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Statin Therapy as Primary Prevention for Persons with HIV: A Synopsis of Recommendations from the U.S. Department of Health and Human Services Antiretroviral Treatment Guidelines Panel

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Abstract

Description: The REPRIEVE trial showed benefits of pitavastatin as preventive therapy for atherosclerotic cardiovascular disease (ASCVD) in people with HIV (PWH). In February 2024, the U.S. Department of Health and Human Services (HHS) Panel for the Use of Antiretroviral Agents in Adults and Adolescents with HIV (ARV Guidelines Panel) developed statin therapy recommendations for PWH. These recommendations were issued in collaboration with representatives from the American College of Cardiology (ACC), American Heart Association (AHA), and the HIV Medicine Association (HIVMA). This synopsis summarizes the development process, the recommendations, and how they supplement the AHA/ACC/Multi-society Cholesterol Guidelines, and outlines gaps in primary prevention of ASCVD for PWH.

Methods: The ARV Guidelines Panel convened a working group of 10 (6 members of the Panel with expertise in HIV-related comorbidities, biostatistics, and pharmacology; and 4 consultants representing ACC, AHA, and HIVMA, with cardiometabolic and HIV management expertise). The working group reviewed REPRIEVE trial data, other studies evaluating the use of statins

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in PWH, and the AHA/ACC/Multi-society cholesterol guidelines to devise recommendations. Recommendations were based on scientific evidence with a rating scheme developed since the 1998 ARV Guidelines' inception. Proposed recommendations were presented to the full ARV Guidelines Panel and rated via vote and approved by the Panel's voting members. These recommendations were then endorsed by ACC, AHA, and HIVMA.

Recommendations: The ARV Guidelines Panel issued a strong recommendation for initiating statin therapy among PWH with 10-year ASCVD risk score $\geq 5\%$, where the absolute benefit from statins in REPRIEVE was greatest. Patients with 10-year ASCVD risk score $< 5\%$, the Panel favored statin but recommended patient-clinician risk discussions considering additional HIV-related factors that can increase ASCVD risk.

Keywords

ASCVD; HIV; cholesterol; statins; primary prevention; cardiovascular

Introduction

Advances in antiretroviral therapy (ART) for human immunodeficiency virus (HIV) have significantly improved life expectancy for people with HIV (PWH) over the past three decades. The causes of morbidity and mortality in PWH, who achieve appropriate viral suppression, are now dominated by conditions not related to Acquired Immunodeficiency Syndrome (AIDS) (1,2). When compared to people without HIV, PWH are at higher risk for many common aging-related diseases such as atherosclerotic cardiovascular disease (ASCVD), likely due to increased prevalence of traditional ASCVD risk factors, prior immune depletion, inflammation caused by HIV viral persistence, toxicity from some antiretroviral (ARV) medications, higher rates of risk factors such as smoking than the general population, or some combination of these factors (1-3). Despite the clear increased risk for ASCVD, there has previously been no definitive clinical data to inform broader or earlier use of primary ASCVD prevention strategies among PWH, when compared to what is recommended in the general population. The recently completed Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE) provided high quality clinical outcomes data to inform the use of hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor (i.e., statin) therapy as primary prevention among PWH. In response to the evidence from REPRIEVE, in February 2024, the United States (U.S.) Department of Health and Human Services (HHS) Panel for the Use of Antiretroviral Agents in Adults and Adolescents with HIV (ARV Guidelines Panel) developed recommendations for use of statin therapy among PWH in collaboration with representatives from the American College of Cardiology (ACC), American Heart Association (AHA), and the HIV Medicine Association (HIVMA) (4). This paper provides a synopsis of the ARV Guidelines Panel's recommendations (Table 1), the process and rationale for developing these recommendations, and how they supplement the AHA/ACC/Multi-society Guidelines for the general population.

Clinical Significance of ASCVD Among People with HIV

With continuous ART and viral suppression, most PWH achieve a life expectancy that has become closer to people without HIV, with the estimated mortality gap now reduced to

10 years or less (1). However, when compared to people without HIV, PWH have about a two-fold higher risk of developing ASCVD, and their age at incident ASCVD diagnosis is about a decade younger (1,2). Factors contributing to the development of early ASCVD include higher prevalence of traditional cardiometabolic risk factors including obesity and smoking, incomplete immune recovery despite effective ART, toxicity of specific ARVs, and ongoing systemic inflammation associated with HIV (2-5). ASCVD risk prediction tools used for the general population tend to underestimate risk among PWH (5,6), and this underperformance is likely due to HIV disease specific factors such as systemic inflammation despite ART (7,8).

