What a Cardiologist Needs to Know About Patients With Human Immunodeficiency Virus Infection

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Introduction

Acquired immunodeficiency syndrome (AIDS) is caused by infection with HIV. According to the Centers for Disease Control and Prevention (CDC), the case definition of AIDS is (1) HIV-infected individuals who have <200 CD4+ T lymphocytes/µL or (2) HIV-infected individuals who have the presence of specific opportunistic infections.1 Opportunistic infections in the CDC’s definition include Pneumocystis carinii pneumonia, Kaposi’s sarcoma, Cytomegalovirus disease, and pulmonary tuberculosis.1 Antiretroviral treatment is recommended for all patients with symptomatic HIV disease and for asymptomatic patients with ≥200 CD4 cells/µL.2

Untreated HIV infection usually progresses to AIDS. Cardiologists are familiar with the cardiovascular complications of AIDS, primarily myocarditis, pericardial effusion, and pulmonary hypertension.3 The introduction of highly active antiretroviral therapy (HAART) in the mid to late 1990s dramatically reduced HIV-associated morbidity and mortality in treated patients, so that they no longer inevitably succumb to opportunistic infections. However, recent studies report increased rates of coronary events in HIV patients or in HIV patients receiving HAART.4,5 Protease inhibitors, a main component of HAART, induce deleterious metabolic effects such as dyslipidemia and insulin resistance.6

The purpose of this article is to review recent studies on the cardiovascular diseases associated with HIV infection and to provide guidance for the prevention and treatment of cardiac disease in HIV patients.

Epidemiology

At the end of 2003, over 1 million people were estimated to be living with HIV or AIDS in the United States.7 Approximately 40 000 new cases occur each year in the United States, ~70% among men and 30% among women.8 Of new infections among men in the United States, the CDC estimates that 60% are a result of homosexual sex, 25% from injection drug use, and 15% through heterosexual sex.7 Of new infections among women in the United States, the CDC estimates that 75% are a result of heterosexual sex and 25% from injection drug use.7

Twenty-five percent of newly infected people in the United States are <35 years of age.7 Among newly infected patients, approximately half are black, 30% are white, and 20% are Hispanic.7 About one quarter of US residents with HIV infection are unaware of their condition.7

The mortality rate among patients with HIV infection has decreased markedly in the United States since the introduction of HAART. For example, in the HIV Outpatient Study, mortality among 1255 patients with at least 1 CD4+ count <100 cells/mm³ declined from 29.4 to 8.8 per 100 patient-years between 1995 and the second quarter of 1997.8 As shown in Figure 1, this decline coincided with the initiation of protease inhibitors (PIs) for 80% of the study population. Similarly, in a European cohort study of 4270 patients who had had a CD4+ count <500 cells/mm³, mortality fell from 23.3 to 4.1 per 100 patient-years between mid-1995 and late 1997 to early 1998.9 The decrease in mortality in these studies was accompanied by a decline in the incidence of opportunistic infections8 and correlated with the intensity of antiretroviral therapy.9

HIV Infection and Coronary Disease

In 1998, severe premature coronary disease was first reported in 2 young men with HIV infection receiving HAART, specifically PIs.10 Some controversy still exists as to whether the rate of coronary events is increased in HIV patients and whether the increase is caused by HAART. The main studies addressing this question are summarized in Table 1.

In a retrospective database study of 36 766 HIV patients treated at Veterans Affairs facilities between 1993 and 2001, no increase in cardiovascular or cerebrovascular events was observed during a mean follow-up of 40 months among patients receiving HAART.11 Similarly, in a meta-analysis of 30 randomized clinical trials, the incidence of myocardial infarction (MI) was not higher in patients receiving protease...
PIs compared with nucleoside reverse-transcriptase inhibitors (NRTIs); however, the duration of treatment was only 1 year, and the number of events was small.12

On the other hand, in the HIV Outpatient Study, MI occurred in 19 of 3247 patients taking but in only 2 of 2425 not taking PIs, and the frequency of MI increased after the introduction of these drugs ($P=0.0125$).4 The Data Collection on Adverse Events of Anti-HIV Drugs Study Group prospectively followed up 23,468 HIV patients for a mean of 1.6 years, with an average exposure to antiretroviral therapy of 1.9 years.5 The risk of MI increased with longer exposure to combination antiretroviral therapy; the adjusted relative rate per year of exposure was 1.26 (95% CI, 1.12 to 1.44; $P<0.001$).

In the French Hospital Database on HIV, MI was diagnosed in 60 of 34,976 patients during a median follow-up of 33 months13; patients prescribed PIs had a significantly higher risk of MI than those not prescribed these drugs, with a relative rate of 2.56. The relative risk for those taking PIs for ≥30 months compared with <18 months was 3.6 (95% CI, 1.8 to 6.2). In the Kaiser Permanente Medical Care Program of Northern California database, 72 coronary events, including 47 MIs, were documented in 4159 HIV patients during a median follow-up of 4.1 years.14 Median exposure time to PIs was 2.8 years. The coronary event rate was similar in patients taking and not taking PIs; however, the rate was higher in HIV patients compared with non-HIV control subjects (6.5 versus 3.8 events per 1000 patient-years; $P=0.003$).

