Cardiovascular Disease Screening and Prevention in HIV
The HIV and Aging Consensus Project

Recommendations:
- While ART has been implicated as a risk factor for cardiovascular disease (CVD) in HIV-infected patients, traditional CVD risk factors remain the most important.
- HIV-infected patients should be encouraged to modify those risk factors that they can. Cessation of cigarette smoking must be emphasized.
- Newer CVD risk calculators may have a role in assessing risk but have not been validated in HIV-infected patients.
- Statin therapy remains the mainstay in treating hyperlipidemia in HIV-infected patients. The more potent statins are effective and less likely to cause drug interactions.

Cardiovascular Disease (CVD) is the leading cause of death in the United States and worldwide[1]. Since the main predictor of heart disease is age, and since HIV-infected patients are living longer and growing older as a result of effective antiretroviral therapy (ART), the prevalence of CVD will increase [2, 3]. We already observe that 6.5% of AIDS-related mortality is attributable to cardiovascular disease [4].

Background
Several population-based studies have investigated the association between HIV, ART, and CVD. A recent review summarized data from the past ten years and indicated that the CVD risk among HIV-infected is nearly two times higher than in non-infected population [5].

Besides aging, the major Framingham risk factors for heart disease include high blood pressure, hyperlipidemia, diabetes mellitus, and cigarette smoking. All of these are widely prevalent among HIV-infected patients. The attributable contribution of these major risk factors to CVD-associated death is well over 90%, and more than 80% of that risk is attributable to lifestyle-modifiable factors, including high blood pressure, hyperlipidemia, diabetes mellitus, and smoking.

It appears that aging HIV-infected patients have increased exposure to traditional risk factors. The rate of smoking, for example, is two to three times higher among the HIV-infected (40-60%) than in the general population, and it has been suggested that the impact of smoking-related morbidity is greater among the HIV-infected [6]. Insulin resistance and diabetes are also more prevalent in HIV-infected patients. Visceral fat accumulation, a poorly understood complication of HIV or ART, may also contribute to CVD risk in certain patients.

Although the reduction in major CVD risks will continue to be an important prevention modality, studies have shown that these risk factors by themselves do not account for all of the observed increased CVD in HIV-infected patients. An analysis of the Veterans Aging Cohort Study (VACS) Virtual Cohort of more than 27,000 primarily male HIV-infected patients reported that HIV-infected veterans had almost 50% increased relative risk of acute myocardial infarction (MI) compared with those without HIV, even after adjustment for traditional Framingham...
risk factors [2]. This association may be due to a complex interaction between HIV infection and ART that results in increased cardiac events.

The DAD (Data Collection in Adverse Effects of Anti-HIV Drugs) observational cohort study investigated the association of ART and CVD in HIV-infected patients and identified a significant increase in MI risk with ART, especially with the use of protease inhibitors (PI). Most of this effect may be due to metabolic effects of protease inhibitors [7].

Other studies have identified non-PI-based ART as also contributing to CVD risk. Islam and others performed a meta-analysis of observational and randomized controlled trials and found that HIV-infected patients on ART had a higher relative risk of CVD compared with those who were not on ART (2 vs 1.61RR) [8].

The investigators also reported that the relative risk of CVD in patients on non-PI-based ART was higher (1.41RR) compared with those on PI-based ART [7]. Among the non-PI-based ART options, nucleoside reverse transcriptase inhibitors (NRTIs), such as abacavir and didanosine, have been associated with increased MI risk in some but not all studies. The mechanism of this potentially increased risk has not been determined. In fact, the most recent meta-analysis by the U.S. Food and Drug administration has suggested that there is no association between abacavir use and MI [9].

Taken together, these studies suggest that some of the increased CVD risk in the setting of HIV is independent of patient demographics or traditional CVD risk factors, and may be due to direct and indirect effects of certain ART regimens.

