CME CREDIT *EDUCATIONAL OBJECTIVE:* Readers will assess the risk of coronary heart disease in patients infected with human immunodeficiency virus

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Coronary heart disease in people infected with HIV

■ ABSTRACT

People infected with human immunodeficiency virus (HIV) are living longer thanks to effective antiretroviral therapy. As this population ages, cardiovascular disease is becoming an important cause of morbidity and death. The authors of this review discuss the magnitude and likely mechanisms of the risk and strategies for managing it.

■ KEY POINTS

Traditional risk factors are the main contributors to cardiovascular disease in this population, although HIV infection is independently associated with increased cardiovascular risk.

Antiretroviral therapy contributes modestly to the risk of coronary heart disease. Antiretroviral combinations that include protease inhibitors cause the most substantial deleterious changes in lipid levels.

Most changes in lipids and insulin resistance can be managed by adding lipid-lowering and antiglycemic agents and may not require changes to the antiretroviral regimen.

Close attention to drug interactions is important when selecting lipid-lowering medications for patients on antiretroviral therapy to avoid dangerous increases in the levels of certain statins.

Addressing modifiable risk factors such as smoking, obesity, and sedentary lifestyle can have a far greater impact on cardiovascular risk than changes in antiretroviral therapy.

WIDESPREAD USE OF antiretroviral therapy has caused a remarkable decline in rates of morbidity and death related to acquired immunodeficiency syndrome (AIDS) and has effectively made human immunodeficiency virus (HIV) infection a manageable—although not yet curable—chronic condition. And as the HIV-infected population on antiretroviral therapy ages, the prevalence of chronic conditions (eg, cardiovascular disease, hepatic disease, pulmonary disease, non-AIDS cancers) and deaths attributable to these conditions have also increased.[1]

Many of the traditional risk factors for cardiovascular disease in the general population, including smoking, dyslipidemia, and diabetes, are common in HIV-infected patients, and HIV infection itself independently increases the risk of coronary heart disease. In addition, different antiretroviral combinations can contribute, in varying degrees, to changes in lipid levels and insulin resistance, further increasing coronary risk.

Ultimately, however, the immunologic benefits of antiretroviral therapy for individual patients far exceed the modest increase in cardiovascular risk associated with certain regimens. In most cases, careful selection of the initial antiretroviral regimen and the addition of lipid-lowering or glucose-controlling medications (with close attention to drug interactions) can effectively manage the metabolic changes associated with antiretroviral therapy and obviate any premature modification of virologically suppressive regimens.

■ TRADITIONAL CARDIAC RISK FACTORS IN HIV PATIENTS

The risk of coronary heart disease in HIV patients is influenced mostly by traditional factors

such as age, smoking, diabetes, and dyslipidemia, including high levels of total cholesterol and low-density lipoprotein cholesterol (LDL-C) and low levels of high-density lipoprotein cholesterol (HDL-C).[2]

In various large cohorts, HIV-infected men had a higher prevalence of smoking,[3] a lower mean HDL-C level,[3,4] and a higher mean triglyceride level[3,4] than men without HIV infection, placing them at greater risk of coronary heart disease. However, even after adjusting for traditional risk factors, rates of atherosclerosis are still higher in people who are infected with HIV than in those who are not.[5]

EFFECT OF HIV INFECTION ON CORONARY RISK

HIV infection has been shown to increase coronary risk.

In the Kaiser Permanente database,[6] HIV-positive patients had a significantly higher rate of hospitalizations for coronary heart disease than did people who were not infected.

Similarly, in a cohort study of almost 4,000 HIV-infected patients and more than 1 million controls, the risk of acute myocardial infarction was 75% higher for HIV-positive patients than for HIV-negative patients, even after adjusting for sex, race, hypertension, diabetes, and dyslipidemia.[5]

The Fat Redistribution and Metabolism (FRAM) cross-sectional study[7] showed that HIV infection was associated with greater carotid intima media thickness, an established marker of atherosclerosis, independently of traditional risk factors and to virtually the same degree as smoking and male sex.

