REVIEW

OPEN

Statins for primary cardiovascular disease prevention among people with HIV: emergent directions

Kathleen V. Fitch, Evelynne S. Fulda, and Steven K. Grinspoon

Purpose of review
While people with HIV (PWH) are living longer due to advances in antiretroviral therapy, recent data have demonstrated an increased risk of cardiovascular disease (CVD) among this population. This increased risk is thought to be due to both traditional (for example, smoking, diabetes) and HIV-specific (for example, inflammation, persistent immune activation) risk factors. This review focuses on the potential for statin therapy to mitigate this increased risk.

Recent findings
Several randomized clinical trials have demonstrated that statins, a class of lipid-lowering medications, are effective as a primary CVD prevention strategy among people without HIV. Among PWH, statins have been shown to lower cholesterol, exert immunomodulatory effects, stabilize coronary atherosclerotic plaque, and even induce plaque regression.

Summary
Prevention of CVD among the aging population of people with controlled, but chronic, HIV is vital. Data exploring primary prevention in this context are thus far limited. The Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE) is ongoing; this trial will inform the field by investigating the effects of pitavastatin calcium as a primary prevention strategy for major adverse cardiovascular events among PWH on antiretroviral therapy (ART) at low-to-moderate traditional CVD risk.

Keywords
cardiovascular disease, HIV, primary prevention, statins

INTRODUCTION

Presently, close to 38 million people are living with HIV worldwide [1]. The median age of people living with HIV (PWH) is projected to increase from 44 years in 2010 to close to 60 years by 2035 and the prevalence of cardiovascular disease (CVD) is projected to triple over this time [2,3]. Widespread availability of antiretroviral therapy (ART) has dramatically decreased incidence of HIV across all global regions and has led to improved survival, with most deaths now attributable to noncommunicable diseases, in particular CVD [4–6]. Large, epidemiological studies have consistently demonstrated that PWH are twice as likely to develop CVD manifestations relative to people without HIV [7–9]. In fact, the global burden of HIV-associated cardiovascular disease has tripled over the past 20 years and presently accounts for 2.6 million disability-adjusted life years [9]. Mechanisms driving the increased risk in PWH include traditional CVD risk factors as well as HIV-specific factors [10,11]. An ideal CVD prevention strategy in PWH would have the capacity to target the unique drivers of CVD in PWH, would have minimal risk, and would not greatly increase pill burden; statin therapy uniquely meets these criteria. In this review, we will discuss evidence for the use of statins as primary CVD prevention strategies, the predominant mechanisms by which statins work to target both traditional and HIV-specific CVD risk factors, and current efforts to explore statins as primary CVD prevention strategies in the setting of HIV.

Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA

Correspondence to Kathleen V. Fitch, Massachusetts General Hospital, 55 Fruit Street, 5LON207, Boston, MA 02114, USA.
Tel: +1 617 724 8015; fax: +1 617 724 8998;
e-mail: kfitch@mgh.harvard.edu

Curr Opin HIV AIDS 2022, 17:293–300

DOI:10.1097/COH.0000000000000752

KEY POINTS

- CVD events occur in PWH on ART with low-to-moderate traditional CVD risk, suggesting that mechanisms beyond those traditionally associated with CVD may play a role.
- Statins are known to address both traditional and HIV-specific mechanisms associated with coronary atherosclerosis, and therefore have unique utility for primary CVD prevention in HIV.
- The ongoing REPRIEVE Trial is evaluating if a statin medication will prevent atherosclerotic CVD events in PWH on ART at low-to-moderate traditional CVD risk and will furnish additional insight into mechanisms underlying HIV-associated CVD.

CONTRIBUTORS TO ATHEROSCLEROTIC CARDIOVASCULAR DISEASE EVENTS IN PEOPLE LIVING WITH HIV: TRADITIONAL AND NONTRADITIONAL RISK FACTORS

It is well known that traditional atherosclerotic CVD risk factors, such as smoking, excess visceral adiposity, dyslipidemia, and diabetes, are prevalent among PWH. However, these risk factors do not account for all of the excess CVD risk [7,8]. Increased CVD events occur in PWH on ART with low-to-moderate traditional CVD risk, suggesting that there are contributors beyond traditional risk. HIV infection is associated with plaque formation facilitators, which may ultimately trigger CVD events. HIV infection is characterized by excess proinflammatory macrophage activation markers (sCD14 and sCD163) [12,13], which may have downstream implications for inflammatory plaque pathogenesis, resulting in vulnerable plaque, which may be more susceptible to rupture [10,12–16].

Additionally, increased thrombosis [17], which is initiated by tissue factor from macrophages and circulating monocytes, may also accelerate inflammation and contribute to CVD events in PWH [18]. While ART use is more prevalent than ever before and may improve CVD event rates as some studies suggest [19], ART alone may not be enough to entirely prevent CVD events in PWH, because residual inflammation, immune activation, coagulation, and arterial inflammation continue even after effective therapy [20,21].