In a study of 1551 Italian HIV patients followed up for a median of 36 months, 25 coronary events (MI in 13 and unstable angina in 12) were diagnosed.15 The cumulative annual incidence of coronary events was 9.8 per 1000 patients in those treated with PIs compared with 0.4 per 1000 in those not treated ($P<0.001$).

Taken together, these studies suggest that the rate of MI is higher in HIV patients taking PIs and that the risk increases as the duration of treatment lengthens. The classic coronary risk factors usually exert their influence for decades before a coronary event occurs. That an increase in risk can be detected after a much shorter exposure to PIs suggests either that they are a potent atherogenic stimulus or that their use is associated with a period of high risk. The coronary event rates in these studies are relatively low but might be expected to be higher as the HIV population ages.

### Clinical Features of Coronary Disease in HIV Patients

Does the clinical expression of coronary disease differ in HIV patients compared to the general population? In Table 2, some of the clinical features of 334 patients, 225 (67%) of whom presented with acute MI, are tabulated from 7 reports.16–22 Only 31 of these patients (9%) were women. Compared with HIV-uninfected patients, the mean or median age of the

### Table 1. Studies Comparing Coronary Event Rates in HIV Patients With Versus Without PIs

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients, n</th>
<th>Age, y</th>
<th>Follow-Up</th>
<th>Events</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bozette et al11</td>
<td>36 766</td>
<td>NA</td>
<td>40 mo</td>
<td>1207 admissions for CVD</td>
<td>No increase in CVD admissions with PIs or with increase in duration of PI treatment</td>
</tr>
<tr>
<td>Coplan et al12</td>
<td>10 986</td>
<td>37 (mean)</td>
<td>1 y</td>
<td>29 MIs</td>
<td>Risk of MI not increased in PI- vs non-PI-treated patients; OR, 1.69; 95% CI, 0.54–7.48</td>
</tr>
<tr>
<td>Holmberg et al4</td>
<td>5672</td>
<td>42.6 (mean)</td>
<td>3.1 y</td>
<td>21 MIs</td>
<td>Risk of MI increased in PI- vs non-PI-treated patients; OR, 7.1; 95% CI, 1.6–44.3</td>
</tr>
<tr>
<td>DAD Study Group5</td>
<td>23 468</td>
<td>39 (median)</td>
<td>1.6 y on PI</td>
<td>126 MIs</td>
<td>Risk of MI increased with increased exposure to PI combination therapy ($P&lt;0.001$)</td>
</tr>
<tr>
<td>Mary-Krause et al13</td>
<td>34 976</td>
<td>37.7 (mean)</td>
<td>33 mo</td>
<td>60 MIs</td>
<td>Risk of MI increased in PI- vs non-PI-treated patients; OR, 2.56; 95% CI, 1.03–6.34</td>
</tr>
<tr>
<td>Klein et al14</td>
<td>4159</td>
<td>42.6 (mean)</td>
<td>3.6 y</td>
<td>72 CHD events, including 47 MIs</td>
<td>Event rates in PI- vs non-PI-treated patients similar but increased in HIV patients vs controls</td>
</tr>
<tr>
<td>Barbaro et al15</td>
<td>1551</td>
<td>35.5 (median)</td>
<td>36 mo</td>
<td>25 coronary events, including 13 MIs</td>
<td>Risk of MI increased in PI- vs non-PI-treated patients; RR, 11.5; 95% CI, 2.7–48.5</td>
</tr>
</tbody>
</table>

CVD indicates cardiovascular disease; OR, odds ratio; and CHD, coronary heart disease.
patients was very young, ranging from a mean or median of 42 to 50 years. This was 5 years older than other HIV patients in the French cohort study and 11 years younger than control non-HIV patients with acute coronary syndromes in our study. More than half of the patients in each of these studies smoked cigarettes at the time of their coronary event. The proportion of patients receiving PIs ranged from 49% to 71%.

Mean HDL cholesterol levels were very low in each of the 3 studies in which they were reported: 32±10 mg/dL, 28±10 mg/dL, and 35±12 mg/dL. These levels were significantly lower than those of HIV patients without coronary disease in the French cohort and lower than non-HIV control subjects with coronary disease in the other 2 studies. Mean LDL cholesterol levels were lower in HIV coronary patients than in non-HIV coronary control subjects in 1 study but not another. In the French cohort, LDL cholesterol levels were much higher in the HIV patients with than in those without coronary disease.

Thus, the typical HIV patient with coronary disease is a male smoker with very low HDL cholesterol levels who is significantly younger than HIV-uninfected patients with coronary disease.

As might be expected in such a population, single-vessel disease is common and the TIMI risk score is low if an acute coronary syndrome is present. The immediate outcome is thus expected to be excellent. Nine deaths (4.8%) occurred in hospital among 189 patients with follow-up reported among the studies included in Table 2.

