HIV-infection is the fourth leading cause of death worldwide [1]. In 2003 alone, HIV-infection caused ~3 million deaths worldwide, and ~40 million persons were living with HIV-infection [2]. The survival of patients with human immunodeficiency virus (HIV) infection has dramatically increased with the use of highly active antiretroviral therapy (HAART) and this therapy significantly reduced the incidence of all acquired immunodeficiency syndrome (AIDS)-defining events [3]. "As a consequence, cardiovascular disease associated with HIV-infection and AIDS (Table 1) or related to "classical" non-HIV-related cardiovascular risk factors and its treatment has become more and more relevant [4]."

Data from the first studies evaluating the incidence of myocardial infarction (MI) in HIV infected patients were mixed, as some investigators found an association [5], while others did not [6].

In 700 HIV-infected patients treated with HAART, nine patients (1.3%) suffered acute coronary events after an average duration of 18 months [7]. Patients with an event were young men (mean, 40 ± 8 years) infected with the virus for several years (average, 7 ± 1 years). However, after initiation of HAART, the patients became hypercholesterolemic and hypertriglyceridemic.

In the HIV outpatients study (HOPS), including 5,672 HIV1-patients, the frequency of MIs increased after the introduction of protease inhibitors (PIs) in 1996. Patients taking PIs were at significantly increased risk for MI (0.6% versus 0.08%; hazard ratio 6·5, 95% CI 0·9-47·8, adjusted for smoking, sex, age, diabetes, hyperlipidemia, and hypertension) [8]. Although occurring infrequently, these events are of clinical and epidemiological significance considering the young age of these patients (mean, 42.6 years).

In a recently published large study, cardiovascular risk was not increased in 36,766 patients treated with PIs at Veterans Affairs facilities between 1993 and 2001 [6]. However, follow-up was shorter than in the HOPS study. Only approximately 1,000 patients received combination therapy with a PI for at least 48 months.

In the large DAD (Data collection on Adverse events of anti-HIV Drugs) study with 23,468 HIV-infected patients, 27% of PI-treated patients had hypercholesterolemia (total cholesterol ≥ 6.2 mmol/l), and 27% showed low HDL-cholesterol (≤ 0.9 mmol/l) [9]. Over 36,199 person-years, 126 patients developed a MI. The incidence of MI increased with longer exposure to combination antiretroviral therapy with an adjusted relative risk per year of exposure of 1.26 (95%CI: 1.12 to 1.41, P < 0.001). Combination antiretroviral therapy was independently associated with a 26% increase in rate of MI per year of exposure over the first 4-6 years of use [10].
The risk of MI seems to be increased in patients with HIV-infection receiving HAART. However, the absolute risk is small and the marked overall benefits of antiretroviral therapy are evident. Thus, individual cardiovascular risk factors should be assessed and treated.

**Pathophysiology of HIV and the Vascular Endothelium**

Endothelial cells play a fundamental role in the basal and dynamic regulation of the circulation (Figure 1). Due to its position between blood and the vascular wall, the endothelium is constantly exposed to potentially noxious circulating agents such as cholesterol, cigarette biproducts, and also infective agents.

Endothelial cells take an important part in the generation of the inflammatory response directed against noxious stimuli. Inflammation due to infection has been clinically recognized for a long time. In contrast, the subclinical inflammatory changes in the arterial wall due to cardiovascular risk factors have only recently emerged as an important pathogenetic factor in atherosclerosis. Indeed, inflammatory markers such as C-reactive protein and interleukins have strong and independent prognostic implications in patients with atherosclerotic vascular disease.

Although HIV-infection causes immunosuppression with attenuated inflammatory response to certain opportunistic infections, HIV-infection causes profound functional alterations of the endothelium resembling the subclinical inflammation in atherosclerosis. Leukocyte adherence to endothelium is enhanced as the expression of cell adhesion molecules increases (Figure 1). Elevated circulating levels of von Willebrand factor, a glycoprotein facilitating platelet adhesion synthesized in endothelial cells and megakaryocytes, are elevated and correlate to circulating levels of inflammatory cytokines such as TNFα and IF-γ. Plasma levels of von Willebrand factor have prognostic relevance in coronary artery disease. A hypercoagulable state is induced depending on plasma HIV load. Expression of protein-S is decreased, and prothrombotic autoantibodies against phospholipids are generated. Finally, HIV-1 induces apoptosis of endothelial cells.

