CONTINUING MEDICAL EDUCATION

The Treatment of Patients With HIV

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SUMMARY

Background: Infection with the human immunodeficiency virus (HIV) remains a major medical challenge.

Methods: Selective literature review, including the current German/Austrian, European, and American guidelines on the treatment of HIV infection in adults.

Results: In Germany, 3000 persons become infected with HIV each year; in 2009, 67 000 persons in Germany were living with HIV. When highly active antiretroviral therapy (HAART) is initiated in time, patients can achieve a nearly normal life expectancy. Nonetheless, in Germany as elsewhere, 30% of patients receive the diagnosis of HIV infection only when they have reached the AIDS stage of the disease or are suffering from advanced immunodeficiency. HAART should be started, at the latest, when the CD4-positive helper cell count drops below 350/µL. Primary drug resistances, accompanying illnesses, and the patient's living circumstances must all be taken into account in the selection of antiretroviral drugs. The goal of treatment is lasting suppression of HIV-RNA to below 50 copies per milliliter of plasma.

Conclusions: HIV testing should be offered to all patients at high risk for HIV infection and all persons newly diagnosed with a sexually transmitted disease. As persons with HIV grow older, their treatment is complicated by increasing comorbidity and requires increased vigilance for possible drug interactions.

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The first cases of acquired immunodeficiency syndrome (AIDS) appeared in the USA in the 1980's, and the disease was soon determined to be due to a newly discovered virus, which was named "human immunodeficiency virus" (HIV). Since then, this infectious disease has spread around the world, with an estimated 33 million persons living with HIV worldwide in 2008 (e1–e4). In Germany, about 67 000 persons were living with HIV in 2009. The annual number of new cases of HIV infection in Germany was on the rise from 2000 onward but has, fortunately, restabilized since 2007 at about 3000 per year (1).

In 1996, ten years after the discovery of HIV, the concept of treating HIV infection with highly active antiretroviral treatment (HAART) was introduced (e5). In HAART, a combination of antiretroviral drugs is used to bring about lasting suppression of HIV replication and thereby prevent the consequences of uncontrolled HIV infection—in particular, the loss of CD4-cell-mediated immunity. Theoretical considerations, as well as the clinical experience to date, suggest that HAART can be a successful method of lifelong treatment for some patients. According to mathematical models, patients' life expectancy may become nearly normal if antiretroviral therapy is started in the early stage of HIV infection (stage A). For example, a 25-year-old, HIV-positive man who is not a drug abuser and starts receiving HAART today has a projected life span of 77.7 years; if he were HIV-negative, his projected life span would be 78.1 years (2). If HAART is started later on, however, life expectancies are much shorter. In another study, the projected life span of a 20-year-old HIV-positive man was determined to be 70 years if the helper cell count was over 200/µL at the start of HAART, but only 62 years for counts between 100/µL and 199/µL, and 52 years for a count under 100/µL (3). Despite the availability of effective treatment, and despite many public education campaigns, HIV infection is still often diagnosed too

Prevalence

About 67 000 persons in Germany are infected with HIV. About 30% of all patients receive the diagnosis of HIV infection only when they have reached the AIDS stage or when their helper cell count is below 200/µL.

BOX 1

Clinical categories (A–C) for classifying the natural course of HIV infection*[1]

- Category A: asymptomatic disease, acute HIV, or PGL
  - HIV positivity without any clinical signs or symptoms
  - acute, symptomatic (primary) HIV infection
  - persistent, generalized lymphadenopathy (PGL)
- Category B: disease manifestations or illnesses that, although not AIDS-defining, nevertheless indicate impaired cellular immunity and are attributable to HIV infection
  - bacillary angiomatosis
  - pelvic inflammatory disease, esp. complications of tubal and ovarian abscesses
  - herpes zoster affecting multiple dermatomes, or recurrent herpes zoster in a single dermatome
  - idiopathic thrombocytopenic purpura (ITP)
  - constitutional manifestations such as fever above 38.5°C or diarrhea for longer than 1 month
  - listeriosis
  - oral hairy leukoplakia (OHL)
  - oropharyngeal or vulvo-vaginal candidiasis that is either chronic (>1 month) or intractable
  - cervical dysplasia or carcinoma in situ
  - peripheral neuropathy
- Category C: AIDS-defining illnesses
  - candidiasis of the bronchi, trachea, lungs, or esophagus
  - CMV infection (except of the liver, spleen, or lymph nodes)
  - HIV-associated encephalopathy
  - herpes simplex infection (for longer than 1 month; bronchitis, pneumonia, esophagitis)
  - histoplasmosis (disseminated or extrapulmonary)
  - isosporiasis, chronic, intestinal, for longer than 1 month
  - Kaposi's sarcoma
  - coccidioidomycosis, disseminated or extrapulmonary
  - cryptococcosis, extrapulmonary
  - cryptosporidiosis, chronic (longer than 1 month), intestinal
  - Burkitt's lymphoma
  - immunoblastic lymphoma
  - primary cerebral lymphoma
  - atypical mycobacterial infection
  - tuberculosis
  - Pneumocystis jirovecii pneumonia (PCP)
  - recurrent episodes of bacterial pneumonia (more than two in a single year)
  - progressive multifocal leukoencephalopathy
  - recurrent Salmonella sepsis
  - cerebral toxoplasmosis
  - wasting syndrome
  - invasive cervical carcinoma

