

## Perspective

# Cardiovascular Complications of HIV Infection

*HIV-infected individuals are at increased risk for cardiovascular events. Widely used cardiovascular disease (CVD) risk calculators to determine indications for statin treatment are not well validated for use in the HIV-infected population. Some experts advocate including HIV infection as an independent risk factor for CVD. The effects of antiretroviral therapy on lipid profiles and the potentially increased risk for cardiovascular events must be taken into account when selecting treatment for HIV-infected individuals. There is increasing evidence that chronic immune activation and inflammation play a role in the pathogenesis of CVD in the context of HIV infection. This article summarizes a presentation by Marshall J. Glesby, MD, PhD, at the Ryan White HIV/AIDS Program Clinical Care Conference held in New Orleans, Louisiana, in December 2015.*

**Keywords:** HIV, cardiovascular disease risk, CVD, antiretroviral therapy, statins, immune activation, inflammation

Cardiovascular disease (CVD) is a major cause of morbidity and mortality in persons with HIV infection. Meta-analyses suggest that CVD risk is increased by approximately 1.5 to 2.0 fold among HIV-infected individuals compared with the general population.<sup>1</sup> Data from the D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) study indicate that CVD accounts for approximately 11% of deaths among HIV-infected individuals,<sup>2</sup> and data from the EuroSIDA study indicate that cardiovascular events account for approximately one-third of non-AIDS-defining clinical events in the HIV-infected population.<sup>3</sup>

## CVD Risk Prediction

A number of CVD risk calculators are available, although the most commonly used have generally not been validated for use in HIV-infected individuals. CVD risk calculators include the American Heart Association (AHA)/American College of Cardiology (ACC) 2013 pooled cohort risk calculator,<sup>4</sup> the Framingham Risk Score,<sup>5</sup> and the D:A:D 5-Year Estimated CVD Risk Equation, which is specific for HIV infection, but has not been validated for use outside of the dataset from which it was derived.

## Management of Dyslipidemia

High- and moderate-intensity statin therapy, based on 10-year risk for first atherosclerotic cardiovascular event, using

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the AHA/ACC 2013 pooled cohort risk calculator are shown in Table 1. The National Lipid Association suggests that lipid goals be based on the number of risk factors present (Table 2), and has indicated that HIV infection status may be counted as a risk factor.<sup>6</sup> However, the effect of antiretroviral therapy on lipids should also be considered in the context of HIV infection.

Numerous studies have shown that lipid effects vary by antiretroviral regimen. In the SWITCH-ER randomized, double-blinded, crossover study of 57 individuals receiving an efavirenz-containing antiretroviral regimen, participants received raltegravir or efavirenz for 2 weeks and were then switched to the opposite treatment for 2 weeks. During the 2 weeks of treatment with raltegravir, there were median reductions of 16 mg/dL in total cholesterol level ( $P < .001$ ), 18 mg/dL in triglyceride level ( $P = .036$ ), 8 mg/dL in LDL-C level ( $P = .004$ ), and 4 mg/dL in HDL-C level ( $P = .005$ ), with a 0.1 reduction in LDL-C:HDL-C ratio ( $P = .97$ ).<sup>7</sup> Efavirenz has been shown to increase HDL-C level, whereas a decrease in HDL-C level was observed after switching to raltegravir, contributing to the lack of substantial change in LDL-C:HDL-C ratio.

In the SINGLE trial of approximately 90 participants who received a regimen of abacavir/lamivudine (slash indicates a coformulation) plus dolutegravir or of tenofovir disoproxil fumarate (TDF)/emtricitabine/efavirenz, increases of 17.1 and 24.0 mg/dL, respectively, were observed in total cholesterol level; 5.2 and 7.9 mg/dL, respectively, in HDL-C level; 8.5 and 13.1 mg/dL, respectively, in LDL-C level; and 17.7 and 18.6 mg/dL, respectively, in triglyceride level, indicating greater increases in levels of atherogenic lipids as well as HDL-C in the group receiving efavirenz.

