The Evolving Landscape of ASCVD Risk Among Patients With HIV

Carlos Malvestutto, MD, MPH

doi: 10.12788/jfp.0412

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.

FACULTY

Carlos Malvestutto, MD, MPH, Associate Professor of Medicine, Division of Infectious Diseases, The Ohio State University Wexler Medical Center, Columbus, Ohio.

DISCLOSURES

Dr. Malvestutto discloses that he serves on an advisory board for ViiV Healthcare Inc and is a clinical investigator in a clinical trial sponsored by Kowa Pharmaceuticals. Dr. Backes has no disclosures to report.

ACKNOWLEDGMENT

Editorial support was provided by Jim Backes, PharmD.

SPONSORSHIP

This activity is sponsored by Primary Care Education Consortium and the Primary Care Metabolic Group and supported by funding from Kowa Pharmaceuticals America, Inc.

CASE SCENARIO

A 48-year-old white man with HIV, metabolic syndrome, nonalcoholic fatty liver disease (NAFLD), and hypertension presents to clinic. He denies current alcohol, tobacco, or illicit drug use, but has a 50-pack-year smoking history. To help guide therapy, a coronary artery calcium (CAC) scan was performed.

Key Information

Laboratory: Lipid panel (mg/dL): total cholesterol 191; LDL-C 118; high-density lipoprotein cholesterol (HDL) 37; triglycerides 180; non-HDL 154

Hepatic enzymes slightly increased; high-sensitivity C-reactive protein 5 mg/dL (<3); glycated hemoglobin (HbA1c) 6.2%

Other: BP 124/78 mm Hg; 10-year ASCVD risk score 4.1%; CAC – 103 (moderate calcium deposits)

Medications: lisinopril, escitalopram, darunavir/cobicistat + tenofovir alafenamide + emtricitabine

INTRODUCTION

The introduction of potent antiretroviral therapy (ART) in the mid-1990s has markedly reduced mortality among persons with human immunodeficiency virus (PWH).[1,2] 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.[1,3] While traditional risk factors such as smoking,[4,5] hypertension,[6,7] and diabetes[8] are more prevalent among PWH than in the general population, such conditions are further exacerbated by chronic human immunodeficiency virus (HIV) infection.[3] Transgender individuals with HIV also have increased atherosclerotic disease (ASCVD) risk due, in part, to the use of hormone therapy in gender-affirming treatment.[9]

As of 2022, approximately 50% of PWH in the United States were >50 years of age, and 80% of that group were men,[10] which further magnifies the overall burden of ASCVD

in PWH since heart disease manifests a decade earlier in men compared with women.[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.[12,13]

Polypharmacy is common among older PWH.[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.[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.[15,16] Increased ASCVD risk in PWH can be partly attributed to higher rates of common risk factors.[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.[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.[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,[19] resulting in prolonged periods of increased chronic inflammation, which is associated with higher rates of ASCVD.[9] 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 (**TABLE 1**).[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.[22-24]

PIs have been associated with significant cardiometabolic toxicities, with the possible exception of atazanavir.[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.[14,27,28]

Insulin resistance drives metabolic changes in PWH, including mixed dyslipidemia.[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).[29] Liver fibrosis due to untreated viral hepatitis or NAFLD in PWH further increases ASCVD risk.[30] Smoking rates in PWH are 2- to 3-fold higher compared with the general population, while physical activity is lower.[3,31,32] 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.[9,32]

Inflammation and immune activation negatively impact atherosclerosis and elevate ASCVD risk in PWH.[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.[33] CAC has also been shown to progress more rapidly in PWH compared with people without HIV.[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.[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.[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.[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

TABLE 1. **Common cardiometabolic abnormalities and ASCVD risk factors among PWH**[3,11,20,21]

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

PWH? Further, it is widely reported that statins are underused and underdosed in PWH.[37] Studies indicate that clinicians are less likely to prescribe statin therapy to high-risk PWH,[38] while those who receive a statin are more likely to receive less-intensive therapy.[39]

Prior studies suggested ASCVD event reductions with statins in HIV-infected cohorts are similar to those in the general population.[40-42] 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).[43] 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.[33] 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.[3,21] Comorbidities in PWH may include NAFLD and coinfection with chronic viral hepatitis B or HCV.[37] Importantly, most statins can be safely used in patients with NAFLD and/or HCV or with mildly elevated hepatic transaminases.[11,32] In fact, drug-induced liver injury and overall mortality were each significantly less frequent among statin users compared with statin nonusers with HIV/HCV or HIV alone.[44] Although liver function monitoring after starting statins is not recommended by the Food and Drug Administration, clinicians may consider checking liver enzymes 1 month after initiating statins in patients who may have preexisting conditions or who take other medications that could increase the risk of liver toxicity. Persistently elevated hepatic transaminases exceeding 3 times the upper limit of normal is the threshold for dose reduction or discontinuing statin therapy.[3,11]