Data from epidemiologic studies have established that ASCVD risk is associated with higher levels of biomarkers of inflammation among PWH compared with controls without HIV (9-14). Recent data also suggest that the relative increase in ASCVD risk associated with HIV is greater among women than age-matched men, when comparing populations with and without HIV (8,15). The mechanisms of gender- and sex-related differences in HIV-associated CVD risk broadly are an area of active investigation that may also be influenced by chronic immune activation (16,17). Finally, structural barriers and health disparities in screening and treatment of ASCVD risk factors likely also contribute to excess ASCVD risk among PWH in the U.S (18,19).

Statins have long been posited to have advantages for PWH over other primary prevention strategies, as statins are associated with a well-described reduction in ASCVD events, as well as its treatment effects on inflammatory pathways (20-22). However, prior to the current ARV Guidelines Panel's recommendations, there were no recommendations for statin therapy as primary ASCVD prevention specifically among PWH (23-26).

American Heart Association (AHA) / American College of Cardiology (ACC) Multi-Society Statin Guideline for the General Population

The 2018 AHA/ACC Multi-society Guideline on the Management of Blood Cholesterol recommend a heart-healthy lifestyle across the spectrum of prevention, as well as using a risk-based approach to guide who should be considered for statin therapy (24). This risk-based approach allows focusing on the intensity of therapy based on an individual's absolute ASCVD risk thereby, providing preventive therapies to people who are likely to benefit the most. The guidelines recommend that estimation of 10-year ASCVD risk is the first step and a patient-clinician risk discussion regarding statin therapy is needed before initiation of a statin. To guide this discussion, the pooled-cohort equations (PCE) are used to estimate 10-year ASCVD risk along with consideration of several risk enhancers not currently captured in the PCE. Briefly, the PCE are a validated sex and race-specific tool based on U.S. populations derived from 5 community-based studies to estimate 10-year ASCVD risk (25). The PCE performs well in risk estimation in a general U.S. population, with high confidence in non-Hispanic Black and White men and women. Performance of the PCE in people from outside the United States or with varying degrees of chronic kidney disease and/or chronic inflammatory disease is highly variable, due to the heterogeneous nature of the populations, differences in prevalence of risk factors, and differences in

population risk for ASCVD (25). Furthermore, the PCE are not validated in those less than 40 years of age.

These guidelines recommend initiation of high intensity statin therapy for persons who are age 40-75 years with a low-density lipoprotein cholesterol (LDL-C) ≥ 190 mg/dL or a high ($\geq 20\%$) 10-year ASCVD risk, and initiation of at least moderate intensity statin therapy for those with diabetes mellitus (Table 1). Among adults who are age 40-75 years with intermediate (7.5-19.9%) consideration of 10-year ASCVD risk, risk enhancing factors (such as HIV infection among others), and patient-clinician discussion are recommended before initiating moderate intensity statin therapy. The guidelines provide a comprehensive overview regarding all risk enhance factors and are not within the scope of this review.

Methods for HHS Antiretroviral Treatment Guidelines Development and Issuance of Recommendations for Statins Use in PWH