*[1] According to the US government's Centers for Disease Control and Prevention (CDC) (24)

late, sometimes with drastic consequences: some patients, for example, already have AIDS by the time they are found to be HIV-positive (1). Persons at elevated risk for HIV infection should, therefore, be routinely offered HIV testing. Knowing about HIV-associated conditions can help physicians diagnose HIV early and initiate HAART in timely fashion.

Methods

In this article, we present current aspects of the epidemiology and treatment of HIV infection in the light of a selective review of the literature, including the German/Austrian, European, and American guidelines. The relevant literature was retrieved by a search on the terms "HIV guidelines" "ART guidelines", and "HAARTguidelines."

Learning objectives

This article should enable the reader to

- become acquainted with the epidemiology of HIV infection,
- know its natural course,
- and understand the main features of its treatment.

The early detection of HIV infection

It is thought that half of all cases of HIV infection in Germany are detected too late, i.e., after the time that retroviral treatment should have been initiated (1). One-third of all patients already have an AIDS-defining disease, or advanced immunodeficiency with a CD4 cell count under 200/µL, at the time of diagnosis. For patients with undiagnosed HIV infection, there is a real, but incalculable, risk of serious adverse consequences until HIV is diagnosed. Early diagnosis is also good for the population at large, as appropriate steps taken thereafter can markedly lessen the spread of HIV to other persons (4). These steps include:

- protected sexual intercourse,
- the use of single-use needles and other equipment,
- and effective treatment of HIV infection.

In Germany, HIV infection is most likely to be diagnosed late in older persons without any known or ascertainable risk of transmission who are immigrants from countries with a high prevalence of HIV, or who are of homosexual orientation (1). HIV is often diagnosed in such persons only after one or more earlier contacts with physicians in which the diagnosis was missed. In a recent study of persons in South Carolina (USA) whose HIV infection was diagnosed late, it was found that just

Diagnosis

Early diagnosis of HIV infection is important, because it markedly lowers the chance of transmission of HIV infection to other persons.

Early detection

It is thought that half of all cases of HIV infection in Germany are detected too late, i.e., after the time that retroviral treatment should have been initiated.

under 20% of them had previously had clinical manifestations that might have aroused suspicion of HIV infection (5).

Classic AIDS-defining illnesses such as *Pneumocystis jirovecii* pneumonia (PCP), cerebral toxoplasmosis, and Kaposi's sarcoma, are now well known *(Box 1, Figure)*. There are other HIV-associated conditions, however, that should lead to the offering of an HIV test, including herpes zoster, oral hairy leukoplakia, oral thrush, and sexually transmitted diseases of any type *(Boxes 1 and 2)*. In Germany, as in some other countries, an HIV test can be performed only with the patient's consent (6).

The initiation of treatment

The best time to begin treatment remains unknown. The medical societies' frequently updated recommendations reflect, on the one hand, the improving side effect profiles and ease of administration of HIV drugs, and, on the other hand, a new appreciation of the dangers of uncontrolled HIV infection, even if the helper cell count is high. Thus, the recommendations issued in recent years have tended to push the start of treatment earlier and earlier *(Table 1)*. There is a consensus that all patients with HIV infection in CDC categories B and C *(see Box 1)* should be treated, regardless of their viral titers and CD4 cell counts (CDC, the US government's Centers for Disease Control and Prevention).