Other studies of subclinical atherosclerosis in HIV patients have yielded disparate results, likely because of differences in study design, methods of measuring carotid thickness, and characteristics of the study populations (eg, prevalence of cardiovascular risk factors and stage of HIV disease). However, a meta-analysis of six prospective cohort studies, three case-control studies, and four cross-sectional studies confirmed that HIV patients had slightly but statistically significantly greater carotid intima media thickness than HIV-negative people.[8]

> **HIV infection has become a manageable, although not yet curable, chronic condition**

MECHANISMS BY WHICH HIV MAY PROMOTE CORONARY HEART DISEASE

The pathogenesis of coronary heart disease in HIV infection has not been fully elucidated, but the virus appears to contribute directly to the accelerated development of atherosclerosis. It may do so through direct effects on cholesterol processing and transport, attraction of monocytes to the intimal wall, and activation of monocytes to induce an inflammatory response and endothelial proliferation.

Effects on lipids

In early HIV infection, levels of total cholesterol and HDL-C are lower. In more advanced infection, lower CD4+ lymphocyte counts have been associated with lower levels of apolipoprotein B and with smaller LDL-C particles, suggesting that HIV affects lipid processing and delivery to vessel walls.[9] HIV infection is also associated with reduced clearance of LDL-C.[10] HIV appears to specifically inhibit the compensatory efflux of excess cholesterol from macrophages, thus promoting the formation of foam cells in atherosclerotic plaque.[11]

Attraction of monocytes to the vessel wall

In vitro studies also suggest that HIV enhances migration of monocytes into the vascular intima during atherosclerotic plaque development by promoting secretion of the chemokine monocyte chemoattractant protein 1[12] and the expression of endothelial cell adhesion molecules such as intercellular adhesion molecule 1, vascular cell adhesion molecule 1 (VCAM-1), and E-selectin.[13]

Inflammation

A recent study suggests that chronic inflammation may be a key contributor to the accelerated development of atherosclerosis in HIV patients. Hsue et al[14] compared carotid intima media thickness and levels of C-reactive protein (a marker of systemic inflammation) in HIV-positive and HIV-negative patients. The carotid intima media thickness was greater in all groups of HIV patients, irrespective of level of viremia or exposure to antiretroviral therapy, than in healthy controls. In addition, C-reactive protein levels remained elevated in

HIV-infected participants regardless of their level of viremia.

These findings suggest not only that HIV-associated atherosclerosis is determined by advanced immunodeficiency, high-level viremia, and exposure to antiretroviral drugs, but also that persistent inflammation due to HIV infection may play an important role in accelerated atherosclerosis.

■ EFFECT OF ANTIRETROVIRAL THERAPY ON CORONARY RISK

Antiretroviral therapy is associated with a small but significant increase in coronary risk.

Medi-Cal,[15] a retrospective study of 28,513 patients, found antiretroviral therapy to be associated with coronary heart disease among patients 18 to 33 years of age (relative risk 2.06, $P < .001$).

The Data Collection on Adverse Events of Anti-HIV Drugs study[16] prospectively followed 23,437 patients for 94,469 person-years. Adjusted for exposure to nonnucleoside reverse transcriptase inhibitors and for hypertension and diabetes, the relative risk of myocardial infarction per year of protease inhibitor exposure was 1.16 (95% confidence interval [CI] 1.10–1.23). The relative risk was lower after adjusting for serum lipid levels but remained significant at 1.10 (95% CI 1.04–1.18).

Reports have been mixed regarding a possible association between myocardial infarction and the nucleoside reverse transcriptase inhibitor abacavir (Ziagen): several studies found a statistically significant association,[17–20] and others did not.[21–23] Differences in study design (observational cohort studies vs prospective randomized clinical trials), populations studied (differing in age, cardiovascular risk factor prevalence, and whether the patients had already been exposed to treatment), and outcome definition probably contributed to the different conclusions.

On the other hand, several studies have shown that suppression of HIV with antiretroviral therapy actually improves some of the surrogate markers of cardiovascular disease. For example:

- Markers of endothelial function such as flow-mediated vasodilation improve significantly within 4 weeks of a patient's starting antiretroviral therapy, regardless of the class of antiretroviral drug used.[24]
- After viral suppression is achieved, levels of the markers of endothelial activation VCAM-1 and P-selectin decline significantly, as do levels of the adipocyte activation marker leptin and the coagulation marker D-dimer.[25,26]
- Levels of the anti-inflammatory markers adiponectin and interleukin 10 increase.[25,26]

Interrupting antiretroviral therapy may increase coronary risk

Not only is uncontrolled viral replication in untreated HIV infection associated with cardiovascular disease, but interrupting antiretroviral therapy may result in a supplementary increase in coronary risk.