The first “Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV” was published in the Morbidity and Mortality Weekly Report in 1998 (27). As advances in ART have continued to evolve over the ensuing 26 years, these guidelines have been maintained as a web-based “living guideline” with updates issued at least annually. The ARV Guidelines Panel includes a multidisciplinary team of members with expertise in HIV clinical practice and research, biostatistics, and pharmacology, etc. All members provide financial disclosure annually, which is publicly available in the guidelines website. A full description of the guidelines development process can be found in Supplemental Table 1. Recommendations in these guidelines are based on scientific evidence and expert opinion, with a rating scheme developed since the guidelines inception in 1998. Scientific evidence from published data are reviewed and assessed by Panel members with expertise in the topic of interests. Each recommendation statement includes a letter (**A**, **B**, or **C**) that represents the strength of the recommendation and a Roman numeral (**I**, **II**, or **III**) that represents the quality of the evidence that supports the recommendation. Supplemental Table 2 provides a schema of the recommendation ratings in the guidelines. Traditionally, these guidelines focus on the use of ART in people with HIV. However, since the REPRIEVE trial established the benefit of pitavastatin use among PWH at low to intermediate ASCVD risk, the Panel felt it was crucial for HIV providers to have a set of recommendations on the optimal use of statins in PWH. To broaden the expertise in CVD and statin use, the ARV Guidelines Panel also invited members from ACC, AHA, and HIVMA to form a writing group of 10 members (6 from the ARV Guidelines Panel, 1 from ACC, 2 from AHA, 1 from HIVMA). The writing group reviewed data from the REPRIEVE study (28, 29) and other studies evaluating the use of statins in HIV(30-36), as well as the AHA/ACC/ Multi-society cholesterol guidelines(24) to draft the recommendations and ratings. The proposed recommendations were presented to the full ARV Guidelines Panel for discussion and further revision, and, ultimately, each rated recommendation statement was voted on and approved by the Panel’s voting members. These recommendations received formal endorsement from ACC, AHA, and HIVMA.

Recommendations for Statin Therapy as Primary Prevention Among Persons with HIV

The ARV Guidelines Panel's recommendations and considerations to inform the use of statin therapy in primary prevention of ASCVD in PWH receiving care in the U.S. are summarized in both in Table 1 and Central Figure. It should be noted the recommendations should be considered in the context of appropriate viral suppression.

Results from the REPRIEVE Study

REPRIEVE was a Phase 3 global randomized controlled trial of oral daily pitavastatin 4 mg versus placebo for the prevention of ASCVD in PWH ages 40 to 75 years and at low-to-intermediate risk based on 10-year ASCVD risk estimates, as determined by the score on the AHA and ACC 2013 PCE risk calculator — a risk of up to 15% for LDL cholesterol (≥ 70 mg/dL [1.81 mmol/L]) in conjunction with LDL cholesterol levels below specific thresholds (28,29). People with known ASCVD were excluded, and further eligibility criteria were based on LDL-C thresholds that varied based on 10-year risk estimates for ASCVD (up to a risk of 15%). The primary outcome was the occurrence of major adverse cardiac events (MACE), defined as a composite of CVD death; myocardial infarction (MI); hospitalization for unstable angina; stroke; transient ischemic attack; peripheral arterial ischemia; revascularization of coronary, carotid, or peripheral artery; or death of undetermined cause. A total of 7,769 PWH who were receiving ART enrolled in the trial, 31% female, 53% from high-income countries, 41% Black, and 35% White, with a median age of 50 years (interquartile range [IQR] 45–55), median 10-year ASCVD risk of 4.5% (IQR 2.1–7.0), median CD4 T lymphocyte (CD4) cell count of 621 cells/mm³ (IQR 448–827), 49% had a prior CD4 nadir < 200 cells/mm³, and 88% had HIV RNA below the lower limit of quantification.

Compared to placebo, pitavastatin was associated with a 36% reduction in MACE (hazard ratio 0.64; 95% CI, 0.48–0.84), with event rates of 7.77 and 4.95 per 1,000 person-years, respectively, over a median follow-up of 5.6 years. A similar treatment effect was present across the individual components of MACE. Median levels of LDL-C were 107 mg/dL at baseline and 74 mg/dL at month 12 in the pitavastatin group compared to 106 mg/dL at baseline and 105 mg/dL at month 12 in the placebo group. Adverse event rates for $\geq$ Grade 3 or treatment-limiting muscle-related symptoms were higher in the pitavastatin group (2.4%) compared to placebo (1.5%), as were rates of incident diabetes mellitus (6.0% vs. 4.7%, incidence rate ratio, 1.35; 95% CI, 1.09 to 1.66).