Even when the CD4 cell count is over 200/µL, in which case the risk of AIDS or another HIV-associated disease is low, uncontrolled HIV infection still poses a risk to health. In one study, patients whose HAART was begun earlier (when the CD4 cell count was above 350/µL) were less likely to have a myocardial infarction than those whose HAART was begun later (below 250/ µL) (9 cases versus 0 cases, with a combined hazard ratio of 7.0 for all non-AIDS-associated diseases) (7). The prognosis of chronic hepatitis C infection is significantly worsened by concurrent HIV infection, but HAART significantly lowers mortality and slows the progression of hepatic fibrosis (8). Several studies have shown that well-preserved immune function with a high helper cell count is associated with slower progression of hepatic fibrosis (9); thus, the early initiation of HAART is generally recommended to all patients who are co-infected with HIV and a hepatitis virus. Furthermore, recent data from the field of cancer epidemiology show that the risk of developing certain

BOX 2

Circumstances in which HIV testing should be offered

- Elevated risk of HIV infection
  - men who have sex with men
  - professional sex workers
  - frequent changes of sex partners (more than 5 per year with anal or vaginal penetration)
  - drug abusers
  - immigrants from countries with a high prevalence of HIV infection, e.g., countries of sub-Saharan Africa
- New diagnosis of a sexually transmitted disease
  - syphilis
  - gonorrhea
  - lymphogranuloma venereum
  - chancroid
  - chlamydia
  - hepatitis B
  - human papilloma virus
  - herpes simplex II
  - trichomoniasis
  - crab lice
  - granuloma inguinale
  - hepatitis A, hepatitis C (when sexually transmitted)

HIV testing should be offered to patients in any of the following situations:

- Frequent changes of sexual partners
- Drug abuse
- Professional sex workers
- Immigrants from countries where HIV is highly prevalent
- Men who have sex with men

HIV testing should additionally be offered in the following situation:

- New diagnosis of a sexually transmitted disease

TABLE 1

Current treatment recommendations of the German/Austrian,*1 European,*2 and American*3 HIV societies

German/Austrian Recommendations	European recommendations	American recommendations
Symptomatic HIV Infection		
Treatment indicated regardless of CD4 cell count and HIV-RNA	Treatment indicated regardless of CD4 cell count and HIV-RNA	Treatment indicated regardless of CD4 cell count and HIV-RNA
Asymptomatic HIV infection		
– CD4 cell count ≥ 500/µL, presence of additional criteria Case-by-case decision – HIV-RNA >100 000 copies/mL Frequent monitoring of CD4 count	– CD4 cell count ≥ 500/µL and comorbidity Offer treatment – HIV-RNA >100 000 copies/mL Frequent monitoring of CD4 count – Individual reasons Offer treatment	– CD4 cell count ≥ 500/µL and pregnancy, HIV nephropathy, HBV infection with treatment indication Treatment indicated – Regardless of comorbidity Treatment recommended or to be considered*4
– CD4 cell count >350–500/µL and one or more additional criteria Treatment recommended Additional criteria for starting treatment: – HIV-RNA >100 000 copies/mL, pregnancy, age >50 years, HCV or highly replicative HBV co-infection, high cardiovascular risk (Framingham risk >20% in ten years), drop in CD4 cell count, plasma viremia >100 000 copies/mL, reduction of infectiveness*6	– CD4 cell count 350–500/µL – HCV coinfection, HBV infection with treatment indication, HIV nephropathy or other type of end organ damage Treatment recommended – Rapid drop in CD4 cell count, HIV-RNA >100000 copies/mL, age >50 years, pregnancy, high cardiovascular risk, malignant neoplasia Treatment to be considered	– CD4 cell count 350–500/µL Treatment moderately to strongly recommended*5
– CD4 cell count <350/µL Treatment indicated	– CD4 cell count 200–350/µL Treatment indicated – CD4 cell count <200/µL Start treatment immediately	– CD4 cell count <350/µL Treatment indicated

*1 www.daignet.de
*2 www.europeanaidsclinicalsociety.org
*3 www.aidsinfo.nih.gov
*4 50% of the experts voted for starting HAART, 50% for optional initiation of treatment
*5 55%of the experts voted for a strong recommendation to start treatment, 45% for a moderate recommendation
*6 50% of the experts voted for inclusion of this criterion

Indication for pharmacotherapy

HAART should be initiated when the CD4 helper cell count drops below 350/µL.