Coronary angioplasty or stenting has often been performed in these patients, and the immediate results have been excellent; however, the restenosis rate appears to be much higher than that of patients without HIV infection. In our series, restenosis developed in 15 of 29 HIV patients compared with 3 of 21 non-HIV control subjects (52% versus 14%; P=0.006). In HIV patients, 22 of 29 patients received stents in the procedure compared with 11 of 21 control subjects; for patients receiving stents, the restenosis rate was 11 of 22 HIV patients versus 2 of 11 control subjects (50% versus 18%; P=0.078). Similarly, in the series of Matetzky et al, restenosis requiring target vessel revascularization occurred in 6 of 14 HIV patients compared with 4 of 38 uninfected control subjects (43% versus 11%; P=0.02).

Restenosis rates are higher after both balloon angioplasty and stenting; no data are available to ascertain whether this problem occurs with drug-eluting stents.

Several patients in these studies underwent coronary bypass surgery, but no large series of HIV patients with long-term follow-up after bypass surgery have been reported. In a series of 37 HIV patients who were followed up for a mean of 28 months after cardiac surgery, of whom 29 received coronary bypass grafts, event-free survival was 81% at 3 years. The most striking feature of this report was that the median age of the bypass patients was only 44 years. No studies have reported graft patency rates after coronary bypass in HIV patients. Atherosclerosis might develop more rapidly in venous bypass grafts in HIV patients because it appears to progress more rapidly in native arteries.

### Surrogate Measures of Atherosclerosis in HIV Patients

#### Endothelial Dysfunction and HIV Medications

Endothelial dysfunction is a feature of early atherosclerosis and a predictor of future cardiovascular events. HIV-infected children have endothelial dysfunction compared with age- and sex-matched control subjects in the absence of cardiovascular risk factors. The use of PIs in HIV-infected adults is associated with endothelial dysfunction as assessed by brachial artery flow-mediated vasodilation. This abnormality appears to be mediated by the atherogenic dyslipidemia induced by PIs.

Soluble adhesion molecules indicative of endothelial damage are elevated in HIV-infected patients. In another study, patients receiving HAART had higher levels of P-selectin, plasminogen activator inhibitor type 1, and tissue plasminogen activator but not soluble intracellular adhesion molecule-1, and there was no significant difference in the levels of these markers between patients receiving PIs and non-NRTIs (NNRTIs).

#### Endothelial Dysfunction and HIV Infection

HIV can damage endothelium through several mechanisms. Tat protein, a small cationic polypeptide that can be released from infected cells, interacts with at least 3 different types of receptors present on the surface of endothelial cells. The resultant activation of several signal transduction pathways...
triggers the expression of adhesion molecules, vascular endothelial growth factor, and platelet activating factor.\textsuperscript{32} As a consequence, Tat protein causes endothelial dysfunction.\textsuperscript{33} The death of CD4 T lymphocytes caused by HIV results in an increase in shed membrane particles from these cells.\textsuperscript{34} Shed membrane particles from T lymphocytes induce endothelial dysfunction, expressed as a reduction in nitric oxide and prostacyclin-induced vasodilatation.\textsuperscript{35}

**Carotid Intima-Media Thickness, HIV Medications, and HIV Infection**

Carotid B-mode ultrasound has been used to assess subclinical atherosclerosis in HIV patients.\textsuperscript{36–40} Carotid plaques were more common in patients receiving PIs than in PI-naive patients in 1 study.\textsuperscript{36} In the larger Swiss HIV Cohort Study, carotid and femoral artery plaques were associated with classic coronary risk factors and not with PI use.\textsuperscript{37} In another study of 423 HIV-infected patients, conventional risk factors but not lipodystrophy or HAART were independent predictors of increased carotid intima-media thickness (IMT).\textsuperscript{40}

We measured carotid IMT in 148 HIV-infected adults and in an age- and sex-matched control group.\textsuperscript{25} Mean carotid IMT was much thicker in HIV patients than in control subjects ($P<0.001$). Predictors of thicker IMT in HIV patients included older age, higher LDL cholesterol, cigarette pack-years, and hypertension. Repeated measurements after 1 year showed rapid progression of carotid IMT in HIV patients but not in control subjects ($P=0.002$). The rapid progression of carotid IMT in HIV patients, in addition to their thicker baseline values, strongly suggests that their rates of coronary and cerebrovascular events will be very high in the future. Carotid IMT correlated with classic risk factors, but progression of carotid IMT also correlated with a low nadir CD4 count. The latter association supports the hypothesis that immune reconstitution stimulates the rapid progression of atherosclerosis in these patients, as discussed below.