In the 5,472-patient Strategies for Management of Antiretroviral Therapy (SMART) trial, the rate of cardiovascular disease events was higher if treatment was interrupted than with continuous treatment, with a hazard ratio of 1.57 (95% CI 1.0–2.46, $P = .05$).[27]

This association between treatment interruption and coronary events does not appear to be related to the level of viremia.[28] Rather, development of cardiovascular disease in HIV-infected patients who interrupt antiretroviral therapy may be mediated, to a large extent, by chronic inflammation in the setting of viral replication. In the treatment-interruption group, levels of the inflammatory cytokine interleukin 6 (IL-6) and the coagulation marker D-dimer were significantly elevated 1 month after randomization, and these differences were strongly associated with death (odds ratio [OR] 12.6, $P < .0001$ for IL-6; OR 13.1, $P < .0001$ for D-dimer). Elevated IL-6 levels were also significantly associated with the development of cardiovascular disease (OR 2.8, $P = .03$).[29]

■ METABOLIC COMPLICATIONS OF ANTIRETROVIRAL THERAPY

Persons with HIV infection may experience metabolic complications that are due to HIV itself or to its treatment.

Cross-sectional studies that included HIV-negative patients as controls have demonstrat-

The benefits of antiretroviral therapy far exceed its cardiovascular risk

TABLE 1

Lipid changes associated with protease inhibitors

PROTEASE INHIBITOR	TOTAL CHOLESTEROL	HDL-C	LDL-C	TRIGLYCERIDES
Atazanavir (Reyataz)[34,35]	No change	No change	Small increase	No change
Atazanavir + ritonavir (Norvir)[34,35]	No change	No change	Moderate increase	Small increase
Darunavir (Prezista) + ritonavir[36]	No change	No change	Small increase	Small increase
Fosamprenavir (Lexiva) + ritonavir[37]	Moderate increase	No change	Small increase	Moderate increase
Lopinavir-ritonavir coformulated (Kaletra)[38]	Moderate increase, more than with ritonavir alone	No change	Small increase, but not more than with ritonavir alone	Moderate increase, but not more than with ritonavir alone
Nelfinavir (Viracept)[35,39]	Small increase	No change	Moderate increase	Small increase
Ritonavir (low dose for boosting)[40]	Small increase	Small decrease	Moderate increase	Moderate increase
Saquinavir (Invirase) + ritonavir[41]	Moderate increase	No change	Small increase	Small increase
Tipranavir (Aptivus) + ritonavir[33]	Moderate increase	Not known	Not known	Large increase

This table is not meant to be used for direct comparative purposes, as it is based on separate studies that compared only a few agents.

ed changes in lipid processing that are known to promote atherosclerosis. For example, persons with HIV infection have smaller LDL-C particles[30] and higher levels of circulating oxidized LDL-C.[31]

In the Multicenter AIDS Cohort Study (MACS), after HIV seroconversion, nonfasting total cholesterol, LDL-C, and HDL-C levels declined, which is consistent with a chronic inflammatory state. After antiretroviral therapy was started, lipid levels returned to baseline levels or slightly higher except for HDL-C, which remained low.[9] These changes may be due to a general "return to health," or they may be direct medication effects.

Similar patterns were seen in the SMART study.[28] Participants randomized to receive intermittent antiretroviral therapy had overall decreases in all lipid levels, with a marked reduction in HDL-C, while those randomized to receive continuous therapy had increased levels of all lipids, including HDL-C, at 12 months. Overall, the ratio of total cholesterol to HDL-C actually increased for participants on episodic therapy, while it decreased in the continuous-treatment group. Along with continued vascular inflammation, the low HDL-C may have contributed to the worse cardiovascular outcomes in patients who received intermittent antiretroviral therapy.