Caveat

When selecting the appropriate antiretroviral medications for the patient, the physician must consider any accompanying illnesses, and whether the patient (if female) wants to have children.

kinds of cancer already begins to rise when the CD4 cell count falls below 500/µL (10).

There is no consensus about the proper time to begin antiretroviral treatment in patients whose CD4 cell count exceeds 350/µL. Some American experts go so far as to recommend treatment to every HIV-positive patient (11), but European (12), including German (13), experts are more conservative and do not recommend treating patients whose CD4 cell count is above 350/µL, except under special circumstances *(Table 1)*. On the other hand, the guidelines have become increasingly individualized, i.e., earlier initiation of treatment is now recommended for high-risk patients who have certain accompanying illnesses or a greater likelihood of progression of HIV disease (e.g., hepatitis co-infection, advanced age).

Therapeutic trials for acute HIV infection have yielded conflicting results to date; thus, for the time being, treatment in such cases should be given only in the setting of a controlled trial. As the treatment of HIV infection is a rapidly changing field, we recommend that treatment should be sought at specialized centers (medical practices or university outpatient clinics specializing in HIV treatment; cf. www.dagnae.de or www.daignet.de for centers in Germany).

The goal of treatment

The treatment of HIV poses a special challenge, as the virus replicates very rapidly (an estimated 10^{10} virus particles, or more, are produced daily) and mutates frequently (ca. 1 new mutation per replication cycle), without any major loss of function of most of its constituent proteins. HIV treatment can succeed over the long term only through lasting, maximal suppression of the viral burden, which not only limits viral replication, but also prevents the development of resistance to the antiviral drugs that are used. Experience has shown that lasting suppression of HIV-RNA below the detection threshold of currently used quantitative tests (20 to 50 copies/mL) is adequate for this purpose (13, 15).

Inadequate control of the viral burden (i.e., an HIV-RNA titer that does not drop below 400 copies/mL) raises the likelihood of selection of drug-resistant mutant viruses that can impair the success of treatment in the intermediate term (16). Patient compliance is also very important for long-term therapeutic success. Fewer than 5% of patients who begin HAART sustain a virological failure of treatment in the first year. Regular and continuous taking of HAART can effectively

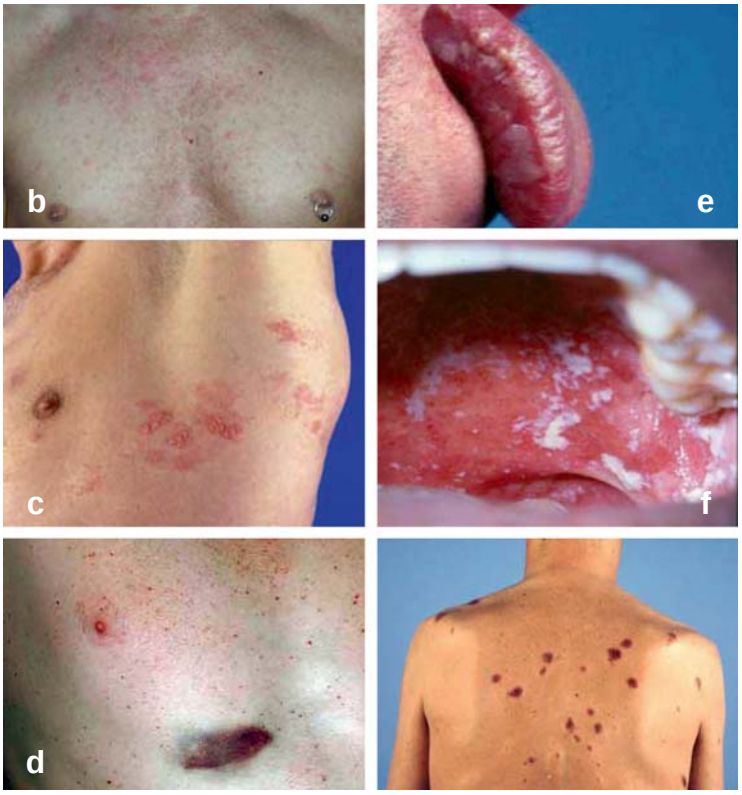

Figure: HIV/AIDS-associated diseases

(a) 20% to 50% of patients with an acute retroviral infection have a characteristic maculopapular rash that is most prominent on the trunk. (b) Herpes zoster on the chest. (c) Petechiae and bruises in HIV-associated thrombocytopenia. (d) EBV-associated oral hairy leukoplakia. (e) HIV-associated thrush (oral candidiasis). (f) Active (soft) foci of Kaposi's sarcoma on the back.