Rationale for the ARV Guidelines Panel's Recommendations According to ASCVD Risk Estimate

The overall findings from REPRIEVE, combined with the observation that equations based on traditional risk factors underestimate ASCVD risk among PWH, informed the Panel's decision to recommend the use of at least moderate-intensity statin therapy as primary prevention among PLWH of age 40 to 75 years with low to intermediate 10-year ASCVD risk ($< 20\%$). To inform whether some participants received greater benefit from pitavastatin, subgroup analyses were performed in REPRIEVE (27,28). Relative risk reductions across

subgroups defined by key demographic and clinical characteristics did not demonstrate a clear interaction with the treatment effect. When incident MACE was stratified by 10-year ASCVD risk score, the absolute reduction in events was greatest for people with ASCVD risk $\geq 5\%$. The estimated number needed to treat over 5 years (NNT₅) to prevent incident MACE events with pitavastatin are reported in Table 2. Of note, the NNT₅ for people with ASCVD risk $\geq 5\%$ was one-quarter to one-third that for those with ASCVD risk $< 5\%$. These subgroup estimates of NNT₅ motivated the Panel to issue separate recommendations for people above and below 5% ASCVD risk. These estimates are based on low numbers of events and should be interpreted with caution.

The relationship between a higher absolute benefit from statin therapy (i.e., lower NNT₅) with higher baseline ASCVD risk estimates is well described. This relationship should be used to inform shared decision-making discussions with PWH on the use of statins (24). Discussions on statin therapy should take into account the benefits along with side effects, costs, drug–drug interaction potential, and other patient-centered factors. The discussion should also include the increased risk of diabetes and muscle-related symptoms reported in REPRIEVE, and rates of other adverse events associated with statin therapy.

The findings from REPRIEVE related to the higher absolute benefit of statin therapy among people with greater ASCVD risk motivated the Panel's decision to issue a stronger recommendation for initiating statin therapy among people with 10-year ASCVD risk score $\geq 5\%$ (**AI**). Where the absolute benefit from statin therapy was more modest among participants with low estimated ASCVD risk ($< 5\%$), the Panel issued a weaker recommendation (**CI**) and highlighted that HIV-related factors that are not considered by the PCE are important to consider during patient-clinician risk discussions. Using a large body of observational data, the AHA identified HIV-related ASCVD risk-enhancing factors that include the following: history of prolonged HIV viremia (whether due to delayed ART initiation, non-adherence, or treatment failure), low current or nadir CD4 count (< 350 cells/mm³), lipodystrophy/lipoatrophy, metabolic syndrome, fatty liver disease, and coinfection with hepatitis C (29). Additional HIV-related factors associated with greater ASCVD risk may include but are not limited to, longer duration of HIV infection and exposure to older ARV drugs with cardiometabolic toxicity (e.g., zidovudine, protease inhibitors or abacavir). Conversely, people diagnosed with HIV who initiated ART with contemporary regimens (e.g., use of integrase inhibitors) at higher CD4 counts (e.g., > 500 cells/mm³) are likely to be at lower absolute ASCVD risk.

Use of Statins Among PWH Aged < 40 Years

REPRIEVE did not enroll PWH under age 40 years, and the PCE does not provide 10-year ASCVD risk estimates for persons younger than 40 age. In the general population, lifestyle modifications to address traditional risk factors (e.g., diet, exercise, smoking cessation, and blood pressure control) are recommended for people younger than 40 (24). Still, some younger individuals would likely benefit from statin therapy, such as people with familial hypercholesterolemia or LDL-C ≥ 190 mg/dL in which high-intensity statin therapy is recommended, or adults with a family history of premature ASCVD which may also favor statin therapy (24). There are insufficient data to inform whether risk enhancers, such

as HIV-related factors, would favor statin therapy among people under 40 years of age. However, some younger PWH may be at increased ASCVD risk in the intermediate term or over lifetime—particularly those with a very long duration of HIV infection (e.g., due to perinatal exposure). Decisions on statin therapy should be individualized among this population.