OVERVIEW OF STATINS FOR PRIMARY CARDIOVASCULAR DISEASE PREVENTION IN THE GENERAL POPULATION

Cardiovascular disease is the leading cause of death worldwide and because of this, effective prevention strategies are essential to lower the burden of CVD. A large body of evidence from randomized clinical trials (RCTs) conducted among people without HIV have consistently demonstrated that statins are effective at reducing the risk of CVD events [22,23▪▪]. Among the large number of RCTs investigating statins as a primary CVD prevention strategy conducted to date in people without HIV, the JUPITER trial [24] is important to highlight. At the time of publication, JUPITER differed from prior statin trials in that it enrolled individuals with elevated levels of high sensitivity C-reactive protein (hsCRP) ($\geq$2 mg/L) and LDL cholesterol (LDL-C) $<$ 130 mg/dL as entry criteria; previous statin trials traditionally selected participants largely based on dyslipidemia. HsCRP has been shown to identify asymptomatic individuals who are at increased risk of CVD events independent of traditional CVD risk factors such as LDL-C; JUPITER investigated whether a statin (rosuvastatin) would decrease major adverse cardiovascular events in individuals with non-elevated LDL-C but with moderate inflammation. Rosuvastatin therapy resulted in a 44% relative reduction in major adverse cardiovascular events relative to placebo. In a sex-specific analysis, women randomized to rosuvastatin had similar decreases in LDL-C and hsCRP levels compared to men, and both women and men had a similar and significant proportional reduction in major adverse cardiovascular events [25].

STATINS' IMPACT ON TRADITIONAL CARDIOVASCULAR DISEASE RISK FACTORS AMONG PEOPLE LIVING WITH HIV

While several statins are currently approved by the Food and Drug Administration and commercially available, the use of select statins in PWH is complicated by, or in some cases contraindicated based on, complex interactions with antiretroviral agents. These interactions may impact statin efficacy and tolerability [26]. Most statins are primarily metabolized by the CYP3A4 system. Certain classes of ART, namely, protease inhibitors inhibit CYP3A4 and thus markedly increase exposure to statins. However, certain statins (rosuvastatin, pravastatin, and pitavastatin) are not metabolized by the CYP3A4 system and thus serve as potential treatments for PWH with dyslipidemia.

Multiple interventional and observational studies have demonstrated the efficacy of statins to safely and effectively lower cholesterol in PWH (Table 1). A recent metanalysis by Banach and colleagues found statin treatment effectively reduced total cholesterol, LDL-C, and non-HDL-cholesterol

Table 1. Efficacy of statins to lower cholesterol among people living with HIV

Trial	Comparison	Population	Time frame	Main finding
Moyle *et al.* [28]	Dietary advice with or without pravastatin	31 PWH on PIs 100% male	24 weeks	Pravastatin group: • ↓TC 17.3% (accounted for by ↓LDL-C)
Calza *et al.* [29]	Bezafibrate vs. Gemfibrozil vs. Fenofibrate vs. Pravastatin vs. Fluvastatin	106 PWH on PIs 77% male Mean age: 44.2	12 months	Statin groups: • ↓TG 34.8% • ↓TC 24.2% • ↓LDL-C 25.9% • ↑HDL-C 23.9%
ACTG A5087 [30]	Fenofibrate vs. Pravastatin	174 PWH	48 weeks	Fenofibrate added pravastatin group: • ↓LDL -8 mg/dl • ↑HDL +5 mg/dl • ↓TG -144 mg/dl • ↑non-HDL +50 mg/dl Pravastatin added fenofibrate group: • ↓LDL –14 mg/dl • ↑HDL +2 mg/dl • ↓TG –66 mg/dl • ↑non-HDL +34 mg/dl
Van der Lee *et al.* [31]	Rosuvastatin	22 PWH	12 weeks	Baseline to week 4: • ↓TC 27.6% • ↓LDL-C 31.8%
Aslangul *et al.* [32]	Rosuvastatin vs. Pravastatin	88 PWH	45 days	Rosuvastatin group: • ↓LDL-c 37% • ↓TC by 19% Pravastatin group: • ↓LDL-C 19% • ↓TC by 7%
INTREPID [33]	Pitavastatin vs. Pravastatin	252 PWH 86% male Mean age: 50	12 weeks, 40-week safety extension	Pitavastatin group: • ↓LDL-C 31.1% Pravastatin group: • ↓LDL-C 20.9%

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PWH, people living with HIV; TC; TG.

(HDL-C), with a slight increase in HDL-C and no significant change in triglycerides in participants with HIV [27].

STATINS' IMPACT ON HIV-SPECIFIC CARDIOVASCULAR DISEASE RISK FACTORS

Statins also exert immunomodulatory effects to decrease monocyte activation - reflected in decreased circulating levels of sCD14, oxidized LDL (oxLDL), and the macrophage-derived phospholipase, Lp-PLA2 [34–36] and decrease T-cell activation [37,38] (Table 2). Effects on these biomarkers are statin specific, for example, in the HIV-infected patieNts and TREatment with PItavastatin vs pravastatin for Dyslipidemia (INTREPID) study, pitavastatin showed a more robust dampening of sCD14, oxLDL, and Lp-PLA2 levels compared to pravastatin [39].

This reduction in immune activation is critical, as immune activation and persistent inflammation in HIV are implicated in the development of CVD, specifically by leading to the development of non-calcified, vulnerable, and inflamed coronary atherosclerotic plaque [14,15,41].

A recent exploration of a proteomic discovery approach assessing 92 proteins to determine the effects of statins (pravastatin and pitavastatin) on key CVD pathways among dyslipidemic individuals with HIV, found that statin treatment was related to a significant reduction in key proteins associated with coagulation, oxidative stress, glucose metabolism, and redox signaling [42]. These findings provide insight into the unique effects of statins in PWH.