Treatment monitoring

When HAART is begun, the patient should be monitored for the development of adverse effects, and the result of treatment should be checked at four weeks.

The goal of treatment

Lasting suppression of HIV-RNA below the detection threshold of current quantitative assays (i.e., below 20 to 50 copies/mL).

TABLE 2

Recommendations of the German and Austrian AIDS societies for the first-line treatment of HIV infection in adults *[1]

Combination drug 1		Combination drug 2
N(t)RTI nucleoside-/nucleotide combinations – tenofovir/emtricitabine – abacavir*[5] /lamivudine	+	NNRTI – efavirenz*[2] – nevirapine*[3] protease inhibitors*[4] – atazanavir/r – darunavir/r – fosamprenavir/r – lopinavir/r – saquinavir/r (Alternative, BII) integrase inhibitors – raltegravir

*[1] A combination of two drugs is recommended for the treatment of HIV infection. The choice of drugs is based on the patient's current drug resistances (if any), accompanying illnesses, and personal circumstances [modified from (11)]

*[2] Not to be given to women who are pregnant or who want to become pregnant

*[3] Use with caution in the presence of liver disease, men with more than 400 CD4+ T-cells/µL, and women with more than 250 CD4+ T-cells/µL. Evidence grade AII for all recommendations except for saquinavir/r; clear recommendation on the basis of surrogate marker studies or cohort data;

*[4] whenever protease inhibitors are used for first-line treatment, the additional administration of low-dose ritonavir(/r) is recommended to improve the pharmacokinetic profile;

[5] administration of abacavir after negative screeining for HLAB 5701, use with caution in the presence of viremia > 10^5 copies/mL and elevated cardiovascular risk (Framingham score >20% /10 years);

BII, generally advisable on the basis of surrogate marker studies or cohort data

N(t)RTI, nucleosidal / nucleotidal reverse transcriptase inhibitors;
NNRTI, non-nucleosidal reverse transcriptase inhibitors

prevent the development of resistance. Forgetting to take tablets more than twice in one month elevates the risk of virological treatment failure by a factor of 2.8, in comparison to patients who never forget to take their medicine (14). Thus, therapeutic success is promoted by a physician-patient relationship founded on mutual trust, with extensive patient education about the nature and properties of the drugs to be taken, their specific side-effect profile, and the results than can be expected from them. Once the physician and the well-informed patient have made a joint decision to proceed to antiretroviral treatment, the goal should be maximal suppression of HIV replication, as this is the decisive criterion for long-term success.

The choice of antiretroviral drugs

As resistance develops rapidly when a single drug is given (monotherapy), antiretroviral drugs are usually given in combination. The drugs to be used should be chosen on the basis of the patient's particular occupational and social characteristics, and any accompanying illnesses. As a rule, the recommended type of drug combination for patients who have not yet been treated for HIV consists of two nucleosidal (nucleotidal) reverse transcriptase inhibitors (N(t)RTI), together with a non-nucleosidal reverse transcriptase inhibitor (NNRTI), a protease inhibitor (PI) boosted with ritonavir, or an integrase inhibitor (INI). The main combinations that are currently recommended by the German and Austrian AIDS societies for antiretroviral treatment in previously untreated adults are listed in *Table 2*.

The initiation of antiretroviral treatment should always be preceded by genotypic HIV resistance testing for the detection of primary drug resistance. Primary resistance is widespread in Germany, as elsewhere: in 2005, for example, 9% of all newly diagnosed cases of HIV infection in the federal state of North Rhine–Westphalia were found to have at least one viral mutation that was associated with resistance to an antiretroviral drug (17).

Any concurrent illnesses and, for women of childbearing age, the patient's desire to have children must be taken into account when antiretroviral drugs are chosen. Efavirenz should not be given to women who want to have children, as it is associated with embryonal neural tube defects (23). Physicians should also exercise special caution when giving efavirenz to mentally ill patients, as this drug is more likely to cause psychiatric complications in this patient group (19). Nevirapine is an NNRTI that can be used as an alternative to efavirenz, but it is more likely to cause strong cutaneous allergic reactions and hepatotoxicity in patients with relatively high CD4 counts. Thus, its use is recommended only for women with a CD4 count below 250/µL and men with a CD4 count below 400/µL.

