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 should become an inherent part of current therapeutic concepts of HIV infection.

Coronary artery disease (CHD)

Premature atherosclerosis in HIV-infected patients was described shortly after the introduction of antiretroviral therapy. The observation was supported by an autopsy trial, reporting a significant increase of atherosclerotic plaques over the last two decades in HIV-infected individuals (Morgello 2002). These data are further supported by the detection of increased coronary artery calcification scores 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).

However, the total incidence of myocardial infarction was small in both 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.

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.

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.

Table 1: Prevention of coronary heart disease

<p>| | |</p>
<table>
<thead>
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<tbody>
<tr>
<td>1)</td>
<td>Cease Smoking</td>
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<tr>
<td>2)</td>
<td>Make healthy food choices</td>
</tr>
<tr>
<td>3)</td>
<td>Normalization of lipids</td>
</tr>
<tr>
<td></td>
<td>a. LDL-Cholesterol:</td>
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<tr>
<td></td>
<td>- low risk (0-1 risk factors): &lt; 160 mg/dl (4.14 mmol/l)</td>
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<tr>
<td></td>
<td>- intermediate risk (2 or more risk factors): &lt; 130 mg/dl (3.36 mmol/l)</td>
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<tr>
<td></td>
<td>- high risk (i.e. CHD or diabetes mellitus): &lt; 100 mg/dl (2.59 mmol/l)</td>
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<tr>
<td></td>
<td>b. HDL-Cholesterol: &gt; 35 mg/dl (0.90 mmol/l) (increased risk &gt; 40 mg/dl)</td>
</tr>
<tr>
<td></td>
<td>c. Triglycerides: &lt; 200 mg/dl (5.17 mmol/l) (increases risk &lt; 150 mg/dl)</td>
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<tr>
<td>4)</td>
<td>Optimize blood glucose value (HbA1c &lt; 6.5 %)</td>
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<tr>
<td>5)</td>
<td>Reduce alcohol consumption (&lt; 15 g/d)</td>
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<tr>
<td>6)</td>
<td>Regular exercise training (1-2 h per week)</td>
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<tr>
<td>7)</td>
<td>Normalization of weight (BMI of 21-25 kg/m²)</td>
</tr>
<tr>
<td>8)</td>
<td>Optimize blood pressure (systolic: &lt; 130 mmHg, diastolic: &lt; 85 mmHg)</td>
</tr>
</tbody>
</table>

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
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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. It corresponds to a dilated and less contractile left ventricle.

**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 cardiomyocytes, 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) 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). 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 scar tissue or coronary artery calcification. 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 (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, 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). 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. Pericardiectomy might be an option in palliative care.

**Cardiac arrhythmias**

Cardiac arrhythmias can depend on medication. Antiretroviral drugs, e.g. 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” tachy-
cardia (Castillo 2002). Further drug combinations such as a macrolide and a chino-

lone 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 concen-
trations 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 staphylo-
coccus 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 As-
pergillus fumigatus, Candida species or Cryptococcus neoformans and are associ-
ated with a worse outcome (Martin-Davila 2005).

Even if non-drug-abusing HIV patients are not more susceptible to infective endo-
carditis, 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 diffi-
cult, an antibiotic therapy has to be started early, even without the microbiology
results.

In most cases, previously damaged valves are affected. Therefore, antibiotic pro-
phylaxis is recommended in all persons with a previously damaged endocardium
and planned interventional procedure, e.g. dental work or operations on the respira-
atory 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 myo-
carditis but in abscesses. Several opportunistic pathogens including toxoplasma and
trypanosomes have been reported to causes abscesses in the heart. These manifesta-
tions 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

<table>
<thead>
<tr>
<th>Pericardial diseases</th>
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<tbody>
<tr>
<td>Pericardial effusion</td>
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<tr>
<td>Pericarditis (viral, bacterial, mycotic)</td>
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<tr>
<td>Neoplasm (Kaposi’s sarcoma, lymphoma)</td>
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<table>
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<tr>
<th>Myocardial diseases</th>
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<tbody>
<tr>
<td>HIV-associated dilated cardiomyopathy</td>
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<tr>
<td>Myocarditis (acute or chronic)</td>
</tr>
<tr>
<td>Neoplasm (Kaposi’s sarcoma, lymphoma)</td>
</tr>
<tr>
<td>Drug side-effects (especially by antiretroviral therapy)</td>
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<table>
<thead>
<tr>
<th>Endocardial diseases</th>
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</thead>
<tbody>
<tr>
<td>Infective endocarditis (bacterial, mycotic)</td>
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<tr>
<td>Nonbacterial thrombotic endocarditis</td>
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<thead>
<tr>
<th>Vascular diseases</th>
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<tbody>
<tr>
<td>Atherosclerosis</td>
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<tr>
<td>Vasculitis, perivasculitis</td>
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<tr>
<td>Pulmonary arterial hypertension</td>
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