The Evolving Landscape of ASCVD Risk Among Patients With HIV

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LEARNING OBJECTIVES

• Summarize the multiple atherosclerotic cardiovascular disease (ASCVD) risk factors commonly present in persons living with human immunodeficiency virus (HIV).
• Identify factors for clinical assessment and risk stratification in persons with HIV (PWH).
• Discuss the clinical challenges of dyslipidemia management among the HIV population, including avoidance of major drug-drug interactions (DDIs).
• Implement appropriate and safe statin therapy in PWH and elevated ASCVD risk.

KEY TAKEAWAYS

• PWH are living longer and developing high rates of cardiometabolic abnormalities, placing this population at elevated risk of ASCVD.
• Antiretroviral therapy (ART) is responsible for reducing opportunistic infections and extending life. However, some ART regimens may be associated with increased incidence of cardiometabolic conditions and significant DDIs with some commonly used statins.
• ASCVD risk is underestimated in PWH, including among routinely used 10-year ASCVD risk calculators.
• Guideline-recommended therapy to manage increased ASCVD risk and low-density lipoprotein cholesterol (LDL-C) in PWH includes the use of statins.

INTRODUCTION

The introduction of potent antiretroviral therapy (ART) in the mid-1990s has markedly reduced mortality among persons with human immunodeficiency virus (PWH). Currently, life expectancy for PWH is approaching that of the general population. As a result, care for PWH has evolved to also manage age-related comorbidities including dyslipidemia, hypertension, and glucose impairment. While traditional risk factors such as smoking, hypertension, and diabetes are more prevalent among PWH than in the general population, such conditions are further exacerbated by chronic human immunodeficiency virus (HIV) infection. Transgender individuals with HIV also have increased atherosclerotic disease (ASCVD) risk due, in part, to the use of hormone therapy in gender-affirming treatment.

As of 2022, approximately 50% of PWH in the United States were >50 years of age, and 80% of that group were men, which further magnifies the overall burden of ASCVD.
in PWH since heart disease manifests a decade earlier in men compared with women.\textsuperscript{11} Even though the proportion of PWH who are virally suppressed has increased as ART regimens have become more potent and better tolerated, chronic HIV infection is associated with increased ASCVD risk, even in the setting of complete viral suppression. In the last decade, the incidence of myocardial infarction and strokes has continued to increase, and ASCVD has emerged as a leading cause of death among PWH.\textsuperscript{12,13}

Polypharmacy is common among older PWH.\textsuperscript{1} Some ART drug classes, including protease inhibitors (PIs) and, to a lesser extent, non-nucleoside reverse transcriptase inhibitors, are associated with significant drug-drug interactions (DDIs) and possible severe drug toxicities.\textsuperscript{14} Therefore, treatment of comorbidities requires careful selection of medications by the clinician. The intent of this discussion is to guide practitioners in assessing ASCVD risk in PWH and safely and effectively managing dyslipidemia.

**ELEVATED ASCVD RISK AMONG PWH**

PWH are 50% to 100% more likely to have an ASCVD event compared with uninfected individuals across all age groups.\textsuperscript{15,16} Increased ASCVD risk in PWH can be partly attributed to higher rates of common risk factors.\textsuperscript{15} However, HIV infection is an independent enhancer of ASCVD risk due to residual immune activation that results in chronic inflammation, increased dyslipidemia, thrombosis, endothelial dysfunction, and vascular inflammation, even in the setting of viral suppression.\textsuperscript{17} Furthermore, after adjustment for traditional risk factors, a clear gradient of ASCVD risk exists among PWH that increases with lower CD4 counts and higher viral loads, indicating the importance of viral control and immune reconstitution with ART.\textsuperscript{18}

Further, it is estimated that up to ~20% of transgender women are living with HIV. Viral suppression rates are lower in this population, possibly due to poor treatment adherence and socioeconomic factors,\textsuperscript{19} resulting in prolonged periods of increased chronic inflammation, which is associated with higher rates of ASCVD.\textsuperscript{13} As noted, hormone therapy as part of gender-affirming treatment in this population is also associated with increased ASCVD risk. Other risk factors associated with HIV and ART are also commonly present in this population (\textbf{TABLE 1}).\textsuperscript{11,20,21}