**Pathogenesis of Atherosclerosis in HIV Patients**

There are several possible explanations for the increase in coronary events in HIV patients. PIs induce deleterious metabolic effects such as dyslipidemia and insulin resistance, as discussed below.\textsuperscript{6} An alternative possibility is that HIV disease is in itself atherogenic. Progressive HIV disease is associated with accelerated T-cell proliferation, heightened T-cell activation, and high levels of inflammatory markers.\textsuperscript{41,42} These immunological perturbations persist even after the introduction of HAART.\textsuperscript{43} Indeed, persistent levels of immune activation are observed even after years of treatment-mediated viral suppression. The level of immune activation has been independently associated with CD4 T-cell nadir,\textsuperscript{44} which was a predictor of progression of carotid IMT in our study.\textsuperscript{25}

**HIV Infection and Atherosclerosis**

Both immunodeficiency and immune reconstitution may be atherogenic. T lymphocytes, of which CD4 cells constitute the major population, play a key role in atherogenesis.\textsuperscript{45,46} CD4 cell activation promotes atherosclerosis through elaboration of proinflammatory cytokines, including tumor necrosis factor and interleukins.\textsuperscript{47} Analogously, T-cell lymphocytes are also involved in the arteriosclerosis that develops in immune-suppressed patients after cardiac transplantation.\textsuperscript{48}

Chronic low-grade inflammation contributes to accelerated atherosclerosis.\textsuperscript{49} C-reactive protein levels are higher in HIV patients than in control subjects,\textsuperscript{29} and subjects with levels of this marker in the upper quartile or quintile have an elevated risk of cardiovascular events.\textsuperscript{50} Some experimental data indicate that C-reactive protein is an active participant in the process of atherogenesis.\textsuperscript{51,52}

Monocyte chemoattractant protein-1 is a potent activator of macrophages and monocytes, stimulating them to migrate to the subendothelial space where they begin phagocytosis of modified lipoproteins to become lipid-laden foam cells, an early step in atherogenesis. Among HIV patients with subclinical atherosclerosis by carotid and femoral ultrasound, monocyte chemoattractant protein-1 plasma levels were higher and the frequency of a mutation in the promoter region of the monocyte chemoattractant protein-1 gene was also higher compared with HIV patients without atherosclerosis.\textsuperscript{53}

Coagulation abnormalities that would predispose to thrombotic events have been described in HIV patients.\textsuperscript{54} Protein S deficiency is the most common, reported in 73% of HIV-infected men in 1 study.\textsuperscript{55} Serum levels of von Willebrand factor are higher in untreated HIV patients than in control subjects, reflecting endothelial activation, but tend to decrease toward normal with HAART.\textsuperscript{56} Platelet activation is also enhanced in HIV patients.\textsuperscript{56} Smoking cigarettes activates platelets and increases coagulability, and smoking rates are very high in HIV patients. Endothelial dysfunction, inflammation, platelet activation, and hypercoagulability interact synergistically to enhance the atherogenic and thrombotic milieu of the arterial wall.

**HIV Treatment**

Antiretroviral treatment is recommended for all patients with symptomatic HIV disease and for asymptomatic patients with $\leq 200$ CD4 cells/$\mu$L.\textsuperscript{2} In asymptomatic patients with $>200$ but $\leq 350$ CD4 cells/$\mu$L, antiretroviral treatment should be considered.\textsuperscript{2} These recommendations are based on data from several studies, including the HIV Outpatient Study, in which patients who started therapy when their CD4 cell counts were between 200 and 350/$\mu$L had lower mortality over 4 years of follow-up compared with patients who waited to start therapy until their CD4 cell counts were $<200$/muL.\textsuperscript{57}

Antiretroviral therapy for HIV infection is complicated and has evolved rapidly over the past few years. Currently, HAART consists of 4 broad classes of drugs: NRTIs, NNRTIs, PIs, and a cell membrane fusion inhibitor. The important features of each of the PIs are listed in Table 3, and the NRTIs and NNRTIs are listed in Table 4. Initial regimens usually consist of 3 drugs: 2 NRTIs with either an NNRTI or a PI.\textsuperscript{5} The superiority of some treatment regimens over others has been demonstrated in randomized trials; however, many important questions about therapy remain.\textsuperscript{2} Changes in drug regimens are often required because of either adverse effects or failure of viral suppression. Incomplete compliance to treatment...
is common as a result of the high incidence of side effects and the inconvenience of taking large number of pills on schedule. The largest class of antiretroviral drugs used to treat HIV is the PIs. PIs block the HIV protease enzyme so that viral proteins constructed within the infected cell cannot be released as active viral particles.\(^5^8\) This is an effective way to disrupt viral replication because it acts specifically at a late-stage mechanism that is essential for viral replication. The side effects caused by PIs include gastrointestinal complaints, sexual dysfunction, disorders of glucose and lipid metabolism, hepatotoxicity, and an increased risk of bleeding.\(^5^8\) These symptoms are frequently severe enough to cause discontinuation of therapy; nausea and vomiting occurred in 75% of patients in 1 study,\(^5^9\) and in another, 25% of patients