**Metabolic Changes Associated with HIV-infection and HAART**

HIV-infection itself is associated with dyslipidemia. Following HIV infection, an early decrease in high-density lipoprotein cholesterol and elevations in triglycerides are observed while low-density lipoprotein cholesterol decreases later in the course of the disease.

Besides reverse transcriptase inhibitors, HIV PIs are key components of antiviral therapy. However, they can cause hyperlipidemia, hyperglycemia, and central obesity [11]. Indeed, insulin resistance and hyperinsulinemia occurs in as much as 25-60% of patients treated with PIs [12]. As a consequence, there is a reduced uptake of serum lipids by fat cells, increased lipolysis in the subcutaneous adipose tissue, and increased production of lipids by hepatocytes.

In addition, PIs, such as ritonavir, indinavir, and amprenavir, upregulate CD36, a scavenger receptor mediating cholesterol uptake in macrophages [13]. HAART therefore directly promotes atherosclerosis independently from the metabolic changes described above.

Furthermore, PIs directly impair endothelium-dependent vasodilation, a marker of vascular damage preceding atherosclerotic changes [11]. Patients treated with PIs show a higher prevalence of atherosclerotic lesions in the carotid arteries than HIV-infected patients naïve to PI
treatment. Carotid intima-media thickness, an independent risk factor for MI and stroke, is increased in hyperlipidemic patients with HIV-infection [14].

**Treatment Strategies**

Although the risk for atherosclerotic vascular disease is increased, the benefits of antiretroviral therapy outweigh the risk [9]. Patients receiving HIV PIs should be screened for hyperlipidemia, hyperglycemia, and hypertension. They may be candidates for lipid-lowering therapies depending on their long-term prognosis and individual risk of cardiovascular disease. Invasive treatment of acute MI does not differ from patients not infected with HIV [15]. However, their restenosis rates after percutaneous coronary intervention are unexpectedly high [16]. Compared to patients not infected with HIV, they are younger, have lower HDL-cholesterol levels, and are more likely to smoke, and to have single-vessel disease [16]. Atazanavir is a PI which may have less impact on lipid elevation in treated patients [17], while both nucleoside and non-nucleoside reverse transcriptase inhibitors may also contribute to lipid elevation in treated patients [17].

The lipid-lowering therapy must be considered according to the antiretroviral therapies [18]. When initiating lipid-lowering therapy, interactions between statins and HIV PIs affecting cytochrome P450 (CYP) function must be considered [19,20]. Simvastatin, atorvastatin, and lovastatin, but not pravastatin and fluvastatin, are metabolized by CYP3A4 and should thus be avoided in persons taking PIs such as ritonavir, atazanavir, and saquinavir. Pravastatin does not alter nelfinavir pharmacokinetics, and thus appears to be safe for concomitant use. However, dose adjustment of pravastatin may be necessary with concomitant use of ritonavir, atazanavir, and saquinavir. Oral antidiabetic drugs such as metformin or PPAR agonists such as thiazolidinediones (e.g. pioglitazone) may be needed. In patients with PI-associated hypertriglyceridemia, the use of a fibrate such as gemfibrozil does not normalize triglyceride levels [21].

**Pharmacologic Interactions between HAART and Cardiovascular Drugs**

As already written caution should be used when antiretrovirus therapy is used together with drugs that are substrates or inhibitors of CYP3A4. Co-administration of PIs, with St. John’s wort (Hypericum perforatum), or products containing it, is expected to substantially decrease concentrations of the PI and may result in suboptimal levels of those drugs and lead to loss of virologic response and possible resistance to the PIs.

Caution should be used when prescribing phosphodiesterase5-inhibitors for erectile dysfunction (e.g., sildenafil, tadalafil, or vardenafil) to patients receiving PIs, including atazanavir. Co-administration of a PI with a phosphodiesterase5-inhibitor is expected to substantially increase the adverse events associated with phosphodiesterase5-inhibitors, including hypotension, visual changes, and priapism.