When HAART is begun in a patient with chronic hepatitis, liver function tests should be performed frequently, as the transaminases may rise. If chronic hepatitis B infection is present, the indication for treating hepatitis B should be considered. If a highly replicative HBV infection (> 2000 IU/mL) with elevated transaminases is present, or if there is advanced hepatic fibrosis, the antiretroviral drugs that are used should also be antiviral inhibitors of HBV polymerase (e.g., tenofovir combined with emtricitabine or lamivudine). Patients with chronic hepatitis C infection for whom pegylated interferon/ribavirin treatment is planned should not be

Adjustment of treatment

If HAART brings the plasma HIV-RNA titer below 50 copies/mL, the treatment should be monitored by further checks of the plasma HIV-RNA titer every three to six months.

Risk of liver damage

Liver function tests should be closely monitored in patients with chronic hepatitis who are receiving HAART, as some HIV drugs are hepatotoxic.

given didanosine, stavudine, or zidovudine, as these drugs exhibit enhanced toxicity when given together with ribavirin.

N(t)RTI doses may need to be adjusted in the presence of renal insufficiency, as these drugs are mainly eliminated by the renal route. Any other medications that the patient is taking should be meticulously checked for possible interactions with antiviral drugs. NNRTI and PI are mainly metabolized by the cytochrome P450 system, and this can have major implications both for HAART and for other medications that are taken at the same time. Thus, depending on the particular antiretroviral drug combination taken by the patient, the concomitant use of (for example) ergotamine, statins, proton-pump inhibitors, antihypertensive or antiarrhythmic medications, or even St. John's wort can produce drug levels that are either subtherapeutic (lack of antiviral efficacy, increased risk of drug resistance) or toxic. Proton-pump inhibitors (PPI) can alter the solubility of antiretroviral drugs, e.g., atazanavir, with clinically relevant effects. Possible drug interactions can now be checked through a variety of Internet-based services (see www.ifi-interaktions-hotline.de or www.hiv-druginteractions.org) (20, 21).

Treatment monitoring

A first evaluation of the response to HAART should be performed four weeks after it is initiated. By this time, the HIV titer should have diminished by a factor of at least 100; if not, drug resistance, inadequate drug absorption, or poor compliance should be suspected. If the viral titer shows a favorable response when first checked, then it can be rechecked every three months thereafter. Effective treatment should suppress the viral titer below the threshold of detection (<50 copies/mL) within six months of the initiation of HAART.

Patients whose immune function is very rapidly reconstituted by HAART, or whose CD4 helper cell count was very low (below 50/ µL) when HAART was initiated, are at risk for the development of immune reconstitution inflammatory syndrome (IRIS). This paradoxical condition is characterized by the worsening of a previously unrecognized underlying disease, or by the new clinical manifestation of an opportunistic infection, even though the helper cell count is higher than before. IRIS is thought to reflect an excessive immune response to an overt or subclinical antigenic stimulus ("overshoot") on the part of an immune system that has just regained its ability to respond. Thus, for example, in a patient with concomitant hepatitis C infection, the transaminases may rise after HAART is begun; or, in a patient with asymptomatic HIV infection, but a low CD4 cell count, tuberculosis may become clinically overt only after the CD4 count has been raised by HAART.

Changes and interruptions of HAART

The antiviral regimen may need to be changed if it is ineffective, if side effects arise, or if new drugs become available that are more effective, better tolerated, or easier to administer.

In virological treatment failure, the plasma virus load may be initially suppressed below the detection threshold of 50 copies/mL, as desired, only to rise above this threshold again multiple times. HAART should then be changed to include as many retroviral drugs as possible that are (still) effective against HIV in the individual patient; these drugs should be chosen on the basis of genotypic HIV resistance testing. Moreover, poor compliance should be considered as a possible differential diagnosis of virological treatment failure. An attempt should be made to improve compliance, if this is the underlying problem.

In Europe, fewer than 10% of all changes in HAART regimen are occasioned by virological treatment failure, while more than half are attributable to drug side effects and to the patients' wishes (22). As patient compliance with continuous HAART is the main prerequisite for successful treatment, the patients' complaints and wishes must always be carefully considered. Side effects and special circumstances will sometimes make interruptions in treatment unavoidable. If such events can be foreseen for an individual patient, then the choice of antiretroviral drugs should take these drugs' different half-lives into account to avoid the functional equivalent of monotherapy with a high risk of drug resistance (NNRTIs).