Major DDIs between statins and ART primarily involve the PIs (**TABLE 2**).[3,42] Importantly, the PI boosters ritonavir and cobicistat, designed to specifically inhibit the metabolism of PIs (and of the INSTI elvitegravir) to achieve higher serum levels, also inhibit cytochrome P450 3A4 enzyme-dependent statins (ie, lovastatin, simvastatin), markedly increasing statin serum levels and potentially resulting in myotoxicity.[11,14,32] Consequently, statin selection should be based on the potential for DDIs with ART (**TABLE 2**).[3,11,21]

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.[37-39] Lipid panels are recommended initially and again with ART modification.[10] Unfortunately, ASCVD risk calculators (ACC/AHA Pooled Cohort Equation, Framingham Risk Score) may underestimate risk in PWH.[3,24] A CAC can be considered in selected individuals when the decision about whether to initiate a statin is uncertain.[11,21]

GUIDELINE REVIEW: TREATMENT

Specific ASCVD risk management recommendations for PWH are evolving from major guideline organizations (**TABLE 3**).[3,11,21] 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.[45] Second, comprehensive management of modifiable risk factors is important.[3,11,21] 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 2. **Statin dose recommendations with HIV protease inhibitors**[3,10]

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

Abbreviations: ATV, atorvastatin; AUC, area under the curve; DRV, darunavir; FPV, fosamprenavir; LPV, lopinavir; NLV, nelfinavir; RTV, ritonavir; SQV, saquinavir; TPV, tipranavir.

[a]Limited data, based on known metabolism of fluvastatin.

TABLE 3. **Key cholesterol guideline recommendations for primary prevention in adults with HIV**[3,11,21]

	ACC/AHA 2018	ESC/EAS 2019	NLA 2015
HIV CV risk status	Risk enhancer[a]	Confers↑ risk	Independent risk factor
Lipid goals and treatment	Optimize TLC including smoking cessation • 40-75 years old with LDL-C 70-189 mg/dL • 10-year ASCVD risk ≥7.5% ○ Favors moderate- to high-intensity statin • 10-year ASCVD risk ≥5% ○ Consider moderate-intensity statin	Many HIV patients qualify as high risk • Goal: LDL-C reduction >50% and LDL-C <70 mg/dL	Emphasize TLC • Diet/exercise • Smoking cessation HIV + 2 other risk factors • Goal: LDL-C <100 mg/dL and non-HDL <130 mg/dL
Preferred statins (based on potential for major DDIs)	None specified	Fluvastatin, pravastatin, pitavastatin, rosuvastatin	Pitavastatin (no dose limits) Atorvastatin or rosuvastatin (with dose limitations)
Other	Consider CAC to further risk stratify Obtain a fasting lipid panel to: • Evaluate ASCVD risk • Monitor and adjust lipid-altering therapy, before and 4-12 weeks after initiating ART	Consider CV imaging (eg, CAC) as a risk modifier in primary prevention patients	Obtain a fasting lipid panel before and after initiating ART

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

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

coinfection.[32] 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.[3] 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 underestimated ASCVD risk, as the CAC indicates significant subclinical disease. Guidelines would favor prescribing a moderate-intensity 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 dyslipidemia 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 appropriate and safe statin therapy implemented among those with elevated ASCVD risk. ●