### TABLE 3. PIs Used

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Typical Dose*</th>
<th>Pills, n/d</th>
<th>Common Adverse Events</th>
<th>Important Drug Interactions†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amprenavir</td>
<td>Agenerase</td>
<td>1200 mg BID</td>
<td>16</td>
<td>Lactic acidosis, periorbital and peripheral numbness, rash, nausea, diarrhea</td>
<td>Lovastatin, simvastatin, bepridil</td>
</tr>
<tr>
<td>Atazanavir</td>
<td>Reyataz</td>
<td>400 mg/d</td>
<td>2</td>
<td>Lactic acidosis, hyperbilirubinemia, ↑ PR interval</td>
<td>Proton pump inhibitors, bepridil</td>
</tr>
<tr>
<td>Fosamprenavir</td>
<td>Lexiva</td>
<td>1400 mg BID</td>
<td>4</td>
<td>Prodrug of amprenavir with higher bioavailability</td>
<td>Flecaainide, propafenone, lovastatin, simvastatin</td>
</tr>
<tr>
<td>Indinavir</td>
<td>Crixivan</td>
<td>800 mg TID</td>
<td>6</td>
<td>Dry eyes, mouth, and skin; nephrolithiasis; hyperbilirubinemia; neutropenia; paronychia; vasculitis</td>
<td>†</td>
</tr>
<tr>
<td>Lopinavir/Ritonavir</td>
<td>Kaletra</td>
<td>400/100 mg BID</td>
<td>6</td>
<td>Pancreatitis, GI side effects common but mild</td>
<td>See ritonavir†</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>Viracept</td>
<td>1250 mg BID or 750 mg TID</td>
<td>9–10</td>
<td>Nephrolithiasis, more diarrhea than other PIs</td>
<td>Amiodarone quinidine, lovastatin, simvastatin, atorvastatin (?)</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>Norvir</td>
<td>600 mg BID</td>
<td>12</td>
<td>Pancreatitis, altered taste sensation</td>
<td>As for nelfinavir; bepridil, clozapine, estradiol, flecaainide, methadone, propafenone</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>Fortovase</td>
<td>1200 mg TID</td>
<td>18</td>
<td>Altered sense of taste</td>
<td>†</td>
</tr>
</tbody>
</table>

GI indicates gastrointestinal.

*The typical dose may not be the dose used with combination therapy.

†All PIs interact with antiarrhythmic drugs, ergots, triazolobenzodiazepines (alprazolam [Xanax], midazolam [Versed], and triazolam [Halcion]), and pan-inducers of the cytochrome P450 enzymes (barbiturates, carbamezepine, ethanol, phenytoin, and rifamycins). These drugs should not be used with PIs.

The largest class of antiretroviral drugs used to treat HIV is the PIs. PIs block the HIV protease enzyme so that viral proteins constructed within the infected cell cannot be released as active viral particles.\(^5^8\) This is an effective way to disrupt viral replication because it acts specifically at a late-stage mechanism that is essential for viral replication. The side effects caused by PIs include gastrointestinal complaints, sexual dysfunction, disorders of glucose and lipid metabolism, hepatotoxicity, and an increased risk of bleeding.\(^5^8\) These symptoms are frequently severe enough to cause discontinuation of therapy; nausea and vomiting occurred in 75% of patients in 1 study,\(^5^9\) and in another, 25% of patients

### TABLE 4. NRTIs and NNRTIs

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Typical Dose*</th>
<th>Common Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTIs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abacavir (ABC)</td>
<td>Ziagen</td>
<td>300 mg BID</td>
<td>Hypersensitivity reaction in ~4%</td>
</tr>
<tr>
<td>Didanosine (ddI)</td>
<td>Videx EC</td>
<td>250 mg/d if &lt;60 kg; 400 mg/d if ≥60 kg</td>
<td>Peripheral neuropathy in 15%, optic neuritis, rare pancreatitis</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>Emtriva</td>
<td>200 mg/d</td>
<td>Stopping may exacerbate hepatitis B</td>
</tr>
<tr>
<td>Lamivudine (3TC)</td>
<td>Epivir</td>
<td>150 mg BID</td>
<td>Generally well tolerated</td>
</tr>
<tr>
<td>Stavudine (d4T)</td>
<td>Zerit</td>
<td>30 mg BID if &lt;60 kg; 40 mg BID if ≥60 kg</td>
<td>Peripheral neuropathy; higher risk in patients with CD4 counts &lt;50</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>Viread</td>
<td>300 mg/d</td>
<td>Nausea; generally well tolerated</td>
</tr>
<tr>
<td>Zalcitabine (ddC)</td>
<td>Hivid</td>
<td>0.375–0.75 mg TID</td>
<td>High rate of peripheral neuropathy, oral ulcers; rarely used because of toxicity</td>
</tr>
<tr>
<td>Ziduvudine (AZT)</td>
<td>Retrovir</td>
<td>300 mg BID</td>
<td>Nausea, headache, fatigue, anemia, neutropenia, neuropathy, myopathy</td>
</tr>
</tbody>
</table>

Combination NRTIs

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Typical Dose*</th>
<th>Common Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZT + 3TC</td>
<td>Combivir</td>
<td>1 tablet BID</td>
<td>Same as AZT</td>
</tr>
<tr>
<td>AZT + 3TC + ABC</td>
<td>Trizivir</td>
<td>1 tablet BID</td>
<td>Same as AZT and ABC</td>
</tr>
</tbody>
</table>

NNRTIs

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Typical Dose*</th>
<th>Common Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delavirdine</td>
<td>Rescriptor</td>
<td>400 mg TID</td>
<td>Rash, fat redistribution, ↑ increased ALT/AST</td>
</tr>
<tr>
<td>Etavirenz</td>
<td>Sustiva</td>
<td>600 mg/d</td>
<td>Rash, CNS symptoms, including insomnia</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>Viramune</td>
<td>200–400 mg/d</td>
<td>Rash, hepatitis</td>
</tr>
</tbody>
</table>

CNS indicates central nervous system.
had to stop their treatment because of side effects.60 The metabolic abnormalities caused by PIs are discussed in the following section.