Over the course of HAART, many patients feel the desire to take a holiday from treatment. One concept that has been proposed involves basing HAART on the CD4 count: if the count exceeds 350/µL, the treatment is paused; if and when the count drops below 250/µL again, the treatment is restarted. Multiple studies have shown, however, that the CD4 cells "won" by HAART generally fall back again to the previous nadir within a short time. Recently, a large-scale international trial of treatment based on the CD4 count had to be prematurely terminated, because significantly more AIDS-

Immune reconstitution inflammatory syndrome (IRIS)

Patients whose immune function is very rapidly reconstituted by HAART, or whose CD4 helper cell count was very low when HAART was initiated, are at risk for IRIS.

Interruption of treatment

Interruption of treatment should be avoided, as it has been found to elevate both HIV-associated mortality and overall mortality.

defining events, non-AIDS-defining events (cardiovascular, renal, and hepatic), and deaths were observed in patients in the CD4-based arm of the trial than in the patients who took HAART continuously regardless of their CD4 count (23). Thus, deliberately interrupting HAART is risky and generally not recommended.

Main conclusions for clinical practice

Very effective treatment for HIV infection is now available in Western industrialized countries. The proper time to begin antiretroviral combination therapy should be determined individually on the basis of the patient's HIV-RNA concentration and CD4 cell count (surrogate markers), clinical stage of HIV infection, personal characteristics, and accompanying illnesses, if any. All such treatments should be preceded by genotypic HIV resistance testing to rule out primary resistance. The treatment of HIV infection is a complex matter; thus, consultative advice from a specialized HIV treatment center with the appropriate experience is always indicated.

Conflict of interest statement

Dr. Vogel has received lecture honoraria and financial support for travel to scientific meetings from Abbott, Tibotec, Gilead, BMS, ViiV Healthcare, Roche, Boehringer-Ingelheim, and Merck.

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Prof. Rockstroh has received lecture honoraria, financial support for travel to scientific meetings, and payment for service on advisory boards from Abbott, Tibotec, Gilead, BMS, ViiV Healthcare, Roche, Boehringer-Ingelheim, and MSD.

Prof. Sprengler has received payment for service on advisory boards from Gilead, BMS, Roche, and Novartis.

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A word to the wise

The treatment of HIV infection is a complex matter. Consultative advice from a specialized HIV treatment center with the appropriate experience is always indicated.

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For eReferences please refer to:
www.aerzteblatt-international.de/ref2810

Case Illustration available at:
www.aerzteblatt-international.de/10m0507

FURTHER INFORMATION ON CME

This article has been certified by the North Rhine Academy for Postgraduate and Continuing Medical Education.

Deutsches Ärzteblatt provides certified continuing medical education (CME) in accordance with the requirements of the Medical Associations of the German federal states (Länder). CME points of the Medical Associations can be acquired only through the Internet, not by mail or fax, by the use of the German version of the CME questionnaire within 6 weeks of publication of the article. See the following website: cme.aerzteblatt.de

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The solutions to the following questions will be published in issue 37/2010.

The CME unit "The Diagnosis and Treatment of Deep Infiltrating Endometriosis" (issue 25/2010) can be accessed until 6 August 2010.

For issue 33/2010 we plan to offer the topic
"The Post Mortem Examination."

Solutions to the CME questionnaire in issue 21/2010:

Anders et al.: "Decubitus Ulcers: Pathophysiology and Primary Prevention."

Answers: 1b, 2d, 3e, 4b, 5b, 6d, 7e, 8a, 9c, 10c

Please answer the following questions to participate in our certified Continuing Medical Education program. Only one answer is possible per question. Please select the answer that is most appropriate.