In addition to the role of ART in CVD risk, several studies have suggested that uncontrolled HIV infection and greater immunosuppression (low CD4 cell counts) are associated with MI and stroke. The SMART (Strategies for Management of Antiretroviral Therapy) study was the first to identify an increase in cardiovascular events with interruption in ART [10]. Treatment interruption was associated with a 2.6-fold increase in risk of HIV disease progression or death and a 57% increase in risk for the composite endpoint of MI, percutaneous coronary intervention/coronary artery bypass grafting, or cardiovascular death (P = .05) [11].

AIDS Clinical Trials Group (ACTG) researchers studied the impact of ART on endothelial function in a randomized study (ACTG 5152) of various ART regimens, and showed that there was improvement in arterial endothelial function with viral suppression regardless of ART regimen [12]. The greater the reduction in HIV RNA level, the greater the improvement in endothelial function, despite substantial differences among the groups in lipid level changes and irrespective of ART regimen. If there is any increase in CVD risk associated with ART, it appears to be counterbalanced by the potentially beneficial effects (possibly anti-inflammatory) of ART on blood vessels.

CVD mortality trends in HIV-infected women parallel those of the general HIV population, with decreasing AIDS-related mortality accompanied by increasing CVD-related mortality. Nevertheless, HIV may have a greater impact on the CVD risk of women compared with men [13]. In the Partners cohort study, the adjusted RR for MI comparing HIV-infected patients with non-HIV-infected patients was 3.0 for women versus 1.4 for men [14].

The proposed pathogenesis of atherosclerosis and arterial disease in HIV infection is a multifactorial and complex process that is incompletely understood (see Figure 1).

Traditional Framingham risk factors are more prevalent among HIV-infected patients. Dyslipidemia is a well-described independent risk factor for CVD, and it occurs in a high proportion of HIV-infected patients. This dyslipidemia is caused by a combination of factors associated with HIV disease, ART regimens, and individual patient characteristics. It has been known since the 1980s that HIV infection is associated with lipid abnormalities, particularly in persons with more advanced disease who are not on
ART. They often have elevations in triglyceride (TG) levels and decreases in high-density lipoprotein (HDL) as well as in low-density lipoprotein (LDL) cholesterol and total cholesterol (TC).

In the 1990s we observed that dyslipidemia may be caused by certain ART. More recently, we have recognized that persistent inflammation associated with both untreated and well-controlled HIV may also contribute to the observed increased CVD risk [15]. HIV-infected patients with elevated C-reactive protein had an odds ratio for acute MI four times higher than that of patients without HIV who had normal C-reactive protein [16].

This may represent a similar mechanism of increased risk that can be seen in patients with other chronic inflammatory conditions, such as rheumatoid arthritis, systemic lupus erythematosus, and inflammatory bowel disease. The effects of persistent HIV infection may increase immune activation and inflammation, reduce the ability of blood vessels to dilate and generate an anticoagulant surface, and facilitate plaque erosion and rupture associated with acute coronary syndromes.

In summary, the observed increased CVD risk in HIV is a consequence of increased traditional risk factors, as well as immune activation, inflammation, and a possible predisposition to thrombosis from uncontrolled HIV viremia.

CVD Risk Assessment
Assessing risk and preventing CVD in HIV-infected patients remains challenging, as traditional risk models tend to underestimate the risk. The Framingham Risk Score was not designed for use in HIV populations, and a recalibration may be needed to adjust for under- or over-prediction [17]. Although new risk assessment algorithms have been proposed, they have not been validated.

Investigators have used data from the D:A:D study to develop a risk calculator and have compared it to the Framingham risk calculator [18]. They included some ART variables in their models in addition to the traditional Framingham risk factors and found that the D:A:D models performed reasonably well in terms of discriminating risks and performed better in terms of predicted-to-observed number of CVD events [19].

Additional studies have assessed the Systematic Coronary Risk Evaluation (SCORE) and Prospective Cardiovascular Munster (PROCAM) equations in comparison with the Framingham risk calculator, but we don’t have a definitive recommendation as to which is the best risk model and calculator for an HIV patient.