Data from cardiovascular imaging studies in individuals without HIV reveal that statins stabilize vulnerable coronary atherosclerotic plaque and even induce plaque regression. Specifically, statins have been shown to decrease atherosclerotic plaque vulnerability features on coronary computed tomography angiography (CTA) and intravascular ultrasound [43–46], to reduce atherosclerotic plaque inflammation on cardiac fluorodeoxyglucose-positron emission tomography (FDG-PET) [47], and

Table 2. Effects of statins on inflammatory biomarkers among people living with HIV

Trial	Comparison	Population	Time frame	Main finding
Toribio *et al.*/ INTREPID [39]	Pitavastatin vs. Pravastatin	126 PWH Median age: 50	52 weeks	Pitavastatin group: • sCD14 ↓10% • oxLDL ↓26.9% • Lp-PLA2 ↓26.6% Pravastatin group: • sCD14 ↑0.6% • oxLDL ↓17.5% • Lp-PLA2 ↓15.5%
SATURN-HIV – 24 [35]	Rosuvastatin vs. Placebo	147 PWH 78% male Median age: 47	24 weeks	Rosuvastatin group: • sCD14 ↓13.4% • proportions of CD14DimCD16+ monocytes ↓38.8% Placebo group: • sCD14 ↑1.2% • proportions of CD14DimCD16+ monocytes ↓11.9%
SATURN-HIV – 48 [36]	Rosuvastatin vs. Placebo	147 PWH 78% male Median age: 47	48 weeks	Rosuvastatin group: • sCD14 ↓10.4$ • proportions of CD14DimCD16+ monocytes ↓41.6% • proportions of CD14+CD16- monocytes ↓52.1% • proportions of CD14+CD16+ monocytes ↓33.7% • Lp-PLA2 ↓12.2 • sCD163 ↓12.3% • sTNF-RI ↓0.7% • fibrinogen ↓6% • IP-10 ↓27.5% Placebo group: • sCD14 ↑0.5% • proportions of CD14DimCD16+ monocytes ↓18.8% • Lp-PLA2 ↓1.7% • IP-10 ↓8.2%
Ganesan *et al.* [37]	Atorvastatin vs. Placebo	24 PWH 91% ART naive 100% male Median age: 30	8 weeks	Atorvastatin group: • proportions of CD4+ HLA-DR+ ↓2.5%, • proportions of CD8+ HLA-DR+ ↓5% • proportions of CD8+HLA-DR+CD38+ ↓3%
Overton *et al.* [40]	Atorvastatin vs. Pravastatin vs. No statin	21 PWH, cryopreserved samples	Statin use >6 months	Atorvastatin group: • Reduction in CD8 T-cell activation (HLA-DR, CD38/HLA-DR) • Reduction in CD8 T-cell exhaustion (TIM-3, TIM-3/PD-1) Pravastatin group: • No effect on CD8 T-cell activation or exhaustion • Increased antigen specific interferon γ production

to reduce noncalcified plaque volume [48,49]. Encouragingly, in more a recent pilot study among PWH [50], statins have also been shown to reduce noncalcified coronary plaque volume by 19.4% (compared with an increase of 20.4% in the placebo group; $P = 0.009$). Based on these data, statins may be uniquely tailored to address important mechanisms of CVD in HIV. However, data exploring primary prevention in this context are limited.

RATIONALE FOR STATIN USE FOR PRIMARY PREVENTION IN PEOPLE LIVING WITH HIV

Statins address both traditional and HIV-specific mechanisms associated with coronary atherosclerosis, and therefore have unique utility for primary CVD prevention in HIV. Specifically, statins are known to reduce CVD risk through their effects on lipids, namely serum LDL-C and total cholesterol, and they are also recognized to have anti-inflammatory, plaque stabilizing, and plaque regression effects [51,52].

In addition, statins are known to have pleiotropic anti-inflammatory and immunomodulatory characteristics, which may also confer cardio-protective effects [53]. Indeed, in vitro, animal, and human studies have shown that statins decrease monocyte activation - reflected in 1) decreased monocyte chemotaxis and endothelial adhesion [54–56], 2) reduced monocyte uptake of oxidized LDL-C [57] and 3) decreased monocyte secretion of cytokines/chemokines and matrix metalloproteinases [58,59]. Moreover, statins decrease T-cell

activation [60–62] while recruiting regulatory T cells [63], suppress endothelial cell activation [64–68], and decrease lipid oxidation [69–71].

SAFETY OF STATINS IN PEOPLE LIVING WITH HIV

Given the elevated risk of CVD among PWH due to both HIV-associated and traditional risk factors, statins may be beneficial for preventing CVD in this population. The potential benefits of statins must be weighed against the risks of their use, especially for PWH, because ART regimens can include cytochrome P450 inhibitors, which can considerably increase stain levels metabolized primarily by this system (simvastatin, atorvastatin, and lovastatin).

Regarding safety of statins, observational cohorts have provided evidence that most statins can safely be prescribed in PWH and previous studies of statins in individuals with HIV used at recommended doses showed that participants had relatively low risk of side effects comparable to people without HIV [32,34,72].

With respect to the potential to induce diabetes development with statin use in PWH, nonrandomized cohort studies have reported contrasting results, with one study showing increased diabetes mellitus (DM) risk [73] and two others suggesting no increased risk [74,75]. In more recent studies, INTREPID, showed that neither pitavastatin nor pravastatin were associated with increases in glucose [33]. In another RCT of rosuvastatin versus placebo among PWH, an effect was demonstrated compared to placebo for insulin resistance but clinically significant changes in the incidence of diabetes, fasting glucose, and hemoglobin A_{1c} were not seen [76].