Question 1

How many people in Germany are infected with HIV?

a) About 35 000
b) About 70 000
c) About 150 000
d) About 300 000
e) About 500 000

Question 2

What percentage of HIV-positive patients in Germany receive the diagnosis of HIV infection when they are already in the AIDS stage or already have a markedly low CD4 helper cell count (below 200/µL)?

a) 50%
b) 30%
c) 25%
d) 20%
e) 15%

Question 3

Untreated HIV infection is associated with an indirect risk for which of the following conditions?

a) Arthritis
b) Hypertension
c) Diabetes
d) Myocardial infarction
e) None of the above

Question 4

In which of the following situations, revealed by clinical history-taking, should an HIV test be recommended?

a) Frequent change of sexual partner
b) Newly diagnosed syphilis
c) Oral hairy leukoplakia
d) Immigration from sub-Saharan Africa
e) All of the above

Question 5

When do the German/Austrian guidelines recommend treatment for HIV infection?

a) When the CD4 helper cell count is below 600/µL
b) When the CD4 helper cell count is below 500/µL
c) When the CD4 helper cell count is below 350/µL
d) When the CD4 helper cell count is below 200/µL
e) Only in the AIDS stage or when the patient has other HIV-associated diseases

Question 6

Which of the following is an AIDS-defining condition?

a) Listeriosis
b) Cerebral toxoplasmosis
c) Peripheral neuropathy
d) Bacillary angiomatosis
e) Pruritus

Question 7

Four weeks ago, you sent a patient to be admitted to the hospital because of suspected Pneumocystis jirovecii pneumonia (PCP). The patient was found to be HIV-positive, PCP was treated, and, one week ago, HAART was initiated. The patient now comes to you and asks when the first check of the HIV virus count should be performed. What do you reply?

a) One week after the start of HAART
b) Two weeks after the start of HAART
c) Four weeks after the start of HAART
d) Eight weeks after the start of HAART
e) Twelve weeks after the start of HAART

Question 8

A 32-year-old, HIV-positive woman comes to your office and tells you that a home pregnancy test was positive yesterday. Her next appointment at the HIV outpatient clinic is in five weeks. What HIV drug is contraindicated during pregnancy because of the risk of development of a neural tube defect in the embryo?

a) Efavirenz
b) Nevirapine
c) Tenofovir
d) Lamivudine
e) Lopinavir/ritonavir

Question 9

An HIV-positive man whom you are following began HAART six months ago. His plasma viral burden is 1230 copies/mL. How low should his plasma HIV-RNA count be by now?

a) <8000 copies/mL
b) <4000 copies/mL
c) <400 copies/mL
d) <50 copies/mL
e) <5 copies/mL

Question 10

A 53-year-old HIV-positive man is admitted to the hospital because of acute renal failure. He has been undergoing HAART for several years. His creatine kinase (CK) value is above 20 000 IU/L. He sustained a myocardial infarction six weeks ago and has been treated with a statin (among other medications) since then to achieve a more favorable cholesterol level. What is now the most important element of the differential diagnosis?

a) Rhabdomyolysis due to a drug interaction between the statin and HAART
b) Contrast-medium-induced renal failure after cardiac catheterization
c) HIV-associated myopathy
d) Autoimmune-associated myositis
e) HIV-associated nephropathy

CONTINUING MEDICAL EDUCATION

The Treatment of Patients With HIV

Martin Vogel, Carolynne Schwarze-Zander, Jan-Christian Wasmuth, Ulrich Spengler, Tilman Sauerbruch, Jürgen Kurt Rockstroh

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CONTINUING MEDICAL EDUCATION

The Treatment of Patients With HIV

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Case Illustration

A 28-year-old woman presents with fever and cough. She has never been seriously ill before. Three weeks ago, she had tonsillitis and shingles. She has lost 10% of her body weight involuntarily over the past three months. Physical examination reveals oral thrush and hairy leukoplakia. The lungs are clear to auscultation. The axillary and inguinal lymph nodes are mildly enlarged. A chest x-ray is unremarkable. Laboratory tests reveal an elevated level of lactate dehydrogenase, anemia, and an elevated erythrocyte sedimentation rate. The oxygen saturation in arterial blood is 95%.

The unusual history of infection (shingles at age 28), along with the physical findings, arouses the suspicion of an immune deficiency. The initial manifestation of a primary immune deficiency at age 28 would be rare. Among the possible causes of acquired immune deficiency, HIV infection is the most likely diagnosis, as the patient has not been under cytotoxic chemotherapy or any other type of immunosuppressive treatment. Further diagnostic testing confirms HIV positivity, a CD4 cell count of 60/µL, and *Pneumocystis jirovecii* pneumonia (PCP). She is diagnosed as suffering from HIV infection in the AIDS stage, with HIV-associated wasting syndrome.

The PCP is treated, and highly active antiretroviral treatment (HAART) is initiated. The patient feels much better and becomes asymptomatic. After three and a half years of HAART, her helper cell count climbs to 304/µL.

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