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

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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) (>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 in 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 metaanalysis by Banach and colleagues found statin treatment effectively reduced total cholesterol, LDL-C, and non-HDL-cholesterol.
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 trial with Pravastatin vs Pitavastatin 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 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                                    |
|                        |                                         |            |            | LDL-C +50 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%                                        |
|                        |                                         |            |            | LDL-C 19%                                        |
|                        |                                         |            |            | TC by 7%                                         |
| INTREPID [33]          | Pitavastatin vs. Pravastatin             | 252 PWH    | 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.
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

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### 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    | 52 weeks   | Pitavastatin group:                                                          |
|                               |                             | Median age: 50 |            | • sCD14 \( \uparrow \) 10%                                                 |
|                               |                             |            |            | • oxLDL \( \downarrow \) 26.9%                                              |
|                               |                             |            |            | • Lp-PLA2 \( \downarrow \) 26.6%                                            |
| SATURN-HIV – 24 [35]          | Rosuvastatin vs. Placebo    | 147 PWH    | 24 weeks   | Rosuvastatin group:                                                          |
|                               |                             | 78% male |            | • sCD14 \( \uparrow \) 13.4%                                               |
|                               |                             | Median age: 47 |            | • proportions of CD14\textsuperscript{Dim}CD16\textsuperscript{+} monocytes \( \downarrow \) 38.8%   |
|                               |                             |            |            | Placebo group:                                                               |
|                               |                             |            |            | • sCD14 \( \downarrow \) 1.2%                                              |
|                               |                             |            |            | • proportions of CD14\textsuperscript{Dim}CD16\textsuperscript{+} monocytes \( \downarrow \) 11.9%   |
| SATURN-HIV – 48 [36]          | Rosuvastatin vs. Placebo    | 147 PWH    | 48 weeks   | Rosuvastatin group:                                                          |
|                               |                             | 78% male |            | • sCD14 \( \uparrow \) 10.4$                                               |
|                               |                             | Median age: 47 |            | • proportions of CD14\textsuperscript{Dim}CD16\textsuperscript{+} monocytes \( \downarrow \) 41.6%   |
|                               |                             |            |            | • proportions of CD14\textsuperscript{+}CD16\textsuperscript{+} monocytes \( \downarrow \) 52.1%   |
|                               |                             |            |            | • proportions of CD14\textsuperscript{+}CD16\textsuperscript{+} monocytes \( \downarrow \) 33.7%   |
|                               |                             |            |            | • Lp-PLA2 \( \downarrow \) 12.2                                              |
|                               |                             |            |            | • sCD163 \( \downarrow \) 12.3%                                             |
|                               |                             |            |            | • sTNF-RI \( \downarrow \) 0.7%                                              |
|                               |                             |            |            | • fibrinogen \( \downarrow \) 6%                                              |
|                               |                             |            |            | • IP-10 \( \downarrow \) 27.5%                                               |
|                               |                             |            |            | Placebo group:                                                               |
|                               |                             |            |            | • sCD14 \( \downarrow \) 0.5%                                               |
|                               |                             |            |            | • proportions of CD14\textsuperscript{Dim}CD16\textsuperscript{+} monocytes \( \downarrow \) 18.8%   |
|                               |                             |            |            | • Lp-PLA2 \( \downarrow \) 1.7%                                              |
|                               |                             |            |            | • IP-10 \( \downarrow \) 8.2%                                               |
| Ganesan et al. [37]           | Atorvastatin vs. Placebo    | 24 PWH    | 8 weeks    | Atorvastatin group:                                                          |
|                               |                             | 91% ART naive |            | • proportions of CD4\textsuperscript{+}HLA-DR\textsuperscript{+} \( \downarrow \) 2.5%  |
|                               |                             | 100% male |            | • proportions of CD8\textsuperscript{+}HLA-DR\textsuperscript{+} \( \downarrow \) 5%  |
|                               |                             | Median age: 30 |            | • proportions of CD8\textsuperscript{+}HLA-DR\textsuperscript{+}CD38\textsuperscript{-} \( \downarrow \) 3%  |
| Overton et al. [40]           | Atorvastatin vs. Pravastatin vs. No statin | 21 PWH, cryopreserved samples | >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                           |
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 statin 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 A1c 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-
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.

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Conflicts of interest

There are no conflicts of interest.

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