Unlike other agents with immune suppressant effects [77], statins have not been shown to have adverse effects on viral replication [78,79]. Indeed, in-vitro studies suggest numerous mechanisms through which statins may actually reduce viral replication – though clinical data suggests little impact on measured changes in plasma HIV viral loads while on statin therapy [80–84].

Despite this, statins continue to be under prescribed by HIV clinicians [85] and underutilized by PWH [86] for multiple reasons including safety concerns, screening calculators which may underestimate risk [87,88], and because efficacy data for the primary prevention of CVD are not yet available.

PREVENTION OF CARDIOVASCULAR DISEASE: CLINICAL GUIDELINES

The challenge in primary prevention of CVD in PWH is identification and risk stratification to better inform the use of pharmacological therapy such as a statin. The 2018 American College of Cardiology (ACC)/American Heart Association (AHA) Guideline on the Primary Prevention of CVD suggests risk estimation utilizing the 10-year CVD risk estimation (pooled cohort equations), although this risk estimation has been shown to underestimate the risk of CVD among PWH [87,88]. In the recent iteration of this guideline the ACC/AHA added that HIV should be considered as a risk-enhancing factor for CVD when starting a clinician-patient discussion on statin therapy initiation [89].

While there are models designed specifically for PWH, including the D:A:D models that provide HIV-specific risk estimators, they are based on white European cohorts [90] and have been shown to underpredict 5-year CVD risk in diverse populations [91▪]. Also, designing and validating CVD risk prediction tools for low- and middle- income countries is needed. Finally, there are insufficient data to recommend routine screening for disease with imaging platforms to evaluate surrogate markers of atherosclerotic CVD including coronary artery calcification. In the future, new approaches such as imaging-techniques or proteomics may enhance risk stratification.

REPRIEVE: AN EFFORT TO INFORM PRIMARY CARDIOVASCULAR DISEASE PREVENTION

The Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE) (NCT02344290) is a prospective, randomized, placebo-controlled trial. The trial enrolled 7769 participants from 2015 to 2019, at over 100 sites, across 12 countries, generating a diverse and representative population of PWH, including a high percentage of women (33%) and nonwhite participants (65%). Participants were randomized 1 : 1 to pitavastatin calcium 4 mg daily or identical placebo. As outlined above, pitavastatin is unique in that it is not metabolized by the CYP3A4 system, thus, contraindications with ART are minimal. In smaller studies, pitavastatin was found to be safe and effective in lowering LDL-C, has not been found to be associated with incidence of diabetes [33], and was shown to lower levels of inflammatory biomarkers [39]: a key advantage to lowering CVD risk among PWH with persistent immune activation and inflammation. Detailed trial inclusion and exclusion criteria have been described previously [92].

The primary objective of REPRIEVE is to determine the effects of pitavastatin calcium as a primary prevention strategy for major adverse cardiovascular events in PWH. Embedded in REPRIEVE is an 800-

participant Mechanistic Substudy of statin effects on coronary plaque indices and critical inflammatory and immune pathways using coronary CTA [93]. Although there are multiple ongoing clinical trials evaluating statins among PWH, REPRIEVE is the largest and is innovative for recruiting participants with low-to-moderate traditional CVD risk [94]. The trial will address urgent national and global priorities relating to CVD prevention among PWH. REPRIEVE will furnish insight into mechanisms underlying HIV-associated CVD and other HIV-associated comorbidities [95]. Specifically, trial results will illuminate the interplay between genetics, traditional CVD risk, lifestyle factors, HIV-specific risk factors, systemic immune activation, and demographics (age, sex, race and global burden of disease region) on incident atherogenesis, plaque remodeling, CVD events and other end-organ comorbidities as well as the role of these factors to mediate statin effects. REPRIEVE will broadly advance our knowledge of the utility and mechanisms of statin effects in subclinical atherosclerotic disease, relevant to the general population and other populations with immune-mediated atherogenesis, including psoriasis, rheumatoid arthritis, and other inflammatory conditions. Immune-mediated mechanisms are increasingly thought to be critical to atherogenesis. The trial will also expand our understanding of statin effects on plaque morphology in participants with subclinical but high-risk atherosclerosis.

CONCLUSION

There is great interest in the potential of statins for primary CVD prevention among PWH. As PWH live longer but experience noncommunicable diseases, in particular CVD, at rates higher relative to people without HIV, having tools on hand that accurately classify CVD risk and that safely and effectively prevent disease without additional burden are essential. Research is ongoing but statins show potential due to their ability to act on multiple pathways implicated in CVD in PWH. REPRIEVE, an ongoing RCT, is testing whether a statin will prevent major adverse cardiovascular events in PWH and is also exploring statin effects on key inflammatory and immune pathways as well as coronary plaque indices. Findings from REPRIEVE are likely to provide essential information to improve CVD prevention in PWH.

Acknowledgements

We would like to thank the investigators, study staff, and participants from the Metabolism Unit at Massachusetts General Hospital as well as REPRIEVE site teams and participants.