**Table 1.** Recommendations for High- and Moderate-Intensity Statin Therapy Based on 10-Year Risk for First ASCVD Event<sup>a</sup>

High-Intensity Statin Therapy (Daily Dose Lowers LDL-C Level by $\geq 50\%$ on Average)	Moderate-Intensity Statin Therapy (Daily Dose Lowers LDL-C Level by 30%-50% on Average)
Atorvastatin 40-80 mg	Atorvastatin 10-20 mg
Rosuvastatin 20-40 mg	Rosuvastatin 5-10 mg
	Simvastatin 20-40 mg
	Pravastatin 40-80 mg
	Lovastatin 40 mg
	Fluvastatin XL 80 mg
	Fluvastatin 40 mg
	Pitavastatin 2-4 mg

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; XL, extended release. Data compiled from the American Heart Association and the American College of Cardiology.<sup>4</sup>

<sup>a</sup>Adults aged 40 to 75 years with an LDL-C level of 70 to 189 mg/dL, no diabetes, and an estimated 10-year ASCVD risk of 7.5% or higher should be treated with moderate- or high-intensity statin therapy.

**Table 2.** National Lipid Association Criteria for ASCVD Risk Assessment, Treatment Goals, and Drug Therapy

Risk Category	Criteria	Treatment Goal <sup>a</sup>	Consider Drug Therapy <sup>a</sup>
Low	≤1 Major ASCVD risk factor Consider other risk indicators, if known <sup>b</sup>	non-HDL-C <130 mg/dL, LDL-C <100 mg/dL	non-HDL-C ≥190 mg/dL, LDL-C ≥160 mg/dL
Moderate	2 Major ASCVD risk factors Consider quantitative risk scoring Consider other risk indicators	non-HDL-C <130 mg/dL, LDL-C <100 mg/dL	non-HDL-C ≥160 mg/dL, LDL-C ≥130 mg/dL
High	≥3 Major ASCVD risk factors Diabetes mellitus (type 1 or 2) 0-1 Other major ASCVD risk factors and no evidence of end-organ damage CKD stage 3B or 4 LDL-C ≥190 mg/dL (severe hypercholes- terolemia) Quantitative risk score reaching the high-risk threshold	non-HDL-C <130 mg/dL, LDL-C <100 mg/dL	non-HDL-C ≥130 mg/dL, LDL-C ≥100 mg/dL
Very high	ASCVD Diabetes mellitus (type 1 or 2) ≥2 Other major ASCVD risk factors or evidence of end-organ damage	non-HDL-C <100 mg/dL, LDL-C <70 mg/dL	non-HDL-C ≥100 mg/dL, LDL-C ≥70 mg/dL

Abbreviations: ASCVD indicates atherosclerotic cardiovascular disease; CKD, chronic kidney disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. Adapted from Jacobson et al.<sup>6,25</sup>

<sup>a</sup>Non-HDL-C cholesterol is total cholesterol minus HDL-C.

<sup>b</sup>HIV infection may be counted as an ASCVD risk factor.

Results from the AIDS Clinical Trials Group (ACTG) A5206 study support observations that TDF appears to reduce levels of atherogenic lipids via a mechanism that remains unclear. In the crossover study, 17 virologically suppressed participants on non-TDF-containing regimens who had some degree of dyslipidemia—defined as elevated triglyceride or non-HDL-C (total cholesterol minus HDL-C) levels—were randomly assigned to add TDF or a placebo to their existing regimen and then to receive a placebo or TDF after a washout period.<sup>8</sup> During treatment with TDF compared with placebo, there were significant reductions in levels of total cholesterol (18% vs 4%;  $P = .01$ ), non-HDL-C (16% vs 2%;  $P = .02$ ), and LDL-C (12% vs 5%;  $P = .04$ ), and nonsignificant differences in levels of HDL-C (an 8% decrease vs a 4% increase;  $P = .93$ ) and triglycerides (a 4% decrease vs a 14% decrease;  $P = .81$ ).