REFERENCES

1. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. Department of Health and Human Services. Accessed April 12, 2022. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/ AdultandAdolescentGL.pdf
2. Marcus JL, Leyden WA, Alexeeff SE, et al. Comparison of overall and comorbidity-free life expectancy between insured adults with and without HIV infection, 2000-2016. *JAMA Netw Open.* 2020;3(6):e207954-e207954.
3. Jacobson TA, Maki KC, Orringer CE, et al. National Lipid Association recommendations for patient-centered management of dyslipidemia: Part 2. *J Clin Lipidol.* 2015;9(6 suppl):S1-122.e121.
4. Mdodo R, Frazier EL, Dube SR, et al. Cigarette smoking prevalence amoung adults with HIV compared with the general adult population in the United States: cross-sectional surveys. *Ann Intern Med.* 2015;162(5):335-344.
5. Asfar T, Perez A, Shipman P, et al. National estimates of prevalence, time-trend and correlates of smoking in US people living with HIV (NHANES 1999-2016). *Nicotine Tobacco Res.* 2021;23(8):1308-1317.
6. Xu Y, Chen X, Wang K. global prevalence of hypertension amoung people living with HIV: a systematic review and meta-analysis. *J Am Soc Hypertens.* 2017;11(8):530-540.
7. Olaiya O, Weiser J, Zhou W, Patel P, Bradley H. Hypertension amound persons living with HIV in medical care in the United States-Medical Monitoring Project, 2013-2014. *Open Foum Infect Dis.* 2018;5(3):ofy028.
8. Hernandez-Romieu AC, Garg S, Rosenbert EI, Thompson-Paul AM, Skarbinski J. Is diabetes prevalence higher amoung HIV-infected individuals compared with the general population? Evidence from MMP and NHANES 2009-2010. *BMJ Open Diabetes Res Care.* 2017;5(1):e000304.
9. Smeaton LM, Kileel EM, Grinsztejn B, et al. Characteristics of REPRIEVE trial participants identifying across the transgender spectrum. *J Infect Dis.* 2020;222(1 suppl):S31-S40.
10. Thompson MA, Horberg MA, Agwu AL, et al. Primary care guidance for persons with human immunodeficiency virus: 2020 update by the HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis.* 2021;73(11):e3572-e3605.
11. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2019;73(24):e285-e350.
12. Feinstein MJ, Bahiru E, Achenbach C, et al. Patterns of cardiovascular mortality for HIV-infected adults in the United States: 1999 to 2013. *Am J Cardiol.* 2016;117(2):214-220.
13. Chow FC, Regan S, Feske S, Meigs JB, Grinspoon SK, Triant VA. Comparison of ischemic stroke incidence in HIV-infected and non-HIV-infected patients in a US health care syste. *J Acquir Immune Defic Syndr.* 2012;60(4):351-358.
14. Kellick KA, Bottorff M, Toth PP. The National Lipid Association's Safety Task F. A clinician's guide to statin drug-drug interactions. *J Clin Lipidol.* 2014;8(3 suppl):S30-46.
15. Triant VA. Epidemiology of coronary heart disease in patients with human immunodeficiency virus. *Rev Cardiovasc Med.* 2014;15(1 suppl 1):S1-8.
16. Currier JS. Update on cardiovascular complications in HIV infection. *Topics in HIV Med.* 2009;17(3):98-103.
17. Hsue PY, Waters DD. HIV infection and coronary heart disease: mechanisms and management. *Nature Rev Cardiol.* 2019;16(12):745-759.
18. Freiberg MS, Chang C-CH, Kuller LH, et al. HIV infection and the risk of acute myocardial infarction. *JAMA Intern Med.* 2013;173(8):614-622.
19. Mizuno Y, Frazier EL, Huang P, Skarbinski J. Characteristics of transgender women living with HIV receiving medical care in the United States. *LGBT Health.* 2015;2(3):228-234.
20. Wang SC, Kaur G, Schulman-Marcus J, et al. Implementation of cholesterol-lowering therapy to reduce cardiovascular risk in persons living with HIV. *Cardiovasc Drugs Ther.* 2020;36(1):173-186.
21. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). *Eur Heart J.* 2019;41(1):111-188.
22. Friis-Moller N, Thiebaut R, Reiss P, et al. Predicting the risk of cardiovascular disease in HIV-infected patients: the data collection on adverse effects of anti-HIV drugs study. *Eur J Cardiovasc Prev Rehabil.* 2010;17(5):491-501.
23. Parra S, Coll B, Aragones G, et al. Nonconcordance between subclinical atherosclerosis and the calculated Framingham risk score in HIV-infected patients: relationships with serum markers of oxidation and inflammation. *HIV Med.* 2010;11(4):225-231.