Financial support and sponsorship

S.K.G. was supported by research grants through NIH U01HL123336, Nutrition and Obesity Research Center of Harvard, Pilot and Feasibility Grant P30 DK40561 and through grants to his institution from Kowa Pharmaceuticals America, Inc, Gilead Sciences, Inc, Theratechnologies, Navidea, and ViiV outside the submitted publication.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
- ■ of special interest
- ■■ of outstanding interest

1. UNAIDS. UNAIDS Fact Sheet – World AIDS Day 2021. 2021.
2. Smit M, Brinkman K, Geerlings S, *et al.* Future challenges for clinical care of an ageing population infected with HIV: a modelling study. Lancet Infect Dis 2015; 15:810–818.
3. Smit M, Cassidy R, Cozzi-Lepri A, *et al.* Projections of noncommunicable disease and healthcare costs among HIV-positive persons in Italy and the U.S. A: a modelling study. PLoS One 2017; 12:e0186638.
4. Neuhaus J, Angus B, Kowalska JD, *et al.* Risk of all-cause mortality associated with nonfatal AIDS and serious non-AIDS events among adults infected with HIV. AIDS 2010; 24:697–706.
5. Mocroft A, Reiss P, Gasiorowski J, *et al.* Serious fatal and nonfatal non-AIDS-defining illnesses in Europe. J Acquir Immune Defic Syndr 2010; 55:262–270.
6. Antiretroviral Therapy Cohort Collaboration. Causes of death in HIV-1-infected patients treated with antiretroviral therapy, 1996–2006: collaborative analysis of 13 HIV cohort studies. Clin Infect Dis 2010; 50:1387–1396.
7. Triant VA, Lee H, Hadigan C, Grinspoon SK. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. J Clin Endocrinol Metab 2007; 92:2506–2512.
8. Freiberg MS, Chang CC, Kuller LH, *et al.* HIV infection and the risk of acute myocardial infarction. JAMA Intern Med 2013; 173:614–622.
9. Shah ASV, Stelzle D, Lee KK, *et al.* Global burden of atherosclerotic cardiovascular disease in people living with HIV. Circulation 2018; 138:1100–1112.
10. Hanna DB, Lin J, Post WS, *et al.* Association of macrophage inflammation biomarkers with progression of subclinical carotid artery atherosclerosis in HIV-infected women and men. J Infect Dis 2017; 215:1352–1361.
11. McKibben RA, Margolick JB, Grinspoon S, *et al.* Elevated levels of monocyte activation markers are associated with subclinical atherosclerosis in men with and those without HIV infection. J Infect Dis 2015; 211:1219–1228.
12. Burdo TH, Lo J, Abbara S, *et al.* Soluble CD163, a novel marker of activated macrophages, is elevated and associated with noncalcified coronary plaque in HIV-infected patients. J Infect Dis 2011; 204:1227–1236.
13. Fitch KV, Srinivasa S, Abbara S, *et al.* Noncalcified coronary atherosclerotic plaque and immune activation in HIV-infected women. J Infect Dis 2013; 208:1737–1746.
14. Subramanian S, Tawakol A, Burdo TH, *et al.* Arterial inflammation in patients With HIV. JAMA 2012; 308:379–386.
15. Zanni MV, Abbara S, Lo J, *et al.* Increased coronary atherosclerotic plaque vulnerability by coronary computed tomography angiography in HIV-infected men. AIDS 2013; 27:1263–1272.
16. Toribio M WM, Hedgire S, Lu MT, *et al.* Macrophage-specific arterial infiltration relates to plaque type and immune activation in HIV. Oral presentation at: Conf Retroviruses Opportunistic Infect Denver, CO 2022.
17. Funderburg NT, Mayne E, Sieg SF, *et al.* Increased tissue factor expression on circulating monocytes in chronic HIV infection: relationship to in vivo coagulation and immune activation. Blood 2010; 115:161–167.
18. Ford ES, Greenwald JH, Richterman AG, *et al.* Traditional risk factors and D-dimer predict incident cardiovascular disease events in chronic HIV infection. AIDS 2010; 24:1509–1517.
19. Klein DB, Leyden WA, Xu L, *et al.* Declining relative risk for myocardial infarction among HIV-positive compared with HIV-negative individuals with access to care. Clin Infect Dis 2015; 60:1278–1280.
20. Funderburg NT. Markers of coagulation and inflammation often remain elevated in ART-treated HIV-infected patients. Curr Opin HIV AIDS 2014; 9:80–86.

21. Siedner MJ, Zanni M, Tracy RP, *et al.* Increased systemic inflammation and gut permeability among women with treated HIV infection in rural Uganda. J Infect Dis 2018; 218:922–926.

22. Yusuf S, Joseph P, Rangarajan S, *et al.* Modifiable risk factors, cardiovascular disease, and mortality in 155 722 individuals from 21 high-income, middle-income, and low-income countries (PURE): a prospective cohort study. Lancet 2020; 395:795–808.

23. ■■ Yourman LC, Cenzer IS, Boscardin WJ, *et al.* Evaluation of time to benefit of statins for the primary prevention of cardiovascular events in adults aged 50 to 75 years: a meta-analysis. JAMA Intern Med 2021; 181:179–185.

In this meta-analysis of eight trials and over 65,000 adults aged 50-75, the authors evaluated the time to benefit of statin therapy for primary prevention of cardiovascular events and found that 2.5 (95% CI, 1.7-3.4) years were needed to avoid 1 cardiovascular event for 100 individuals treated with a statin, suggesting that statin medications for the primary prevention of cardiovascular events may reduce cardiac events for some adults.

24. 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; 359:2195–2207.

