Among others chlorprothixene, flupendixol, haloperidol, pimozide, risperidone, sertindole	Theoretically: neuroleptics ↑ [1-4] TPV, DRV: potential for severe, life-threatening reactions such as cardiac arrhythmia	**Avoid combination:** pimozide. Other neuroleptics: monitor side-effects. Better: atypical neuroleptics (less anticholinergic effects).

NNRTIs		
Neuroleptics (see above) [1,2]	1. Theoretically: neuroleptics ↓↑ 2. Clozapine (active metabolite ↑) 3. pimozide: QT-prolongation	See above.

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Oral contraceptives

Drugs	Interactions	Comments
PIs		
Ethinylestradiol (EE), norethindrone (NE)	LPV/r: EE ↓ 42 %, NE ↓ 17 % [1,2] NFV: EE ↓ 47 % , NE ↓ 18 % [1] TPV/r: EE ↓ 50 % [1] DRV: EE ↓ 44 %, NE 14 % ↓ [1]	**Avoid combination.** No hormonal contraception. Use additional contraceptive methods.
	ATV: EE ↑ 48 % NE ↑ 110 % RTV: EE ↓ [2]	Monitor hormonal side-effects, possibly reduce dose.
	FPV/r: EE ↑ 32 %, NE ↑ 18 % APV ↓ 22 % (Cmin 20 % ↓) [1]	FPV/r: **avoid combination** as APV-levels may decrease.
	IDV: EE ↑ 24 %, NE ↑ 26 % [2]	No dose adjustment.
	SQV: no hormonal effect on SQV-levels at a single dose SQV [3]	Insufficient data. Use additional contraceptive methods.
NNRTIs		
Ethinylestradiol (EE), norethindrone (NE) [1,4]	EFV: EE ↑ 37 % [1]	Investigation incomplete.
	NVP: EE ↓ 29 %, NE ↓ 18 % [4]	Use additional contraceptive methods.
Medroxyprogesterone acetate [6]	EFV, NVP: no clinically significant interactions	
NRTIs		
TDF [5]	No clinically significant interactions	
CCR5-Inhibitors		
Ethinylestradiol 30 µg, levonorgestrel 100 µg [7]	Maraviroc 100 BID: no clinically significant interactions	

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Phosphodiesterase type 5 (PDE 5) inhibitors

Drugs	Interactions	Comments
PIs		
Sildenafil [1-5,7]	Sildenafil (single dose 100 mg) + RTV 500 BID: sildenafil ↑ 1000 % IDV: sildenafil (25 mg) ↑ 304 %	PIs: Sildenafil: 25 mg every 48h. IDV: sildenafil 12.5 mg every 48h [2,6].
Tadalafil	TPV/r, DRV/r: tadalafil ↑ [1]	DRV/r: tadalafil 10 mg every 72h.
Vardenafil	TPV/r, DRV/r: vardenafil ↑ [1] IDV: vardenafil ↑ 1600 %, IDV ↓ 30 % [2]	DRV/r: vardenafil 2.5 mg every 72h.
NNRTIs		
Sildenafil, tadalafil, vardenafil	Theoretically: PDE5 inhibitors ↓↑	Lowest initial dose. Adjust dose individually.
CCR5-Inhibitors		
PDE5-Inhibitors	No clinically significant interactions	

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Proton pump inhibitors (PPIs), H2-blockers, antacids

Drugs	Interactions	Comments
PIs		
PPIs, H2-blockers, antacids	Theoretically: ATV ↓ [3], NFV ↓ [13], IDV ↓ [1], TPV/r ↓ [1] (PIs require an acidic pH-value)	**Avoid combination:** PPIs. Take H2-blockers only within 10h interval and TDM. Antacids: 2h interval.
	No interactions: LPV/r tablets [9], FPV [6], DRV [5]	
Antacids	Theoretically: ATV ↓, IDV ↓ [1], TPV/r ↓ 25 - 29 % [11]	ATV, IDV, TPV/r: use antacids 2h before or after PI-intake.
PPIs: omeprazole 40 mg	ATV ↓ 76 % (Cmin 78 % ↓) [3]	ATV, NFV: **avoid combination.**
	NFV, active metabolite ↓ (Cmin ↓) [13]	
	IDV ↓ [8]	IDV: TDM.
	Healthy subjects: SQV ↑ 82 % [12], HIV+ patients: SQV ↑ 57 % [14]	Monitor side-effects of SQV.
H2-blocker: cimetidine 400 BID	Theoretically: cimetidine ↑ SQV 1200 TID vs. SQV 1200 BID: SQV ↑ 120 % [10]	PIs: **avoid combination.** Theoretical alternatives: ranitidine, famotidine.
Ranitidine	FPV/r: APV ↓ 18 - 30 % [1,7]	Interaction unlikely.
Famotidine	1. ATV 400 QD: ATV ↓ 40 - 50 % 2. ATV/r 300/100 QD: ATV-levels like ATV/TDF QD 3. ATV/r 400/100 QD: ATV-levels like ATV/r 300/100 QD [4]	ATV/r: H2-blockers with at least 10h interval and only in combination with boosted ATV.
Cisapride	Risk of QT-prolongation ↑ [1]	**Avoid combination.**
NNRTIs		
Cimetidine [2]	Theoretically: EFV, NVP ↑	Theoretical alternative: ranitidine.