Studies comparing lipid changes during treatment with elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (TAF) and treatment with elvitegravir/cobicistat/emtricitabine/TDF indicate that increases in levels of total cholesterol, LDL-C, HDL-C, and triglycerides were statistically significantly lower with the TAF-containing than the TDF-containing regimen over 48 weeks, possibly reflecting the lower plasma concentrations of tenofovir associated with TAF use. However, there was no statistically significant difference in change in total cholesterol:HDL-C ratio.<sup>9</sup>

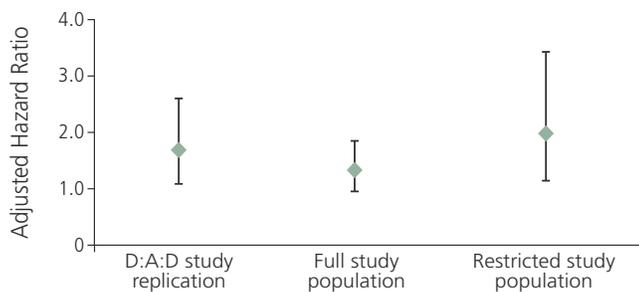
Questions remain regarding the association between abacavir and MI risk, but it may be reasonable to avoid use

of abacavir for some individuals at high risk for cardiovascular events. There has been some concern that any increased risk for MI associated with abacavir use reflected a channeling bias in earlier observational studies,<sup>10-12</sup> in which participants at increased risk of nephrotoxic effects who might also have increased concurrent CVD risk factors were more likely to be given abacavir. However, a recent update from the D:A:D cohort indicates an approximately 2-fold increased risk of MI with current abacavir use (use within the past 6 months) after adjustment for time period and other CVD risk factors, with a rate of 0.47 per 100 person-years with current abacavir use versus 0.21 per 100 person-years with no abacavir use (relative risk, 1.98).<sup>13</sup>

A recent analysis of data from the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD), a collaboration of 6 clinical cohorts throughout North America, yielded somewhat different information. As shown in Figure 1, analysis of the full study population, including all patients on antiretroviral therapy that did not include abacavir at study entry, showed a nonstatistically significant increase in risk for MI with abacavir use.<sup>14</sup> A replication of the D:A:D analysis adjusted for various risk factors showed a statistically significantly increased hazard ratio (HR) of approximately 1.7, although the HR was not statistically different after adjustment for additional risk factors not used in the initial D:A:D analysis. An analysis that included antiretroviral treatment-naïve persons who initiated treatment showed a statistically significantly increased HR for MI risk associated with abacavir use (which was not necessarily used in the initial regimen), after adjustment for numerous risk factors. These data have yet to be published in full.

The US Food and Drug Administration and an independent group performed a systematic review and meta-analysis that included 26 controlled trials in which participants were randomly assigned to receive abacavir, which ideally eliminates channeling bias. As shown in Figure 2, the meta-analysis found no substantial increase in risk for MI associated with abacavir use in academic center, National Institutes of Health (NIH) ACTG, or manufacturer trials, or all trials combined.<sup>15</sup> However, the studies were generally not of long duration and the absolute number of events was relatively low.

Although a summary of all of the observational studies examining CVD risk in association with abacavir use is beyond



**Figure 1.** Risk of myocardial infarction with abacavir use in North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) analyses. Full study population included all users of antiretroviral therapy that did not include abacavir at study entry. Restricted study population included antiretroviral therapy-naïve individuals initiating treatment (not necessarily including abacavir). For the D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) study replication, hazard ratio was adjusted for cumulative exposure to abacavir, age, sex, race, presence of risk factors for HIV infection, calendar year, body mass index, smoking status, years since initiation of antiretroviral therapy, and cohort. For the restricted study population, hazard ratio was adjusted for age; sex; race; presence of risk factors for HIV infection; calendar year; smoking status; coinfection with hepatitis C virus; concomitant hypertension, diabetes mellitus, or renal impairment; high levels of total cholesterol or triglycerides; statin use; CD4+ cell count; HIV RNA level; history of clinical AIDS; previous use of protease inhibitors; and cohort. Adapted with permission from Palella et al.<sup>14</sup>

the scope of this article, the data are mixed, and there may never be a definitive answer to this question. Nonetheless, numerous observational studies with their inherent biases suggest that abacavir may contribute to MI risk, leading many experts to avoid its use in individuals with substantial CVD risk.