The recently updated IDSA/HIVMA HIV primary care guidelines recommend obtaining a baseline fasting blood glucose and/or hemoglobin A1C and a fasting lipid profile prior to and within three months after starting ART to screen for metabolic syndrome, diabetes mellitus, and dyslipidemia [20]. The fasting lipid profile should be obtained three to six months after initiating or switching ART and then every twelve months thereafter. Blood pressure and weight with body mass index (BMI) calculation should be performed at least annually.
**Figure 1. Factors Contributing to Atherosclerosis and Arterial Injury in HIV-Infected Individuals.** Atherosclerosis and arterial disease in human immunodeficiency virus (HIV)–infected individuals is a multifactorial process involving the virus, antiretroviral therapy, traditional risk factors for cardiovascular disease, and genetic predisposition. Each arrow represents a potential target for research and therapeutic intervention (Adapted from [16]).

**Management of CVD Risk**
Care of the aging HIV-infected patient includes proper management of blood pressure, diabetes risk reduction, smoking cessation, and treatment of dyslipidemia to reduce the cardiovascular risk. All of the available guidelines emphasize the importance of adherence to a heart-healthy lifestyle that includes regular exercise, following a low-glycemic-index diet, maintaining BMI < 25 kg/m², and smoking cessation. Smoking cessation might be the single most important factor in reducing CVD risk. Both aspirin and statins are effective for primary and secondary CVD prevention in the general population.

The guiding principle of CVD risk management is that a patient's absolute CVD risk determines the intensity of interventions. The HIVMA/IDSA and ACTG refer to the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) from 2003 for goals of lipid parameters. Risk is determined by counting CVD risk factors and calculating the Framingham Risk Score.

The recent (2013) American College of Cardiology/American Heart Association (ACC/AHA) guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults, however, represents a major shift from prior cholesterol management guidelines. The ACC/AHA guidelines address the broader outcome of clinical atherosclerotic CVD (ASCVD), which includes CVD, MI, stroke, and peripheral arterial disease, not just MI or CV death.

The ACC/AHA guidelines do not emphasize treatment-specific goals based on LDL targets [21]. These guidelines take a different approach to many aspects of lipid management, including the evaluation of patients for lipid-lowering therapy, the use
and monitoring of lipid-lowering agents, and the use of treatment targets.

The ACC/AHA guidelines focus on treatment of LDL-C that is based on risk and not on LDL-C level. Risk assessment is used to identify patients to treat, and the intensity of treatment is based on clinical trials evidence; without LDL targets. To estimate ten-year ASCVD risk, the ACC/AHA guidelines employ a new global risk-assessment tool with new pooled cohort risk equations adapted for different genders and race (non-Hispanic whites and African-Americans in the U.S.). The Pooled Cohort Equations CV Risk Calculator can be found at [http://my.americanheart.org/professional/StatementsGuidelines/PreventionGuidelines/PreventionGuidelines_UCM_457698_SubHomePage.jsp](http://my.americanheart.org/professional/StatementsGuidelines/PreventionGuidelines/PreventionGuidelines_UCM_457698_SubHomePage.jsp).

The ACC/AHA guidelines have not been validated in HIV-infected patient populations. A recent study compared the ACC/AHA and NCEP/ATP III recommendations among 108 HIV patients without known CVD and obtained contrast-enhanced cardiac computed tomography angiography to evaluate the cohort for high-risk morphology (HRM) plaque formation [22]. The study found that by applying the 2013 ACC/AHA guidelines, a higher percentage (26% vs 10%) of subjects with and without HRM coronary plaque would receive statin therapy relative to applying the recommendations from NCEP guidelines.

Statins represent the primary ASCVD prevention intervention. Statins are an attractive option in HIV because, in addition to their cholesterol-lowering properties, they have anti-inflammatory effects that may further reduce CVD and all-cause mortality.