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Statins (Lipid-lowering drugs)

Drugs	Interactions	Comments
PIs		
Lovastatin, simvastatin [1,9]	Theoretically: statins ↑ [3,6-8] NFV: simvastatin (20 mg) ↑ 506 % SQV/r 400/400 BID: simvastatin (40 mg) ↑ 3059 % [10] Case report: rhabomyolyse, acute renal failure with ATV 400, simvastatin (80 mg) [17]	**Avoid combination:** simvastatin, lovastatin [2]. Theoretical alternatives: pravastatin (DRV/r: low initial dose), fluvastatin.
Atorvastatin [1,5,9,10-12]	NFV < FPV/r < TPV/r: atorvastatin ↑ (10 mg) 75 - 936 % LPV/r: atorvastatin ↑ (20 mg) 590 % DRV/r: atorvastatin (10 mg) ↓ 15 % versus atorvastatin (40 mg) alone SQV/r 400/400 BID: atorvastatin (40 mg) ↑ 450 % [10]	Start with a low initial dose of atorvastatin (10 mg) [2]. Theoretical alternatives: pravastatin (DRV/r: low initial dose), fluvastatin.
Pravastatin	LPV/r: pravastatin (20 mg) ↑ 30 % DRV/r: pravastatin (40 mg) ↑ 80 - 500 % [16] SQV/r 400/400 BID: pravastatin (40 mg) ↓ 35 % [10]	DRV/r: low initial dose of pravastatin.
NNRTIs		
Atorvastatin, lovastatin, simvastatin	EFV: statins ↓ 40 - 58 % [3,7,13] NVP: theoretically: statins ↓ [4,14,15]	Theoretical alternatives: pravastatin, fluvastatin.

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Anti-tuberculosis drugs

Drugs	Interactions	Comments
PIs		
Rifampicin [1,2]	APV, IDV, LPV/r ↓ 75 - 89 % Theoretically: TPV, DRV ↓ SQV/r: 11 patients with symptoms of hepatocyte damage [2,3]	**Avoid combination.** Side-effects: e.g. increased transaminases, sickness, vertigo, erythema, swollen cheeks.

Rifabutin	Studies including unboosted PIs [1,2]: ATV, FPV, IDV, SQV, DRV: rifabutin ↑ 173 - 200 % IDV ↓ 33 % , SQV ↓ 40 % , DRV ↓ Studies including boosted PIs [1,2,4]: LPV/r, TPV/r: rifabutin ↑ 300 % NFV 750 TID + rifabutin 300 QD: rifabutin ↑ 207 %, NFV ↓ 32 % [2]	**Caution:** unboosted PIs because of subtherapeutic levels. PI/r approved dose + rifabutin 150 mg three times a week: If side-effects occur, reduce dose of rifabutin. Exception: NFV 1250 BID + rifabutin 150 mg QD.
NNRTIs		
Rifampicin	EFV ↓ 26 % [1,2,5,6] NVP: Cmin 68 % ↓ [2,7,8]	EFV: **possible.** EFV 800 QD; patients < 60 kg EFV 600 QD, TDM. NVP: **avoid combination.**
Rifabutin	EFV: rifabutin ↓ 38 % [1] NVP: no significant interactions [2]	EFV: rifabutin: 450 QD or 600 two or three times a week. NVP: no dose adjustment.
CCR5-Inhibitors		
Rifampicin	Maraviroc 100 BID + rifampicin 600 QD: maraviroc ↓ 67 % [9]	Maraviroc 600 BID.
Rifabutin		Maraviroc 600 BID [10].

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Antivirals

Drugs	Interactions	Comments
NRTIs		
Aciclovir	AZT: increased lethargy [2]	
	TDF: additive nephrotoxicity	TDF: monitor creatinine [1].
Cidofovir	AZT: haematotoxicity ↑ [3]	AZT: see probenecid. TDF.
	TDF: additive nephrotoxicity	Monitor creatinine [1].
Foscarnet	AZT: risk of anemia ↑ [4] (lower compared to ganciclovir)	AZT: **avoid combination, if possible.**
	TDF: additive nephrotoxicity	TDF: monitor creatinine [1].
Ganciclovir, Valaciclovir	AZT: haematotoxicity ↑ [5,6]	AZT: **avoid combination, if possible.** Alternatives: foscarnet + AZT, ganciclovir + ddI.
	ddI: risk of lactic acidosis and pancreatitis ↑ Ganciclovir i. v.: ddI ↑ 70 % [6,12,13]	ddI: closely monitor amylase, lipase and lactate.
	TDF: additive nephrotoxicity	TDF: monitor creatinine [1].
Interferons	AZT: haematotoxicity ↑ [7]	Possibly reduce AZT.
Ribavirin	AZT: in vitro AZT-antagonism; in vivo case reports about increasing viral load, increased risk of mitochondrial toxicity [8].	AZT: **avoid combination.**
	d4T: in vitro antagonism; in vivo risk of lactic acidosis and haematotoxicity ↑ [9-11]	d4T: **avoid combination.**
	ddI: in vitro: ddI + ribavirin: active metabolite ↑, lactic acidosis, pankreatitis ↑↑ [1]	Closely monitor amylase, lipase and lactate. ddI: **avoid combination.**
	TDF: no interactions known [14]	

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