### The Emerging Role of Inflammation

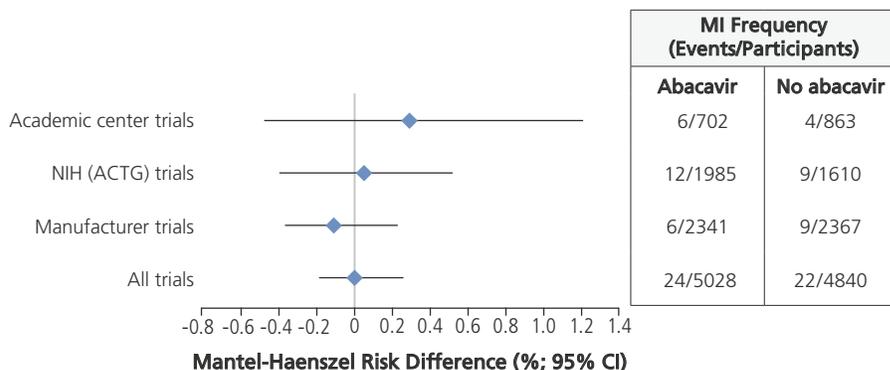
Unstable plaque in coronary arteries is more prone to rupture and to result in cardiovascular events than stable plaque. One study used multidetector spiral coronary computed tomography angiography among 41 HIV-infected and 101 uninfected individuals with a median age of 45 to 48 years matched for major CVD risk factors. HIV-infected individuals were significantly more likely to have high-risk plaques, including low-attenuation plaque ( $P = .02$ ), which was more likely to be associated with the macrophage activation marker soluble (s)CD163.<sup>16</sup> However, it does not appear that widely used CVD risk calculators identify individuals with high-risk morphologic features. In a study of 150 HIV-infected participants, the 2013 ACC/AHA risk calculator indicated that statin treatment was recommended for only approximately 25% of those with high-risk plaques, and the 2004 Adult Treatment Panel III cholesterol guidelines recommended treatment for

only approximately 10% of those with high-risk plaques (Figure 3).<sup>17</sup>

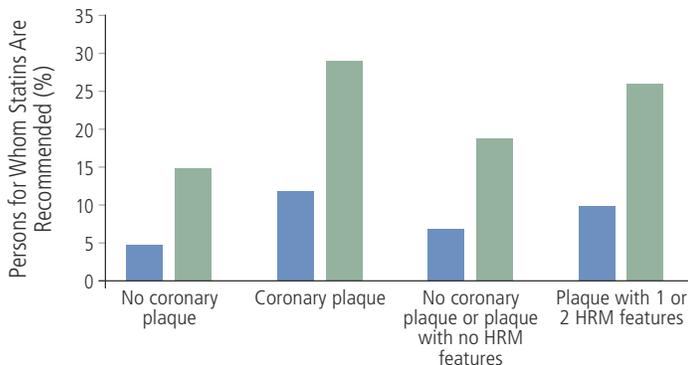
An early indication of the potential effects of inflammation on CVD came from findings in the SMART (Strategies for Management of Anti-Retroviral Therapy) trial, in which more than 5000 participants were randomly assigned to receive continuous antiretroviral therapy or to discontinue antiretroviral therapy (drug-conservation arm) when CD4+ cell count exceeded 350/ $\mu$ L and then resume therapy when it fell below 250/ $\mu$ L.<sup>18</sup> The study was ended early due to excess mortality and clinical events in the drug-conservation arm, including a 50% increase in cardiovascular events compared with the arm receiving continuous treatment. One analysis of participants from the drug-conservation arm showed an association between both the degree of increase of the inflammatory marker soluble interleukin-6 and the degree of decrease of HDL particle number with the magnitude of increase in HIV viral load at 1 month after interruption of antiretroviral therapy.<sup>19</sup> Such findings suggest that increased inflammation with accompanying viremia might contribute to an increased risk for cardiovascular events.