25. Mora S, Glynn RJ, Hsia J, *et al.* Statins for the primary prevention of cardiovascular events in women with elevated high-sensitivity C-reactive protein or dyslipidemia: results from the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) and meta-analysis of women from primary prevention trials. Circulation 2010; 121:1069–1077.

26. Rosenson RS, Colantonio LD, Burkholder GA, *et al.* Trends in utilization of statin therapy and contraindicated statin use in HIV–infected adults treated with antiretroviral therapy from 2007 through 2015. J Am Heart Assoc 2018; 7:e010345.

27. Banach M, Dinca M, Ursoniu S, *et al.* A PRISMA-compliant systematic review and meta-analysis of randomized controlled trials investigating the effects of statin therapy on plasma lipid concentrations in HIV-infected patients. Pharmacol Res 2016; 111:343–356.

28. Moyle GJ, Lloyd M, Reynolds B, *et al.* Dietary advice with or without pravastatin for the management of hypercholesterolaemia associated with protease inhibitor therapy. AIDS 2001; 15:1503–1508.

29. Calza L, Manfredi R, Chiodo F. Statins and fibrates for the treatment of hyperlipidaemia in HIV-infected patients receiving HAART. AIDS 2003; 17:851–859.

30. Aberg JA, Zackin Ra Fau - Brobst SW, Brobst Sw Fau - Evans SR, *et al.* A randomized trial of the efficacy and safety of fenofibrate versus pravastatin in HIV-infected subjects with lipid abnormalities: AIDS Clinical Trials Group Study 5087. AIDS Res Hum Retroviruses 2005; 21:757–767.

31. Van Der Lee M, Sankatsing R, Schippers E, *et al.* Pharmacokinetics and pharmacodynamics of combined use of lopinavir/ritonavir and rosuvastatin in HIV-infected patients. Antivir Ther 2007; 12:1127–1132.

32. Aslangul E, Assoumou L, Bittar R, *et al.* Rosuvastatin versus pravastatin in dyslipidemic HIV-1-infected patients receiving protease inhibitors: a randomized trial. AIDS 2010; 24:77–83.

33. Aberg JA, Sponseller CA, Ward DJ, *et al.* Pitavastatin versus pravastatin in adults with HIV-1 infection and dyslipidaemia (INTREPID): 12 week and 52 week results of a phase 4, multicentre, randomised, double-blind, superiority trial. The Lancet HIV 2017; 4:e284–e294.

34. Eckard AR, Jiang Y, Debanne SM, *et al.* Effect of 24 weeks of statin therapy on systemic and vascular inflammation in HIV-infected subjects receiving antiretroviral therapy. J Infect Dis 2014; 209:1156–1164.

35. Funderburg NT, Jiang Y, Debanne SM, *et al.* Rosuvastatin treatment reduces markers of monocyte activation in HIV-infected subjects on antiretroviral therapy. Clin Infect Dis V 58 2014; 588–595.

36. Funderburg NT, Jiang Y, Debanne SM, *et al.* Rosuvastatin reduces vascular inflammation and T-cell and monocyte activation in HIV-infected subjects on antiretroviral therapy. J Acquir Immune Defic Syndr 2015; 68:396–404.

37. Ganesan A, Crum-Cianflone N, Higgins J, *et al.* High dose atorvastatin decreases cellular markers of immune activation without affecting HIV-1 RNA levels: results of a double-blind randomized placebo controlled clinical trial. J Infect Dis 2011; 203:756–764.

38. De Wit S, Delforge M, Necsoi CV, Clumeck N. Down regulation of CD38 activation markers by atorvastatin in HIV patients with undetectable viral load. AIDS 2011; 25:1332–1333.

39. Toribio M, Fitch KV, Sanchez L, *et al.* Effects of pitavastatin and pravastatin on markers of immune activation and arterial inflammation in HIV. AIDS 2017; 31:797–806.

40. Overton ET, Sterrett S, Westfall AO, *et al.* Effects of atorvastatin and pravastatin on immune activation and T-cell function in antiretroviral therapy-suppressed HIV-1-infected patients. AIDS 2014; 28:2627–2631.

41. Yarasheski KE, Laciny E, Overton ET, *et al.* 18FDG PET-CT imaging detects arterial inflammation and early atherosclerosis in HIV-infected adults with cardiovascular disease risk factors. J Inflamm 2012; 9:26.

42. Toribio M, Fitch KV, Stone L, *et al.* Assessing statin effects on cardiovascular pathways in HIV using a novel proteomics approach: Analysis of data from INTREPID, a randomized controlled trial. EBioMedicine 2018; 35:58–66.

43. Inoue K, Motoyama S, Sarai M, *et al.* Serial coronary CT angiography–verified changes in plaque characteristics as an end point: evaluation of effect of statin intervention. JACC: Cardiovasc Imaging 2010; 3:691–698.

44. Kodama K, Komatsu S, Ueda Y, *et al.* Stabilization and regression of coronary plaques treated with pitavastatin proven by angioscopy and intravascular ultrasound: the TOGETHAR Trial. Circ J 2010; 74:1922–1928.

45. Nakamura T, Obata J-e. Kitta Y, *et al.* Rapid stabilization of vulnerable carotid plaque within 1 month of pitavastatin treatment in patients with acute coronary syndrome. J Cardiovasc Pharmacol 2008; 51:365–371.

46. Shimojima M, Kawashiri M-A, Nitta Y, *et al.* Rapid changes in plaque composition and morphology after intensive lipid lowering therapy: study with serial coronary CT angiography. Am J Cardiovasc Dis 2012; 2:84–88.