All PIs inhibit metabolism of the cytochrome P450 system, specifically at the 3A4 enzyme. Thus, they interact with many other drugs (see Table 3), including many drugs used in cardiac patients. Several cases of rhabdomyolysis have been reported with the combination of a PI and a statin; eg, nelfinavir and simvastatin caused death as a result of severe rhabdomyolysis in 1 patient.62 Simvastatin should not be used in patients taking PIs, and the dose of atorvastatin should be adjusted downward. Pravastatin is safe because it is not metabolized by the cytochrome P450 system.

NRTIs inhibit viral replication by being incorporated into viral DNA; because they are defective structural analogs of the viral nucleotides, they prematurely terminate viral strand synthesis. NRTIs are generally well tolerated and do not inhibit the cytochrome P450 system; however, they do cause mitochondrial toxicity, expressed clinically as peripheral neuropathy, myopathy, lactic acidosis, hepatic steatosis, pancreatitis, and lipodystrophy.63

Like NRTIs, NNRTIs target HIV reverse transcriptase but by a different mechanism: NNRTIs block DNA elongation by directly binding to the reverse transcriptase enzyme.63,64 The antiviral potency and good tolerability of NNRTIs make them a favored component of HAART regimens, particularly because toxicity and viral cross-resistance do not overlap with NRTIs. Their most frequently reported side effects are rash, elevation of liver enzymes, and fat redistribution.63,64

The newest class of antiretroviral drugs, the fusion inhibitors, are represented by enfuvirtide (Fuzeon).65 This medication prevents conformational changes necessary for the fusion of virions to host cells. Because this drug is costly and has to be injected, it generally is reserved for patients in whom other antiretroviral regimens have failed.

**Adverse Metabolic Effects of HIV Treatment**

The interrelationships among HIV disease, its treatment, and coronary risk factors are complex and incompletely understood. Lower CD4 counts in untreated HIV patients are associated with lower total blood cholesterol, lower HDL cholesterol, and higher triglyceride levels.66 PIs induce hyperlipidemia and insulin resistance in HIV patients independently of the changes in body composition discussed in the following section.67 The effects of PIs on lipid metabolism appear to be drug specific. For example, ritonavir increases triglycerides and lowers HDL cholesterol slightly with no increase in LDL cholesterol,68,69 whereas indinavir has no effect on lipoproteins but causes insulin resistance.70 Amprenavir has no effects on lipoproteins,69 but lopinavir/ritonavir increases triglycerides with no effect on LDL or HDL cholesterol or on insulin resistance.71 These studies were of short duration and involved HIV-negative subjects to isolate the effects of the drugs. More pronounced changes are seen in HIV patients treated for longer periods, as outlined below.

A clearer picture of the lipid changes associated with HIV disease and its treatment can be appreciated from a report of the Multicenter AIDS Cohort Study.72 The 50 HIV patients included in this study had blood samples available from before their HIV status converted to positive, from before HAART was initiated a mean of 7.8 years later, and at 4 visits during treatment. HAART included at least 1 PI in 48 of 50 cases. As shown in Figure 2, total and LDL cholesterol decreased after the onset of HIV disease but returned to preinfection levels or higher with therapy, whereas HDL cholesterol levels decreased markedly after the onset of HIV and did not recover. Triglycerides were measured only once, during treatment, and were elevated at 225 mg/dL.

In a recent summary of clinical studies of the effects of PIs on lipids in HIV patients, these drugs were found to increase total cholesterol by 66%, LDL cholesterol by 37%, and triglycerides by 80% at 48 weeks.73 After 64 weeks of treatment, mean increases were 40% in total cholesterol, 148% in triglycerides, and 19% in LDL cholesterol. In a cross-sectional study of HIV patients, total cholesterol exceeded 240 mg/dL in 27% of those receiving a PI, 23% receiving an NNRTI, 44% receiving a PI and an NNRTI, 10% receiving only an NRTI, and 8% of untreated patients.74 Triglyceride levels >200 mg/dL were present in 40% of PI-treated patients, 32% of those treated with NNRTIs, 54% of those receiving both PIs and NNRTIs, 23% of NRTI-treated patients, and 15% of the untreated. The prevalence of diabetes ranged from 1.1% in untreated patients to 4.3% of those treated with both a PI and an NNRTI but is likely to be an underestimate.74

The long-term consequences of these metabolic abnormalities are likely to include an increase in coronary events and stroke. Replacement of a PI with nevirapine, efavirenz, or abacavir has been shown to reduce LDL cholesterol and triglyceride levels and to increase HDL cholesterol.75