Figure 4 illustrates the potential roles of chronic immune activation and inflammation in the pathogenesis of CVD in the context of HIV infection. Acute HIV infection results in a massive depletion of CD4+ cells throughout the gastrointestinal tract, which permits microbial translocation through the gut into the circulation, and this translocation may drive immune activation and inflammation. Other potential contributors to ongoing inflammation include low-level HIV replication during antiretroviral therapy and viral coinfection, particularly with cytomegalovirus, hepatitis B virus, or hepatitis C virus.

In a study that assessed inflammation of the arterial wall using positron emission tomography and computed tomography scans to measure uptake of tracer in metabolically active macrophages that infiltrated affected vessels, greater inflammation (measured as target-to-background ratio) was found among 27 HIV-infected participants with a mean age of 52 years than among 27 uninfected individuals with matched Framingham Risk scores and a mean age of 54 years;



**Figure 2.** Results from a US Food and Drug Administration meta-analysis of academic center, National Institutes of Health (NIH) AIDS Clinical Trials Group (ACTG), and manufacturer trials indicating that there is no increased risk of myocardial infarction (MI) associated with abacavir use. Adapted from Ding et al.<sup>15</sup>



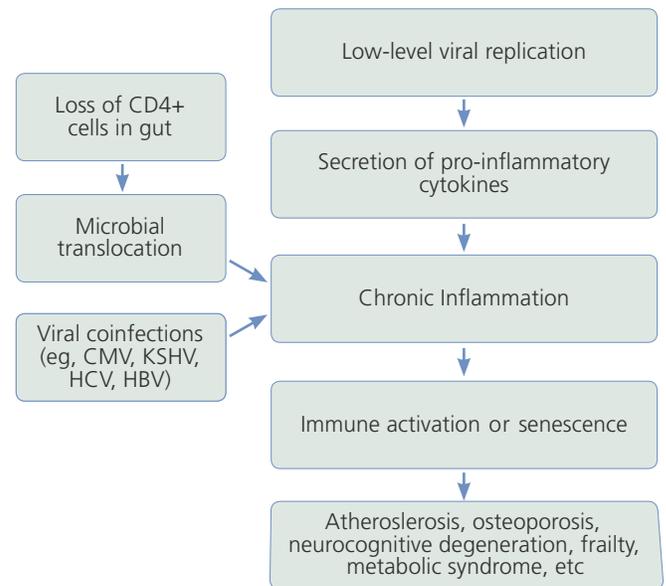
**Figure 3.** Proportion of HIV-infected individuals studied for whom statin treatment was recommended based on 2013 American College of Cardiology (ACC)/American Heart Association (AHA) and 2004 Adult Treatment Panel (ATP) III guidelines, according to coronary plaque status. HRM indicates high-risk morphologic. Adapted from Zanni et al.<sup>17</sup>

inflammation in the HIV-infected group was comparable to that in the 27 uninfected individuals with established atherosclerotic CVD and a mean age of 69 years.<sup>20</sup> The sCD163 marker of macrophage activation was significantly correlated with target-to-background ratio in HIV-infected individuals ( $P = .03$ ). Such findings support the potential role of inflammation in CVD risk in the context of HIV infection.

In a study that assessed whether statin therapy might have a beneficial effect on inflammation, 40 HIV-infected individuals with subclinical coronary atherosclerosis and aortic inflammation (detected by positron emission tomography [PET] imaging) and LDL-C levels below 130 mg/dL were randomly assigned to receive atorvastatin 20 mg with dose escalation to 40 mg or placebo for 12 months.<sup>21</sup> Treatment with atorvastatin did not substantially affect arterial inflammation, although data were not available for 19 participants. However, treatment with atorvastatin did reduce noncalcified plaque volume and other high-risk plaque features.