PI including atazanavir has been shown to prolong the PR-interval. Abnormalities in atrioventricular (AV) conduction were asymptomatic and limited to first-degree AV-block with rare exceptions. No second- or third-degree AV-block was observed. Therefore PIs should be used with caution in patients with preexisting conduction system disease or when they are used together with other drugs that prolong the PR-interval including beta-blockers, non-diidropyridine calcium-antagonists, and digoxin.
References


<table>
<thead>
<tr>
<th>Etiology</th>
<th>Comment</th>
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<tbody>
<tr>
<td>Pericardium and effusions</td>
<td>Pericardial effusion frequent in HIV-infected patients. Large effusion causing tamponade rare. Pericardial effusion due to tuberculosis infection (may be associated with myocarditis) frequent in developing countries. Other causes: bacterial pericarditis, Kaposi’s sarcoma, and lymphoma.</td>
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<tr>
<td>Kaposi’s sarcoma</td>
<td>Often disseminated. Cardiac problems infrequent.</td>
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<tr>
<td>Myocardium</td>
<td>Left ventricular systolic dysfunction most often clinically silent. Complex pathogenesis (direct virus effect, inflammatory response, autoantibodies). Specific cause in &lt;20% of patients. Rare causes: toxoplasmosis, tuberculosis, cryptococcosis, histoplasmosis, aspergillosis, candidosis, cytomegalovirus, and herpes simplex. HIV itself can cause myocarditis.</td>
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<tr>
<td>Lymphoma</td>
<td>Non-Hodgkin B-cell lymphoma. Primary cardiac lymphoma extremely rare.</td>
</tr>
<tr>
<td>Drug toxicity</td>
<td>Amphotericin B, doxorubicin, foscarnet, interferon alpha, zidovudine (see arrythmia).</td>
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<tr>
<td>Pulmonary hypertension</td>
<td>Inflammation, genetic factors Possibly leading to right heart failure. Plexogenic arteriopathy found most commonly as in immunocompetent patients.</td>
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<tr>
<td>Endocardium / valves</td>
<td>Infective endocarditis causing valvular insufficiency Bacterial etiology in intravenous drug abusers, most often S. aureus and Streptococcus viridans. HIV-infection itself is not associated with bacterial endocarditis. Tricuspidal valve often involved. Embolization of clots (frequently clinically silent).</td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td>HAART HAART may cause metabolic syndrome and lipodystrophy. Premature atherosclerosis of coronary, cerebral, and peripheral arteries.</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>No specific association with HIV-infection Arrhythmia due to cardiomyopathy or myocarditis, as well as myocardial infiltration in cardiac lymphoma. HIV itself does not cause rhythm disturbances. Ganciclovir (antiviral therapy against cytomegalovirus) may induce ventricular tachycardia. Interferon alpha (AV-block, sudden death) Pentamidine and pyrimethamine, used for treatment of toxoplasmosis (QT-prolongation, torsades de pointes) Trimethoprim-sulfamethoxazole, used for P. carinii prophylaxis (QT-prolongation, torsades de pointes)</td>
</tr>
<tr>
<td>Aneurysmatic vascular disease</td>
<td>Inflammation Premature aortic and cerebrovascular aneurysms described in patients with HIV-infection.</td>
</tr>
</tbody>
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[From 4]
Figure 1. Schematic illustration of the pathogenesis of an atherosclerotic plaque. The endothelium produces and releases a broad spectrum of vasoactive substances such as nitric-oxide (NO) and endothelin-1 (ET-1), which regulate vascular function and structure. Leukocytes adhering to adhesion molecules on vascular endothelial cells migrate through the vascular wall to the subendothelial space where they accumulate as foam cells and undergo apoptosis. The resulting cell debris as well as matrix constituents degraded by matrix metalloproteinases constitute the plaque core, which is covered by a fibrotic cap of varying thickness. There is crosstalk between inflammatory cells such as lymphocytes and platelets by the CD40L pathway. AII angiotensin II; AT1 angiotensin subtype 1 receptor; B2 bradykinine receptor; Bk bradykinine; COX cyclooxygenase; CRP C-reactive protein; eNOS endothelial nitric oxide synthase; ET endothelin; IL interleukin; LDL-R LDL receptor; MCP-1 monocyte chemotactic protein; MMP matrix metalloproteinases; NO nitric oxide; PDGF platelet-derived growth factor; SR scavenger receptor; Thr thrombine; T thrombine receptor; TXA2 thromboxane; TX thromboxane receptor. [From 4]