**Lipodystrophy and the Metabolic Syndrome**

HIV-associated fat redistribution, also called lipodystrophy or lipoatrophy, is characterized by a selective loss of fat from the
HDL cholesterol, and hypertension. Lipodystrophy in HIV patients is associated with metabolic abnormalities, including insulin resistance, impaired glucose tolerance, elevated triglycerides, low HDL cholesterol, and hypertension. Lipodystrophy becomes clinically evident in 20% to 35% of patients after a 1 or 2 years of combination HAART. The type and duration of antiretroviral therapy are strongly associated with the development and severity of lipodystrophy. Combination therapy with a PI and 2 NRTIs, particularly stavudine with didanosine, is most likely to induce severe lipodystrophy. Exercise training, either alone or with metformin, has been reported to improve body composition in patients with lipodystrophy.

Hypertension occurs in up to one third of HIV patients. NNRTIs or PIs have been linked to hypertension in some studies but not in others. The hypertension associated with HIV appears to be linked to insulin resistance and the metabolic syndrome.

Risk Factor Profiles of HIV Patients
Several studies have examined the coronary risk factor profiles in cohorts of HIV patients. In a Norwegian cross-sectional study, a 10-year coronary heart disease risk >20% was twice as common among patients receiving HAART compared with a matched control group without HIV (11.9% versus 5.3%). A similar high level of risk was documented in HIV patients in the United Kingdom and the United States. High smoking rates, low HDL cholesterol levels, and the other components of the metabolic syndrome are the main contributors to risk in HIV patients.

Coronary risk assessment in these studies was based on the Framingham risk calculator. However, this system has never been validated in HIV patients and would underestimate true risk if HIV-specific factors related to altered immunity accelerate atherosclerosis.

Treatment of Coronary Risk Factors in HIV Patients
At this time, there is no direct evidence that treating risk factors improves the outcome of HIV patients; however, in the absence of outcome data, it appears reasonable to extrapolate from the treatment of traditional risk factors in non-HIV patients. The Adult AIDS Clinical Trials group recommends that dyslipidemia be managed according to the guidelines of the National Cholesterol Education Program Adult Treatment Panel III (NCEP).

Several issues are specific to HIV patients. All current PIs are metabolized by the cytochrome P450 system in which all statins except pravastatin are also metabolized. In healthy volunteers, the PI combination of ritonavir and saquinavir has been shown to increase the area under the curve for 24-hour blood statin level by 30-fold for simvastatin and by 79% for atorvastatin, whereas the area under the curve decreased by 50% for pravastatin. Simvastatin and lovastatin are contraindicated in patients taking PIs, and atorvastatin should be used cautiously. Pravastatin is safe but limited by its lower potency with respect to LDL cholesterol lowering. The cholesterol absorption inhibitor ezetimibe has not been studied in HIV patients but represents an attractive approach to LDL cholesterol lowering because of its lack of drug-drug interactions. The newer PI, atazanavir, does not appear to be associated with lipid abnormalities, so switching HIV patients to this drug represents an alternative approach to lipid management.

NNRTIs also affect the P450 cytochrome 3A4 enzyme, but in complex ways. Delavirdine inhibits it and thus carries the same constraints with respect to statin use as PIs. Efavirenz is a mixed inducer and inhibitor of this enzyme, and few data are available to define how this NNRTI affects statin concentrations.

Many HIV patients have elevated triglycerides. Fibrates (bezafibrate, fenofibrate, and gemfibrozil) appear to reduce triglycerides effectively in HIV patients receiving HAART; however, fibrates are conjugated by glucuronidation with renal elimination. Ritonavir and nelfinavir are known inducers of glucuronidation and thus could diminish the efficacy of fibrates. Fibrates should be used cautiously in combination with statins because of the increased risk of myopathy. Niacin is an alternative choice to lower triglycerides but may be a poor choice for many HIV patients because of its propensity to worsen blood glucose levels. It should be remembered that triglycerides are not a primary treatment target according to the NCEP guidelines and that there is limited evidence that correcting the laboratory abnormality of hypertriglyceridemia will reduce coronary events.

Hypertriglyceridemia is often accompanied by the other components of the metabolic syndrome: low HDL cholesterol, increased remnant lipoproteins, small LDL particle size, abdominal obesity, hypertension, insulin resistance and glucose intolerance, a proinflammatory state, and a prothrombotic state. Even in the absence of HIV disease, the metabolic syndrome is associated with increased cardiovascular risk. The primary treatment target for the metabolic syndrome is obesity, and recommended measures include diet and exercise. Even modest reductions in body weight improve the dyslipidemia, hypertension, and glucose intolerance, as well as levels of inflammatory and thrombotic markers.
Similar to other patients with chronic infection, HIV patients have higher levels of high-sensitivity C-reactive protein compared with age- and sex-matched control subjects. C-reactive protein was an independent predictor of 5-year mortality in 1 small study of HIV-infected women. The antiinflammatory effects of statins might thus contribute to any benefit these drugs might have in HIV patients, as they also might in patients without HIV disease.