A previously published cohort study has identified a significant survival benefit for HIV-infected statin users who were virologically controlled on ART. Thresholds for initiating statin therapy were derived from large randomized controlled trials. The choice of statin and dose was recommended based on estimated level of risk for a patient (Table 1). If the patient had major cardiovascular risk factors such as clinical ASCVD, LDL-C>190 mg/dL, or age 40 to 75 years with diabetes mellitus, or if the calculated ten-year risk of ASCVD was >7.5%, then the guidelines recommended moderate-to high-intensity statin therapy. The definition of high-intensity statin therapy is LDL-C reduction of >50% and that of moderate-intensity therapy is a reduction of 30% to 50%.

### Table 1: Summary of key recommendations from the 2013 ACC/AHA cholesterol guideline

<table>
<thead>
<tr>
<th>Groups most likely to benefit from statin therapy</th>
<th>Recommended statin intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary prevention for patients with clinical ASCVD</td>
<td>High intensity</td>
</tr>
<tr>
<td>Primary prevention for LDL-C&gt;190 mg/dL</td>
<td>High intensity</td>
</tr>
<tr>
<td>Primary prevention for diabetics aged 40–75 years with LDL-C 70–189 mg/dL and without clinical ASCVD</td>
<td>≥7.5% 10-year risk—high intensity &lt;7.5%10-year risk—moderate intensity</td>
</tr>
<tr>
<td>Primary prevention for non-diabetics aged 40–75 years with an estimated 10-year ASCVD risk &lt;7.5%</td>
<td>Moderate to high intensity if appropriate after clinician–patient discussion</td>
</tr>
</tbody>
</table>
Choice of statin and dose intensity are listed in Table 2. Statin doses that have been used in clinical trials of primary prevention include low- to moderate-intensity (pravastatin 40 mg; lovastatin 20 to 40 mg; atorvastatin 10 mg) and high-intensity (atorvastatin 40 mg; rosuvastatin 20 mg) therapy. No trials have directly compared the effects of low- to moderate-intensity with high-intensity statin therapy for primary prevention.

Because simvastatin and lovastatin interact with cytochrome P450 3A4 (CYP3A4) inhibitors, as is the case with most PIs, these statins should avoided with PIs or cobicistat that inhibit CYP3A4. Dose modification may be needed for most statins and PIs, NNRTIs, and the pharmacokinetic enhancer cobicistat because potential drug interactions increase the risk of severe statin adverse events such as rhabdomyolysis. Atorvastatin, if used, should be initiated at low dosage (10 mg) and titrated slowly upward. Lovastatin and simvastatin are contraindicated for use by patients taking PIs or cobicistat. Other available statins include rosuvastatin, pitavastatin, and fluvastatin. These have not been as well studied but may be used with most PIs started at low dosage and increased incrementally, if indicated; in general, maximum dosages should not be used.

Table 2: Choice of Statin and Dose Intensity Options

<table>
<thead>
<tr>
<th>Statin</th>
<th>Dose and Expected LDL-C % lowering</th>
</tr>
</thead>
<tbody>
<tr>
<td>atorvastatin (Lipitor)</td>
<td>10mg 20mg 40mg 80mg</td>
</tr>
<tr>
<td>pravastatin (Pravacol)</td>
<td>10mg 20mg 40mg 80mg</td>
</tr>
<tr>
<td>rosuvastatin (Crestor)</td>
<td>5mg 10mg 20mg 40mg</td>
</tr>
<tr>
<td>fluvastatin (Lescol)</td>
<td>20mg 40mg 80mg</td>
</tr>
<tr>
<td>simvastatin (Zocor)</td>
<td>5mg 10mg 20mg 40mg</td>
</tr>
<tr>
<td>pitavastatin (Livalo)</td>
<td>1mg 2mg 4mg</td>
</tr>
<tr>
<td>lovastatin (Mevacor)</td>
<td>10mg 20mg 40mg 80mg</td>
</tr>
</tbody>
</table>