Some lipid changes associated with antiretroviral therapy may actually be beneficial. For example, nonnucleoside reverse transcriptase inhibitors may raise HDL-C levels. However, such increases alone do not necessarily offset the other lipid changes or translate to an observed improvement in coronary risk.[32]

The degree of dyslipidemia and specific lipid changes differ among the different classes of antiretroviral drugs and even among the individual drugs within each class. Furthermore, the magnitude of the observed lipid changes varies widely among patients on the same antiretroviral regimen, reflecting the likely important role of host genomics.

While the protease inhibitors and nonnu-

TABLE 2

Lipid changes associated with nonnucleoside reverse transcriptase inhibitor use

NONNUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITOR	TOTAL CHOLESTEROL	HDL-C	LDL-C	TRIGLYCERIDES
Efavirenz (Sustiva)[43]	Increase	Increase	Increase	Increase
Etravirine (Intelence)[45]	No change	No change	No change	No change
Nevirapine (Viramune)[44]	Increase	Larger increase than with efavirenz	Increase	Smaller increase than with efavirenz

cleoside reverse transcriptase inhibitors have well-described effects on lipids (described in greater detail in the following sections), there have been no reported significant changes in lipid profiles or cardiovascular risk associated with the newest classes, ie, fusion inhibitors such as enfuvirtide (Fuzeon), CC chemokine receptor type 5 (CCR5) receptor inhibitors such as maraviroc (Selzentry), or integrase inhibitors such as raltegravir (Isentress).

Impact of protease inhibitors on lipids
Most protease inhibitors raise lipid levels, but the drugs in this class appear to differ in important ways (**TABLE 1**).[33–41]

Ritonavir (Norvir) and ritonavir-boosted protease inhibitor combinations cause the most significant increases in lipids. Currently, ritonavir is used in low doses to boost the levels of most other protease inhibitors as the standard of care in protease inhibitor-based regimens. However, in most patients, giving ritonavir with protease inhibitors raises lipid levels, particularly triglycerides.

Most boosted protease inhibitor regimens have similar effects on lipid levels, with some exceptions.

Tipranavir (Aptivus) plus ritonavir, for example, markedly raises total cholesterol and triglyceride levels and would not be recommended for patients with dyslipidemia at baseline.[33]

Atazanavir (Reyataz)[34,35] plus ritonavir and **darunavir** (Prezista)[36] plus ritonavir cause more modest lipid changes. Unboosted atazanavir raises lipid levels only minimally, if at all,[34,35] but it is no longer a preferred regimen

according to US Department of Health and Human Services guidelines.[42]

Impact of nonnucleoside reverse transcriptase inhibitors on lipids
Nonnucleoside reverse transcriptase inhibitors are also associated with lipid abnormalities, but to a lesser extent than the protease inhibitors (**TABLE 2**).[43–45]

Efavirenz (Sustiva), a nonnucleoside reverse transcriptase inhibitor, when added to a regimen of two or three nucleoside reverse transcriptase inhibitors, resulted in modest increases in all lipids, including HDL-C (a potentially beneficial change) at 96 weeks compared with a regimen of three nucleoside reverse transcriptase inhibitors only.[43]

Nevirapine (Viramune), compared with efavirenz, results in a more favorable lipid profile in previously untreated patients, as shown by larger increases in HDL-C and smaller increases in triglycerides at 48 weeks.[44]

Etravirine (Intelence), the newest nonnucleoside reverse transcriptase inhibitor, does not appear to cause any further increase in lipids when added to a regimen containing darunavir-ritonavir and nucleoside agents.[45]

Impact of nucleoside reverse transcriptase inhibitors on lipids
As a class, nucleoside reverse transcriptase inhibitors have been associated with mitochondrial toxicity and insulin resistance,[46] but the lipid changes associated with them are generally less significant than those caused by protease inhibitors or nonnucleoside reverse transcriptase inhibitors. Nevertheless, within

The risk of coronary heart disease in HIV patients is influenced mostly by traditional factors

the class, there is considerable variability in lipid changes associated with specific agents.

Stavudine (Zerit), for example, is associated with hypertriglyceridemia.