24. Triant VA, Perez J, Regan S, et al. Cardiovascular risk prediction functions underestimate risk in HIV infection. *Circulation.* 2018;137(21):2203-2214.
25. d'Arminio Monforte A, Reiss P, Ryom L, et al. Atazanavir is not associated with an increased risk of cardio or cerebrovascular disease events. *AIDS.* 2013;27(3):407-415.
26. Ryom L, Lundgren JD, El-Sadr W, et al. Cardiovascular disease and use of contemporary protease inhibitors: the D:A:D internation prosepctive multicohort study. *Lancet HIV.* 2018;5(6):e291-e300.
27. Vos AG, Venter W. Cardiovascular toxicity of contemporary antiretroviral therapy. *Curr Opin HIV AIDS.* 2021;16(6):286-291.
28. Venter WDF, Sokhela S, Simmons B, et al. Dolutegravir with emtricitabine and tenofovir alafenamide or tenofovir disoproxil fumarate versus efavirenz, emtricitabine, and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection (ADVANCE): week 96 results from a randomised, phase 3, non-inferiority trial. *Lancet HIV.* 2020;7(10):e666-e676.
29. Platt L, Easterbrook P, Gower E, et al. Prevalence and burden of HCV co-infection in people living with HIV: a global systematic review and meta-analysis. *Lancet Infect Dis.* 2016;16(7):797-808.
30. Cervo A, Sebastiani G, Milic J, et al. Dangerous liaisons: NAFLD and liver fibrosis increase cardiovascular risk in HIV. *HIV Med.* 2022 Feb 24. [online ahead of print] doi: 10.1111/hiv.13274
31. Rahmanian S, Wewers ME, Koletar S, Reynolds N, Ferketich A, Diaz P. Cigarette smoking in the HIV-infected population. *Proc Am Thorac Soc.* 2011;8(3):313-319.
32. Feinstein MJ, Hsue PY, Benjamin LA, et al. Characteristics, prevention, and management of cardiovascular disease in people living with HIV: a scientific statement from the American Heart Association. *Circulation.* 2019;140(2):e98-e124.
33. Hoffmann U, Lu MT, Olalere D, et al. Rationale and design of the Mechanistic Substudy of the Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE): effects of pitavastatin on coronary artery disease and inflammatory biomarkers. *Am Heart J.* 2019;212:1-12.
34. Kingsley LA, Jennifer D, Jacobson L, et al. Incidence and progression of coronary artery calcium (CAC) in HIV-infected and HIV-uninfected men. *AIDS.* 2015;29(18):2427.
35. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med.* 2008;359(21):2195-2207.
36. Toribio M, Fitch KV, Sanchez L, et al. Effects of pitavastatin and pravastatin on markers of immune activation and arterial inflammation in INTREPID: a randomized trial in HIV. *AIDS.* 2017;31(6):797.
37. Mosepele M, Molefe-Baikai OJ, Grinspoon SK, Triant VA. Benefits and risks of statin therapy in the HIV-infected population. *Curr Infect Dis Rep.* 2018;20(8):20.
38. Ladapo JA, Richards AK, DeWitt CM, et al. Disparities in the quality of cardiovascular care between HIV-infected versus HIV-uninfected adults in the United States: a cross-sectional study. *J Am Heart Assoc.* 2017;6(11):e007107.
39. Boccara F, Miantezila Basilua J, Mary-Krause M, et al. Statin therapy and low-density lipoprotein cholesterol reduction in HIV-infected individuals after acute coronary syndrome: results from the PACS-HIV lipids substudy. *Am Heart J.* 2017;183:91-101.
40. Moore RD, Bartlett JG, Gallant JE. Association between use of HMG CoA reductase inhibitors and mortality in HIV-infected patients. *PLoS One.* 2011;6(7):e21843.
41. Lang S, Lacombe JM, Mary-Krause M, et al. Is impact of statin therapy on all-cause mortality different in HIV-infected individuals compared to general population? Results from the FHDH-ANRS CO4 cohort. *PLoS One.* 2015;10(7):e0133358.
42. Rasmussen LD, Kronborg G, Larsen CS, Pedersen C, Gerstoft J, Obel N. Statin therapy and mortality in HIV-infected individuals; a Danish nationwide population-based cohort study. *PLoS One.* 2013;8(3):e52828.
43. Grinspoon SK, Fitch KV, Overton ET, et al. Rationale and design of the Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE). *Am Heart J.* 2019;212:23-35.
44. Byrne DD, Tate JP, Forde KA, et al. Risk of acute liver injury after statin initiation by human immunodeficiency virus and chronic hepatitis C virus infection status. *Clin Infect Dis.* 2017;65(9):1542-1550.
45. Borges ÁH, Neuhaus J, Sharma S, et al. The effect of interrupted/deferred antiretroviral therapy on disease risk: a SMART and START combined analysis. *J Infect Dis.* 2019;219(2):254-263.