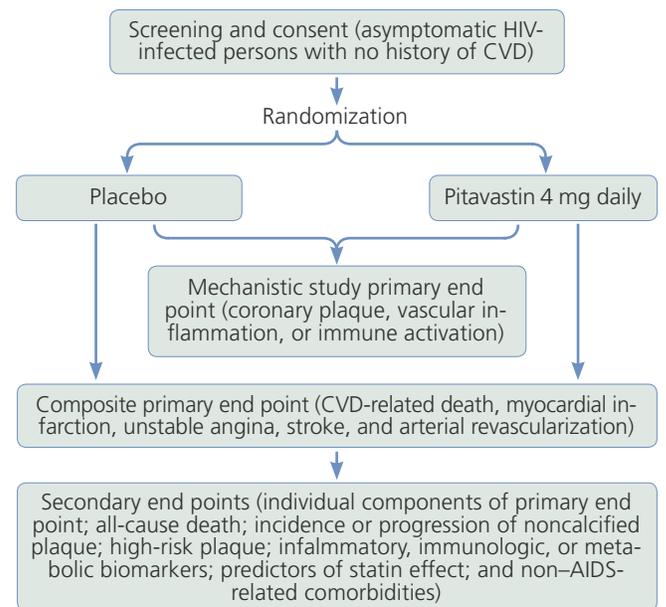
The REPRIEVE (Randomized Trial to Prevent Vascular Events in HIV) trial is currently underway to examine the efficacy of pitavastatin in preventing cardiovascular events in asymptomatic HIV-infected individuals with no history of CVD (Figure 5). Eligible participants have an estimated 10-year risk for cardiovascular events of less than 7.5% and an LDL-C level of less than 190 mg/dL, an estimated risk of 7.5% to 10.0% and an LDL-C level of less than 160 mg/dL, or an estimated risk of 10.0% to 15.0% and an LDL-C level of less than 130 mg/dL. A target population of 6500 individuals aged 40 to 75 years are being randomly assigned to receive pitavastatin 4 mg daily or placebo, with a planned 6-year follow-up period (<https://clinicaltrials.gov, NCT02344290>). The composite primary end point in the REPRIEVE trial is CVD-related death, MI, unstable angina, stroke, and arterial revascularization. A mechanistic substudy is examining the effects of pitavastatin on coronary plaque, vascular inflammation, and immune activation among 800 participants.

Pitavastatin is a newer statin not thought to have interactions with antiretroviral drugs and thus far not associated with



**Figure 4.** The potential roles of chronic immune activation and inflammation in the pathogenesis of cardiovascular disease in HIV-infected individuals. CMV indicates cytomegalovirus; HBV, hepatitis B virus; HCV, hepatitis C virus; KSHV, Kaposi sarcoma–associated herpesvirus. Adapted from Martin et al.<sup>26</sup>

increased risk for diabetes. In a randomized trial of approximately 200 HIV-infected individuals, pitavastatin reduced total cholesterol and LDL-C levels substantially more than did pravastatin 40 mg over 12 months, without significant differences between arms in HDL-C and triglyceride levels.<sup>22</sup>



**Figure 5.** Design of the REPRIEVE (Randomized Trial to Prevent Vascular Events in HIV) trial, which is examining the efficacy of pitavastatin in preventing cardiovascular events in asymptomatic HIV-infected individuals with no history of cardiovascular disease CVD). Adapted with permission from the REPRIEVE protocol team.

With regard to CVD risk, the most important risk factor to address is smoking status. Although somewhat controversial, data from a Danish study indicated that 3 of 4 MIs among people with HIV infection were associated with ever having smoked compared with 1 of 4 MIs among matched uninfected controls.<sup>23</sup> Data from the D:A:D cohort indicate that the risk of MI is lower among persons who have stopped smoking than those who currently smoke (incidence rate ratio, relative to those who never smoked, decreased from 3.73 to 3.00 within the first year after smoking cessation and to 2.07 after  $\geq 3$  years).<sup>24</sup>

## Conclusions

CVD risk stratification tools for the general population are generally not validated for use in the HIV-infected population. It is reasonable to use the Framingham Risk score or AHA/ACC pooled cohort risk calculator for HIV-infected individuals and to consider HIV infection a risk factor, as suggested by the National Lipid Association. Inflammation and immune activation are likely important contributors to atherosclerosis, although much remains to be learned about its pathogenesis in HIV-infected individuals. Whether statins are indicated more broadly in the HIV-infected population remains unclear, and data from the REPRIEVE trial may help to address this question. 

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