An important challenge in assessing ASCVD risk in PWH is that widely used risk calculators such as the 2013 American College of Cardiology/American Heart Association (ACC/AHA) Pooled Cohort Equations and the Framingham Risk Score may underestimate ASCVD risk in PWH.\textsuperscript{22-24}

PIs have been associated with significant cardiometabolic toxicities, with the possible exception of atazanavir.\textsuperscript{25,26}

Other contemporary ART classes, including integrase strand transfer inhibitors (INSTIs), may not directly increase cardiovascular (CV) risk, although significant weight gain has been observed with the use of INSTIs and with the nucleoside reverse transcriptase inhibitor tenofovir alafenamide.\textsuperscript{14,27,28}

Insulin resistance drives metabolic changes in PWH, including mixed dyslipidemia.\textsuperscript{3,11,20} PWH often present with low levels of high-density lipoprotein cholesterol (HDL-C), elevated triglycerides, and normal to moderately elevated low-density lipoprotein cholesterol (LDL-C). Approximately 14% of PWH in North America are co-infected with the hepatitis C virus (HCV).\textsuperscript{29} Liver fibrosis due to untreated viral hepatitis or NAFLD in PWH further increases ASCVD risk.\textsuperscript{30} Smoking rates in PWH are 2- to 3-fold higher compared with the general population, while physical activity is lower.\textsuperscript{3,11,32} Higher rates of substance abuse (eg, alcohol, illicit drugs) and mood disorders also contribute to ASCVD risk, while gender-based discrimination and violence are more widespread and associated with poor health outcomes.\textsuperscript{9,32}

Inflammation and immune activation negatively impact atherosclerosis and elevate ASCVD risk in PWH.\textsuperscript{10,11,21} Compared with those without HIV, PWH have increased high-risk noncalcified carotid plaque, which is even observed in young PWH with few traditional CV risk factors.\textsuperscript{33} CAC has also been shown to progress more rapidly in PWH compared with people without HIV.\textsuperscript{34} In addition to their lipid-lowering properties, statins may also help to reverse atherosclerosis caused by chronic inflammation in PWH. Rosuvastatin has been shown to reduce ASCVD events in patients without HIV with increased inflammatory markers but normal LDL-C, as well as to decrease markers of immune activation and vascular inflammation, compared with placebo in a small trial of PWH.\textsuperscript{10,35} Another trial in PWH demonstrated improvements in biomarkers of immune activity and inflammation with pitavastatin, which produced significantly greater reductions of soluble CD14, oxidized LDL-C, and lipoprotein-associated phospholipase 2 compared with pravastatin.\textsuperscript{36} Collectively, statins appear to mitigate some of the unique risk factors that accelerate atherosclerosis and predispose PWH to CV events.

**STATIN THERAPY IN HIV POPULATIONS AND THE IMPACT ON ASCVD AND MORTALITY**

Statin therapy remains the foundation for lowering LDL-C and managing CV risk factors observed in PWH.\textsuperscript{3,11,21} Challenges persist, however, including the avoidance of major DDIs and addressing disparities in access to care and inconsistencies in management of traditional risk factors in different populations. Critical questions are still being answered including, do statins reduce ASCVD events in...
Common cardiometabolic abnormalities and ASCVD risk factors among PWH

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mixed dyslipidemia</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
</tr>
<tr>
<td>Insulin resistance/glucose impairment</td>
<td></td>
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<tr>
<td>Systemic inflammation</td>
<td></td>
</tr>
<tr>
<td>Endothelial dysfunction</td>
<td></td>
</tr>
<tr>
<td>Weight gain, ↑ central obesity</td>
<td></td>
</tr>
<tr>
<td>Thrombosis</td>
<td></td>
</tr>
<tr>
<td>Immune activation</td>
<td></td>
</tr>
<tr>
<td>Hepatic steatosis</td>
<td></td>
</tr>
<tr>
<td>Gut dysbiosis</td>
<td></td>
</tr>
<tr>
<td>↑ ↑ behavioral/lifestyle factors</td>
<td></td>
</tr>
<tr>
<td>Gender-affirming treatments</td>
<td></td>
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</tbody>
</table>

PWH? Further, it is widely reported that statins are underused and underdosed in PWH. Studies indicate that clinicians are less likely to prescribe statin therapy to high-risk PWH, while those who receive a statin are more likely to receive less-intensive therapy.