The fact that the ACC/AHA guidelines do not recommend LDL-C targets does not mean that lipid panels should not be measured. Lipid panels should be checked at least annually to see if the prescribed statin therapy has put the patient in a reasonable range for ASCVD risk. Likewise, if LDL-C <40 mg/dL, it may be too low, and the patient’s statin dosage should be lowered. Finally, if the patient’s LDL-C is not low enough for moderate to high ASCVD risk, then clinicians should emphasize lifestyle modifications.
Some patients are unable to take statin medications because of side effects—most commonly myalgias and other muscular symptoms. Clinicians may consider multiple interventions to control statin myopathy (e.g., switching statin, dose reduction, alternative dosing schedules, Coenzyme Q10 supplementation). In general, clinicians should discontinue statin therapy until symptoms are evaluated. They should consider other conditions that might increase the risk for muscle symptoms, such as hypothyroidism, kidney/liver disease, rheumatologic disorders, steroid myopathy, low Vitamin D status, or primary muscle diseases. If, after two months without statin therapy, muscle symptoms or elevated creatinine kinase levels do not resolve completely, clinicians should consider other causes of muscle symptoms.

The ACC/AHA guidelines have generated controversy, since they present a simpler approach than previous guidelines and focus on the broader ASCVD risk and not just CVD risk. The AHA/ACC calculator includes diabetes mellitus, but only as a yes/no question. Issues that may affect risk with diabetes mellitus include patient age, sex, other CV risk factors, duration of the disease, and whether the patient has type 1 or type 2. The ACC/AHA calculator does not include family history of premature CVD in the model and may underestimate risk in patients with very strong family histories of CV events.

Based on current data, there is not enough evidence to suggest that HIV-infected patients need a more aggressive approach to the management of CVD risk compared with that recommended for uninfected people. But efforts to apply the newer 2013 ACC/AHA guidelines broadly would raise the level and intensity of CVD preventive management for aging HIV-infected patients compared with the NCEP/ATP III guidelines. Before initiating statin therapy, clinicians should engage in a patient discussion of the potential for ASCVD risk, potential benefits of statin therapy, potential for adverse effects, medication interactions, and patient preferences.

Non-statin lipid-lowering agents such as niacin, fibers, fish oil, and ezetimibe have not shown enough benefit in randomized trials to merit recommendation in the 2013 ACC/AHA guidelines. The triglyceride level is a primary target of lipid-lowering therapy only when the triglyceride level exceeds 500 mg/dL, because of the associated risk of pancreatitis. Although high triglyceride levels may be a modest independent risk factor, triglycerides are most associated with other cardiovascular risk factors (e.g., low HDL-C level, hypertension, obesity, inflammation, and insulin resistance).

For triglyceride levels below 500 mg/dL, LDL-C should be targeted to reduce CVD risk. For higher triglyceride levels, where the primary goal of treatment is to prevent pancreatitis, fibrates are the preferred initial therapy. Dietary intervention can also have a dramatic effect on triglyceride levels. Patients should restrict saturated fats and trans-fats, emphasize intake of omega-3 fatty acids and mono-unsaturated fats, limit simple carbohydrates and calories, and reduce alcohol intake. Fish oil in a dose of 3 grams per day can lower triglyceride levels by up to 25%.

Summary

The prevalence of cardiovascular disease is increasing as HIV-infected patients live longer, age, and acquire traditional cardiovascular disease risk factors. The new ACC/AHA guidelines introduce several major paradigm shifts. These include aiming for ASCVD risk reduction as opposed to targeting LDL-C levels, promoting the use of evidence-based doses of statins as first-line therapy, and utilizing a new risk calculator and risk cut point to guide initiation of statin therapy. Although lowering cardiovascular risk is focused on statin therapy and lifestyle modification, controlling virus levels is crucial as well.

Updated in Feb. 2016, by James M. Sosman, MD FACP AAHIVS Medical Director, HIV Care Program & MATEC-WI Dvrs. General Medicine & Infectious Disease Professor of Medicine U Wisconsin School of Medicine & Public Health.
References