Tenofovir (Viread), for another example, in combination with emtricitabine (Emtriva) and the nonnucleoside reverse transcriptase inhibitor efavirenz (the three drugs are contained in a formulation called Atripla) was associated with a smaller increase in fasting total cholesterol than with zidovudine-lamivudine and efavirenz at 96 weeks.[47]

A recent placebo-controlled, crossover, pilot study of 17 HIV-infected patients suggested that tenofovir may actually have independent lipid-lowering properties.[48]

Abacavir, as discussed above, has been reported to be associated with a higher risk of myocardial infarction, but this is debatable.

■ MANAGING CORONARY RISK FACTORS IN HIV-INFECTED PATIENTS

Cardiovascular risk assessment

In HIV patients, cardiovascular risk can be assessed using models derived from large epidemiologic studies such as the Framingham Heart Study.[49]

Current guidelines from the Infectious Diseases Society of America and the AIDS Clinical Trials Group (ACTG) for evaluating and managing dyslipidemia in HIV-infected adults are based on the National Cholesterol Education Program Adult Treatment Panel III.[50] They recommend obtaining a fasting lipid profile before starting antiretroviral therapy and within 3 to 6 months after starting a new regimen.

The guidelines also recommend stratifying risk by counting the number of cardiovascular risk factors, as is done for the general population. If the patient has more than two factors, the Framingham equation should be used to calculate the 10-year risk of myocardial infarction or cardiac death. Interventions should be offered for modifiable cardiovascular risk factors such as smoking, hypertension, physical inactivity, and diabetes mellitus. LDL-C goals should be determined, and lipid-lowering drugs should be initiated accordingly. If triglyceride levels are 200 to 500 mg/dL and levels of "non-HDL-C" (total cholesterol minus the HDL-C level) are high, a statin is recom-

mended. If the triglyceride level is higher than 500 mg/dL, a fibrate should be started.[51]

Dyslipidemia management

In HIV patients, statin and fibrate therapy must be considered cautiously, given the important drug interactions with protease inhibitors and especially ritonavir. Many statins are metabolized by cytochrome P3A4, which protease inhibitors inhibit.

Statins generally considered safe to use with most protease inhibitors:
- Pravastatin (Pravachol)
- Rosuvastatin (Crestor)
- Atorvastatin (Lipitor).

Exceptions and caveats:
- Pravastatin should not be prescribed with boosted darunavir.
- Data for fluvastatin (Lescol) in HIV-infected patients on antiretroviral therapy are limited.
- Lovastatin (Mevacor) and simvastatin (Zocor) are contraindicated with protease inhibitor therapy.[52]
- In contrast to the increase in statin levels seen with protease inhibitors, efavirenz lowers levels of simvastatin, pravastatin, and atorvastatin.[53,54]

TABLE 3[50,52–57] summarizes the effects of protease inhibitors and nonnucleoside reverse transcriptase inhibitors on statin levels.

Ezetimibe (Zetia), which is metabolized independently of the cytochrome P450 system, has been shown to be safe and effective when given to HIV-infected patients on antiretroviral therapy.[58]

Fenofibrate (Lofibra) is recommended by current guidelines for patients with elevated triglyceride levels (> 500 mg/dL).[51] In the ACTG 5087 study, a combination of fenofibrate plus pravastatin was found to be safe and effective in improving lipid profiles.[59]

Long-acting niacin resulted in significant improvements in triglycerides, total cholesterol, HDL-C, and LDL-C after 48 weeks of use, although insulin sensitivity worsened.[60]

Fish oil has been shown to be an effective alternative to fibrates, or it can be used in combination with them.[61]

Switching antiretroviral agents vs adding lipid-lowering agents. In some patients with significant dyslipidemia, switching antiretro-

HIV appears to contribute directly to accelerated development of atherosclerosis

TABLE 3

Effect of protease inhibitors and nonnucleoside reverse transcriptase inhibitors on statins