Prior studies suggested ASCVD event reductions with statins in HIV-infected cohorts are similar to those in the general population. The need for a large primary prevention, randomized, placebo-controlled statin trial to assess the effect of statins beyond lipid-lowering in PWH was recognized by the National Institutes of Health, with the development of the Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE). This trial has enrolled >7700 PWH in 12 countries between the ages of 40 and 75 years, randomized to either pitavastatin 4 mg daily or matching placebo. The REPRIEVE trial is primarily designed to measure the impact of statin therapy on ASCVD outcomes in PWH, but also includes an important substudy evaluating the relationship between immune and inflammatory biomarkers and coronary plaque. The trial is scheduled to be completed in 2023, with results expected shortly thereafter.

**CLINICAL CHALLENGES AND CONCERNS**

ASCVD risk assessment and management of dyslipidemia among PWH is essential. Comorbidities in PWH may include NAFLD and coinfection with chronic viral hepatitis B or HCV. Importantly, most statins can be safely used in patients with NAFLD and/or HCV or with mildly elevated hepatic transaminases. In fact, drug-induced liver injury and overall mortality were each significantly less frequent in patients with untreated dyslipidemia, diabetes mellitus, or a high calculated ASCVD risk. Consequently, statin selection should be based on the potential for DDIs with ART.

**CLINICAL ASSESSMENT AND RISK STRATIFICATION**

All adult PWH require ASCVD risk assessment. Statins are underprescribed and underdosed in PWH, resulting in lower LDL-C reduction. Lipid panels are recommended initially and again with ART modification. Unfortunately, ASCVD risk calculators (ACC/AHA Pooled Cohort Equation, Framingham Risk Score) may underestimate risk in PWH. A CAC can be considered in selected individuals when the decision about whether to initiate a statin is uncertain.

**GUIDELINE REVIEW: TREATMENT**

Specific ASCVD risk management recommendations for PWH are evolving from major guideline organizations. After ASCVD risk assessment, an initial emphasis on therapeutic lifestyle changes cannot be overstated. Increasing physical activity, smoking cessation, and maintaining mental health wellness are a few components that reduce ASCVD risk and improve quality of life for PWH. Early initiation of ART and maintenance of viral suppression are critical to limit ASCVD events and overall mortality for all PWH. Interrupted ART is strongly associated with an increase in acute ASCVD events and death. Second, comprehensive management of modifiable risk factors is important. Lastly, statins should be considered for all adult PWH with established ASCVD, untreated dyslipidemia, diabetes mellitus, or a high calculated ASCVD risk. Statin therapy should also be considered for PWH with moderate calculated ASCVD risk or with HIV-related risk-enhancing factors such as prolonged viremia, low CD4 nadir, metabolic syndrome, history of NAFLD, or HCV.
TABLE 1. Common cardiometabolic abnormalities and ASCVD risk factors among PWH

- Mixed dyslipidemia
- Hypertension
- Insulin resistance/glucose impairment
- Systemic inflammation
- Endothelial dysfunction
- Weight gain, ↑ central obesity
- Thrombosis
- Immune activation
- Hepatic steatosis
- Gut dysbiosis
- ↑ ↑ behavioral/lifestyle factors
- Gender-affirming treatments