Little research has been done on smoking cessation in HIV patients, and no smoking cessation guidelines specific to this population have been formulated. The prevalence of cigarette smoking in HIV patients has been reported to be as high as 70% to 80% in some areas, and HIV patients appear to be less likely to have contemplated quitting compared with other smokers. Smokers who quit progress through the stages of precontemplation, contemplation, preparation, action, and maintenance, and low self-efficacy is an independent predictor of failure to quit. Both of these factors suggest that HIV patients may be resistant to smoking cessation therapy. Innovations that have been tested in pilot studies of HIV-infected smokers include a nurse-managed, peer-led intervention and the provision of cellular telephones to low-income, HIV-infected smokers to facilitate counseling. Smoking cessation is probably more important in HIV patients than in other smokers because many of the complications of HIV besides atherosclerosis are facilitated by smoking. This risk factor should be a major focus of attention by the physician in HIV patients.

**HIV-Related Left Ventricular Dysfunction and Myocarditis**

In the era before HAART, congestive heart failure caused by HIV-induced left ventricular dysfunction was diagnosed in 2% of all HIV patients, most commonly in those with the lowest CD4 counts. Global left ventricular dysfunction was detected by echocardiography in 15% of randomly selected HIV patients in 1 series. Myocardial biopsy revealed myocarditis with cardiotropic viral infection in almost all HIV patients in 1 series. Heart failure and left ventricular dysfunction were markers of a dismal prognosis. In the pre-HAART era, in autopsy studies of patients with HIV, myocarditis was identified in more than half of the 71 patients evaluated, and biventricular dilatation was present in 10% of cases. Even in HIV-infected children, depressed left ventricular function and increased left ventricular wall thickness predicted mortality independently of CD4 count. Histological studies show evidence of myocyte hypertrophy or evidence of myocarditis. However, the exact pathogenesis of dilated cardiomyopathy in the setting of HIV infection remains unknown and may involve direct effect of HIV on the heart, toxic effects from antiretroviral therapy, increased cytokine activity, opportunistic infections, illicit drug use, and/or nutritional disorders. The incidence of myocarditis, cardiomyopathy, and heart failure decreased substantially with the introduction of HAART.

**HIV-Related Pulmonary Hypertension**

The incidence of HIV-associated pulmonary hypertension before the advent of HAART was 0.5%. The pathogenesis of HIV-associated pulmonary hypertension is an intriguing puzzle. In patients without HIV infection, a recent report linked infection with human herpesvirus 8 (HHV-8) to primary pulmonary hypertension. HHV-8 is one of the causal agents for Kaposi’s sarcoma; although only a small fraction of patients infected with HHV-8 develop Kaposi’s sarcoma, the magnitude of immunosuppression predicts risk. The seroprevalence of HHV-8 remains high in populations at risk for HIV such as homosexual men in San Francisco. For patients with HIV, HHV-8 may thus be a causative agent for pulmonary hypertension, but this has not yet been demonstrated.

The effect of antiretroviral treatment on pulmonary hypertension is not known; however, in a recent report from the Swiss Cohort Study, pulmonary artery pressure increased in untreated patients but decreased in patients treated with HAART. The oral endothelin receptor antagonist bosentan improved exercise tolerance and hemodynamic measurements in a small study of HIV patients.

**Other HIV-Associated Cardiac Issues**

In a study of HIV patients before HAART, the incidence of pericardial effusion was 11% per year. Most of the effusions were small and asymptomatic. However, AIDS patients with pericardial effusion had a significantly shorter 6-month survival rate compared with AIDS patients without effusions (36% versus 93%). In a retrospective study performed in an urban population, pericardial effusions associated with HIV were the most common type of effusion, representing more than one third of cases. The incidence of pericardial effusions after the introduction of HAART remains unknown.

In patients with HIV infection, Kaposi’s sarcoma represents the most common neoplasm, and cardiac involvement has been reported in autopsy studies. Multiple case reports of primary and secondary cardiac lymphomas in HIV patients that are usually B-cell lymphomas have been reported.

**Conclusions**

The patient introduced at the beginning of this article was started on a β-blocker for his hypertension and a statin medication for his hyperlipidemia, and he was counseled to continue smoking cessation. He underwent exercise treadmill testing after a 6-month period on HAART, and the results were normal. He was then prescribed exercise therapy and recommended smoking cessation. The patient was monitored closely for any cardiac issues related to his HIV infection, and he continued to improve on HAART.
testing, which showed diffuse ST-segment depression <1 minute after exercise. Cardiac catheterization revealed left main and triple-vessel coronary disease, for which he underwent CABG surgery. Because the patient’s lipids have remained difficult to control, he has been changed from Kaletra to Atazanavir.

The long-term effects of HIV infection, the metabolic side effects of HIV medication, and the natural history of CABG in this patient remain unclear. One possible algorithm for evaluating and treating patients with HIV is shown in Figure 4. While studies on these issues are ongoing, cardiologists should remain aware of the possibility of HIV-associated cardiovascular complications in their patients with HIV infection, especially atherosclerosis, and treat all risk factors aggressively.

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References


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