47. Tawakol A, Fayad ZA, Mogg R, *et al.* Intensification of statin therapy results in a rapid reduction in atherosclerotic inflammation: results of a multicenter fluorodeoxyglucose-positron emission tomography/computed tomography feasibility study. J Am Coll Cardiol 2013; 62:909–917.

48. Burgstahler C, Reimann A, Beck T, *et al.* Influence of a lipid-lowering therapy on calcified and noncalcified coronary plaques monitored by multislice detector computed tomography: results of the new age II pilot study. Invest Radiol 2007; 42:189–195.

49. Hiro T, Kimura T, Morimoto T, *et al.* Effect of intensive statin therapy on regression of coronary atherosclerosis in patients with acute coronary syndrome: a multicenter randomized trial evaluated by volumetric intravascular ultrasound using pitavastatin versus atorvastatin (JAPAN-ACS [Japan Assessment of Pitavastatin and Atorvastatin in Acute Coronary Syndrome] Study). J Am Coll Cardiol 2009; 54:293–302.

50. Lo J, Lu MT, Ihenachor EJ, *et al.* Effects of statin therapy on coronary artery plaque volume and high-risk plaque morphology in HIV-infected patients with subclinical atherosclerosis: a randomised, double-blind, placebo-controlled trial. Lancet HIV 2015; 2:e52–e63.

51. Stone NJ, Robinson JG, Lichtenstein AH, *et al.* 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014; 63:2889–2934.

52. Nissen SE, Nicholls SJ, Sipahi I, *et al.* Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. JAMA 2006; 295:1556–1565.

53. Greenwood J, Mason JC. Statins and the vascular endothelial inflammatory response. Trends Immunol 2007; 28:88–98.

54. Fujino M, Miura S, Matsuo Y, *et al.* Pitavastatin-induced downregulation of CCR2 and CCR5 in monocytes is associated with the arrest of cell-cycle in S phase. Atherosclerosis 2006; 187:301–308.

55. Han KH, Ryu J, Hong KH, *et al.* HMG-CoA reductase inhibition reduces monocyte CC chemokine receptor 2 expression and monocyte chemoattractant protein-1-mediated monocyte recruitment in vivo. Circulation 2005; 111:1439–1447.

56. Montecucco F, Burger F, Pelli G, *et al.* Statins inhibit C-reactive protein-induced chemokine secretion, ICAM-1 upregulation and chemotaxis in adherent human monocytes. Rheumatology (Oxford) 2009; 48:233–242.

57. Han J, Zhou X, Yokoyama T, *et al.* Pitavastatin downregulates expression of the macrophage type B scavenger receptor, CD36. Circulation 2004; 109:790–796.

58. Guo H, Shi Y, Liu L, *et al.* Rosuvastatin inhibits MMP-2 expression and limits the progression of atherosclerosis in LDLR-deficient mice. Arch Med Res 2009; 40:345–351.

59. Waehre T, Damas JK, Gullestad L, *et al.* Hydroxymethylglutaryl coenzyme a reductase inhibitors down-regulate chemokines and chemokine receptors in patients with coronary artery disease. J Am Coll Cardiol 2003; 41:1460–1467.

60. Bu DX, Tarrio M, Grabie N, *et al.* Statin-induced Kruppel-like factor 2 expression in human and mouse T cells reduces inflammatory and pathogenic responses. J Clin Invest 2010; 120:1961–1970.

61. Kwak B, Mulhaupt F, Myit S, Mach F. Statins as a newly recognized type of immunomodulator. Nat Med 2000; 6:1399–1402.

62. Singh P, Kohr D, Kaps M, Blaes F. Influence of statins on MHC class I expression. Ann N Y Acad Sci 2009; 1173:746–751.

63. Mira E, Leon B, Barber DF, *et al.* Statins induce regulatory T cell recruitment via a CCL1 dependent pathway. J Immunol 2008; 181:3524–3534.

64. Mulhaupt F, Matter CM, Kwak BR, *et al.* Statins (HMG-CoA reductase inhibitors) reduce CD40 expression in human vascular cells. Cardiovasc Res 2003; 59:755–766.

65. Romano M, Diomede L, Sironi M, *et al.* Inhibition of monocyte chemotactic protein-1 synthesis by statins. Lab Invest 2000; 80:1095–1100.

66. Veillard NR, Braunersreuther V, Arnaud C, *et al.* Simvastatin modulates chemokine and chemokine receptor expression by geranylgeranyl isoprenoid pathway in human endothelial cells and macrophages. Atherosclerosis 2006; 188:51–58.

67. Zheng C, Azcutia V, Aikawa E, *et al.* Statins suppress apolipoprotein CIII-induced vascular endothelial cell activation and monocyte adhesion. Eur Heart J 2013; 34:615–624.

68. Zineh I, Luo X, Welder GJ, *et al.* Modulatory effects of atorvastatin on endothelial cell-derived chemokines, cytokines, and angiogenic factors. Pharmacotherapy 2006; 26:333–340.

69. Aviram M, Dankner G, Cogan U, *et al.* Lovastatin inhibits low-density lipoprotein oxidation and alters its fluidity and uptake by macrophages: in vitro and in vivo studies. Metabolism 1992; 41:229–235.