TABLE 2. Statin dose recommendations with HIV protease inhibitors

<table>
<thead>
<tr>
<th>Statin</th>
<th>Effect of PIs and cobicistat on statin</th>
<th>Statin dose recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>Moderate AUC ↑↑</td>
<td>Avoid TPV/RTV</td>
</tr>
<tr>
<td></td>
<td>Use lowest starting dose: LPV/RTV</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dose limit 20 mg: DRV/RTV, FPV/RTV, SQV/RTV, or FPV alone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dose limit 40 mg: NLV</td>
<td></td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>No data with most PIs except NLV</td>
<td>Appropriate dosing and monitoring, except not recommended with NLVa</td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>Minor/modest AUC changes</td>
<td>No dose adjustments needed</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>Mostly minor/modest AUC changes, except with DRV AUC ↑ 81%</td>
<td>No dose adjustments needed except use lower starting dose: DRV</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>Some moderate AUC ↑↑; others only minor AUC changes</td>
<td>Dose limit 10 mg: ATV/RTV, LPV/RTV</td>
</tr>
<tr>
<td></td>
<td>Use lowest effective dose: DRV/RTV</td>
<td></td>
</tr>
<tr>
<td>Lovastatin</td>
<td>All PIs and cobicistat: AUC ↑↑↑</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>All PIs and cobicistat: AUC ↑↑↑</td>
<td>Contraindicated</td>
</tr>
</tbody>
</table>

Abbreviations: ACC/AHA, American College of Cardiology/American Heart Association; ESC/EAS, European Society of Cardiology/European Atherosclerosis Society; NLA, National Lipid Association; TLC, therapeutic lifestyle changes.

a Limited data, based on known metabolism of fluvastatin.

TABLE 3. Key cholesterol guideline recommendations for primary prevention in adults with HIV

<table>
<thead>
<tr>
<th>HIV CV risk status</th>
<th>ACC/AHA 2018</th>
<th>ESC/EAS 2019</th>
<th>NLA 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid goals and treatment</td>
<td>Optimize TLC including smoking cessation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 40-75 years old with LDL-C 70-189 mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 10-year ASCVD risk ≥7.5%</td>
<td>Many HIV patients qualify as high risk</td>
<td></td>
</tr>
<tr>
<td></td>
<td>o Favors moderate- to high-intensity statin</td>
<td>• Goal: LDL-C reduction &gt;50% and LDL-C &lt;70 mg/dL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 10-year ASCVD risk ≥5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>o Consider moderate-intensity statin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preferred statins (based on potential for major DDIs)</td>
<td>None specified</td>
<td>Fluvastatin, pravastatin, pitavastatin, rosuvastatin</td>
<td>Pitavastatin (no dose limits)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Atorvastatin or rosuvastatin (with dose limitations)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>Consider CAC to further risk stratify</td>
<td>Consider CV imaging (eg, CAC) as a risk modifier in primary prevention patients</td>
<td>Obtain a fasting lipid panel before and after initiating ART</td>
</tr>
<tr>
<td>Obtain a fasting lipid panel to:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Evaluate ASCVD risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Monitor and adjust lipid-altering therapy, before and 4-12 weeks after initiating ART</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ACC/AHA, American College of Cardiology/American Heart Association; ESC/EAS, European Society of Cardiology/European Atherosclerosis Society; NLA, National Lipid Association; TLC, therapeutic lifestyle changes.

*Defined as a clinical condition or factor that is associated with ASCVD and used to inform therapy decisions.

Coinfection. Statins may also be indicated for PWH without dyslipidemia with low to moderate calculated ASCVD risk as they improve underlying abnormalities (eg, inflammation, immune activation, endothelial dysfunction) beyond LDL-C. The results of the REPRIEVE trial will help to determine the role of statins in this population.
**CASE SCENARIO (CONT'D)**

This PWH has multiple cardiometabolic issues and underesti-

mated ASCVD risk, as the CAC indicates significant subclinical
disease. Guidelines would favor prescribing a moderate-inten-
sity statin and carefully selecting an agent based on potential
for DDIs (noting that cobicistat inhibits CYP3A4). A statin is not
contraindicated due to the NAFLD and slightly elevated hepatic
transaminases.

**SUMMARY**

PWH are living longer and commonly develop cardiometabolic
conditions and accelerated atherosclerosis because of
traditional risk factors and underlying chronic inflammation.
ASCVD risk in PWH is often underestimated, and dyslipid-
emia management can pose challenges for the clinician,
including the avoidance of major DDIs. Guidelines suggest
ASCVD risk should be assessed for all adult PWH and appro-
priate and safe statin therapy implemented among those
with elevated ASCVD risk.

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