STATIN	PROTEASE INHIBITORS	NONNUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS
Atorvastatin (Lipitor)	Caution (moderately increase atorvastatin's area under the curve [AUC]) Use lowest starting atorvastatin dose	Allowed with appropriate dosing and monitoring Efavirenz (Sustiva)[53] and etravirine (Intelence)[54] decrease atorvastatin's AUC No data for nevirapine (Viramune) May need higher atorvastatin starting dose
Fluvastatin (Lescol)	Use not recommended with nelfinavir (Viracept) Use of other protease inhibitors is allowed with appropriate dosing and monitoring	Allowed with appropriate dosing and monitoring Etravirine may increase fluvastatin's AUC[54] May need lower fluvastatin starting dose with etravirine
Lovastatin (Mevacor)	Contraindicated (greatly increase lovastatin's AUC[52])	Allowed with appropriate dosing and monitoring Decreases simvastatin's AUC May need higher lovastatin starting dose
Pravastatin (Pravachol)	Allowed with appropriate dosing and monitoring[50] Decrease pravastatin's AUC, except for darunavir (Prezista), which increases pravastatin's AUC by 81%[55]	Allowed with appropriate dosing and monitoring Efavirenz decreases pravastatin's AUC,[53] but no change with etravirine[54] No data for nevirapine May need higher pravastatin starting dose with efavirenz
Rosuvastatin (Crestor)	Allowed with appropriate dosing and monitoring Lopinavir-ritonavir (Kaletra) and tipranavir (Aptivus) + ritonavir (Norvir) increase rosuvastatin's AUC[56] May need to start rosuvastatin at lower dose with lopinavir-ritonavir Superior to pravastatin in HIV patients in one study[57]	Allowed with appropriate dosing and monitoring
Simvastatin (Zocor)	Contraindicated (greatly increase simvastatin's AUC[52])	Allowed with appropriate dosing and monitoring Efavirenz[53] and etravirine[54] decrease simvastatin's AUC No data for nevirapine May need higher simvastatin starting dose

viral agents may lower lipid levels without compromising virologic control.[62] However, due to the multifactorial nature of dyslipidemia in HIV patients on antiretroviral therapy, switching the HIV therapy alone may not result in sufficient improvement in the lipid profile[45] and may be associated with virologic failure, particularly among patients who have underlying treatment-resistant HIV.[63]

In many cases, adding lipid-lowering agents may be more beneficial than switching the antiretroviral therapy. For example, a randomized trial in HIV-infected patients with hyperlipidemia found that adding a lipid-lowering agent such as pravastatin or bezafibrate to the unchanged antiretroviral regimen resulted in greater improvement in total cholesterol, LDL-C, and triglyceride levels than switching from a protease inhibitor to either nevirapine or efavirenz.[64]

Given the complexity of prescribing lipid-lowering therapies to patients on antiretroviral therapy, we recommend that providers check with a pharmacist or refer to package inserts and other medical literature if they are unfamiliar with these drug interactions and responses to lipid-lowering therapies.

Managing insulin resistance

Diabetes mellitus is a well-known risk factor for coronary heart disease. The Data Collection on Adverse Events of Anti-HIV Drugs study found a higher incidence of coronary heart disease in HIV-infected patients, with higher rates in those with longer duration of diabetes.[65] The prevalence of diabetes in HIV-infected populations varies, depending on demographic characteristics,[65,66] prevalence of coinfection with hepatitis C virus,[66] and prevalence of exposure to antiretroviral drugs[67] in the study population.

Drugs that lessen insulin resistance include the thiazolidinedione rosiglitazone (Avandia) and the biguanide metformin (Glucophage). In a randomized trial, both drugs, alone or in combination, improved insulin sensitivity in HIV-infected patients, but neither lessened the amount of visceral or subcutaneous fat.[68]

Smoking cessation

Smoking is another well-known modifiable risk factor for coronary heart disease.

The prevalence of smoking is usually higher in HIV patients than in HIV-negative people. For example, a French cohort study reported smoking prevalence rates of 56.6% in HIV-infected men vs 32.7% in HIV-negative men; in women, the rates were 58% vs 28.1%. The 5-year relative risk of coronary heart disease in HIV-infected vs HIV-negative persons was 1.20 for men and 1.59 for women. The estimated attributable risk due to smoking was 65% for men and 29% for women.[3]

Therefore, smoking cessation should be a top priority in managing cardiovascular risk in HIV-infected patients. In fact, control of modifiable risk factors through lifestyle changes such as smoking cessation, dietary changes, and exercise is likely to have a significant impact on cardiovascular risk in this population. ∎

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