70. Giroux LM, Davignon J, Naruszewicz M. Simvastatin inhibits the oxidation of low-density lipoproteins by activated human monocyte-derived macrophages. Biochim Biophys Acta 1993; 1165:335–338.

71. Vasankari T, Ahotupa M, Toikka J, *et al.* Oxidized LDL and thickness of carotid intima-media are associated with coronary atherosclerosis in middle-aged men: lower levels of oxidized LDL with statin therapy. Atherosclerosis 2001; 155:403–412.

72. Singh S, Willig JH, Mugavero MJ, *et al.* Comparative effectiveness and toxicity of statins among HIV-infected patients. Clin Infect Dis 2011; 52:387–395.

73. Lichtenstein KA, Hart RL, Wood KC, *et al.* Statin use is associated with incident diabetes mellitus among patients in the hiv outpatient study. J Acquir Immune Defic Syndr 2015; 69:306–311.

74. Overton ET, Kitch D, Benson CA, *et al.* Effect of statin therapy in reducing the risk of serious non-AIDS-defining events and nonaccidental death. Clin Infect Dis 2013; 56:1471–1479.

75. Spagnuolo V, Galli L, Poli A, *et al.* Associations of statins and antiretroviral drugs with the onset of type 2 diabetes among HIV-1-infected patients. BMC Infect Dis 2017; 17:43.

76. Erlandson KM, Jiang Y, Debanne SM, McComsey GA. Rosuvastatin worsens insulin resistance in HIV-infected adults on antiretroviral therapy. Clin Infect Dis 2015; 61:1566–1572.

77. Paton NI, Goodall RL, Dunn DT, *et al.* Effects of hydroxychloroquine on immune activation and disease progression among HIV-infected patients not receiving antiretroviral therapy: a randomized controlled trial. JAMA 2012; 308:353–361.

78. Moncunill G, Negredo E, Bosch L, *et al.* Evaluation of the anti-HIV activity of statins. AIDS 2005; 19:1697–1700.

79. Negredo E, Clotet B, Puig J, *et al.* The effect of atorvastatin treatment on HIV-1-infected patients interrupting antiretroviral therapy. AIDS 2006; 20:619–621.

80. del Real G, Jimenez-Baranda S, Mira E, *et al.* Statins inhibit HIV-1 infection by down-regulating Rho activity. J Exp Med 2004; 200:541–547.

81. Amet T, Nonaka M, Dewan MZ, *et al.* Statin-induced inhibition of HIV-1 release from latently infected U1 cells reveals a critical role for protein prenylation in HIV-1 replication. Microbes Infect 2008; 10:471–480.

82. Giguere JF, Tremblay MJ. Statin compounds reduce human immunodeficiency virus type 1 replication by preventing the interaction between virion-associated host intercellular adhesion molecule 1 and its natural cell surface ligand LFA-1. J Virol 2004; 78:12062–12065.

83. Gilbert C, Bergeron M, Methot S, *et al.* Statins could be used to control replication of some viruses, including HIV-1. Viral Immunol 2005; 18:474–489.

84. Nabatov AA, Pollakis G, Linnemann T, *et al.* Statins disrupt CCR5 and RANTES expression levels in CD4 (+) T lymphocytes in vitro and preferentially decrease infection of R5 versus X4 HIV-1. PLoS One 2007; 2:e470.

85. Park TE, Yusuff J, Sharma R. Use of aspirin and statins for the primary prevention of myocardial infarction and stroke in patients with human immunodeficiency virus infection. Int J STD AIDS 2016; 27:447–452.

86. Clement ME, Park LP, Navar AM, *et al.* Statin utilization and recommendations among HIV- and HCV-infected veterans: a cohort study. Clin Infect Dis 2016; 63:407–413.

87. Zanni MV, Fitch KV, Feldpausch M, *et al.* 2013 American College of Cardiology/American Heart Association and 2004 Adult Treatment Panel III cholesterol guidelines applied to HIV-infected patients with/without subclinical high-risk coronary plaque. AIDS 2014; 28:2061–2070.

88. Triant VA, Perez J, Regan S, *et al.* Cardiovascular risk prediction functions underestimate risk in HIV infection. Circulation 2018; 137:2203–2214.

89. 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:e285–e350.

90. Friis-Moller N, Ryom L, Smith C, *et al.* An updated prediction model of the global risk of cardiovascular disease in HIV-positive persons: the Data-collection on Adverse Effects of Anti-HIV Drugs (D:A:D) study. Eur J Prev Cardiol 2016; 23:214–223.

91. ■ Anikpo I, Agovi AM, Cvitanovich MJ, *et al.* The data-collection on adverse effects of anti-HIV drugs (D:A:D) model for predicting cardiovascular events: external validation in a diverse cohort of people living with HIV. HIV Med 2021; 22:936–943.

This study evaluated the performance of the updated D:A:D model for 5-year CVD risk in a diverse group of PWH engaged in HIV care, investigators found that the D:A:D model underpredicts 5-year CVD risk in the diverse population of PWH included for analysis.

92. 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.

93. 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.

94. Bernal E, Marín IM, Masiá M, Gutiérrez F. Statins in HIV-infected patients: potential beneficial effects and clinical use. AIDS Rev 2017; 19:59–71.

95. Grinspoon SK, Douglas PS, Hoffmann U, Ribaudo HJ. Leveraging a landmark trial of primary cardiovascular disease prevention in human immunodeficiency virus: introduction from the REPRIEVE coprincipal investigators. J Infect Dis 2020; 222:S1–S7.