Considerations on Choice of Statin Therapy in People with HIV

In REPRIEVE, pitavastatin was chosen in part due to less drug–drug interaction potential with certain ARV medications compared with other statins (30,31). While there are no comparative effectiveness trials of different statins among PWH, there are studies which support the treatment effect of other moderate-intensity statins for lipid lowering, reductions in inflammation and immune activation, and a treatment effect on surrogate measures of ASCVD (Table 3). Pitavastatin, atorvastatin, and rosuvastatin are all associated with greater reductions in LDL-C among PWH than pravastatin. In addition, pitavastatin (4 mg daily), rosuvastatin (10 mg daily), and high-dose atorvastatin (80 mg daily) all have demonstrated reductions in inflammatory, monocyte, and T-cell immune activation biomarkers among PWH (32–34). Finally, in two separate Phase 2 placebo-controlled randomized trials of statin therapy in PWH, atorvastatin (initiated at 20 mg daily) was associated with reductions in coronary noncalcified plaque by computed tomography angiography, and rosuvastatin 10 mg daily was associated with slower progression of common carotid artery intima-media thickness (35,36). Cumulatively, these data motivated the ARV Guidelines Panel’s recommendation for use of at least moderate-intensity statins to include pitavastatin 4 mg daily (**AI**), atorvastatin 20 mg daily (**AII**), or rosuvastatin 10 mg daily (**AII**).

Considerations for Dosing of Statin Therapy

Statin intensity consists of three categories—high, moderate, and low—based on the LDL-C lowering effect (24). Table 3 outlines the statin agents and doses that qualify for each intensity based on their anticipated LDL-C lowering effects. Specifically, for every 39 mg/dL (1 mmol/L) reduction in LDL-C, there is approximately a >20% reduction in ASCVD events and a 10% reduction in all-cause mortality (36). However, it should also be noted that the magnitude of LDL-C lowering is variable in clinical practice.

Considerations on Drug-Drug Interactions between Statin Therapies and ARV Medications

ART is recommended for all PWH and most commonly consist of a second-generation integrase inhibitor (e.g. bictegravir or dolutegravir) in combination with two nucleoside reverse transcriptase inhibitors in current clinical practice (27). These medications are not expected to have significant pharmacokinetic interactions with statins. However, interactions between statins and some other ARV drugs may occur and may lead to an increase or decrease in statin drug exposure. Before starting a statin, clinicians should consult resources to screen for drug-drug interactions (DDIs) and to determine which ARV drugs and which statin can be safely taken together or if dosage adjustment is necessary. Some resources with focus on interactions between ARV drugs and statins include the Liverpool

HIV Drug Interaction Checker (<https://www.hiv-druginteractions.org/checker>) or the HHS Antiretroviral Treatment Guidelines (27, 38). As people with HIV may have multiple comorbidities and may take multiple medications, before starting a statin, clinicians are advised to carefully review the medication profile to assess for significant interactions.

The potential for DDIs varies among the statins based on their susceptibility to cytochrome P450 (CYP) enzymatic and transporter-mediated interactions. Pitavastatin, pravastatin, and rosuvastatin are not significantly metabolized by CYP enzymes. Atorvastatin, lovastatin, and simvastatin are primarily metabolized by CYP3A4, whereas fluvastatin is a major substrate of CYP2C9. All statins are susceptible to interactions related to drug transporters (e.g., OATP1B1) (39).

In general, DDIs are expected between certain statins and cobicistat- or ritonavir-containing regimens, as well as the recently approved long-acting injectable medication lenacapavir. Ritonavir and cobicistat are potent inhibitors of CYP3A4 enzymes and are used as pharmacokinetic boosters to increase the drug concentrations and half-lives of some ART. The magnitude of the interaction and management strategy vary based on the individual statin and ARV drugs. Lovastatin and simvastatin are **contraindicated** with cobicistat- or ritonavir-boosted ARV drugs, whereas no dosage adjustment is needed when these ARV drugs are used with pitavastatin. With atorvastatin or rosuvastatin, statin dose reduction, a switch to an alternative statin, or increased monitoring for statin-related adverse effects may be necessary, depending on the concomitant ARV drug (see Table 4) (38).

Adverse Effects with Statin Therapy

Statin therapy is generally well tolerated and safe; however, some side effects have been observed. The 2018 AHA/ACC/Multi-society Guidelines introduced the terminology *statin-associated side effects*, as opposed to *statin intolerance*, when these adverse effects occur (24). The reason for this nomenclature is because the majority of people are able to tolerate statin re-challenge with an alternative statin. The most frequent adverse events are statin-associated muscle symptoms, as reported in 5% to 25% of people (40). Further, there has been no evidence of tendonitis or tendon rupture associated with statins (40).

All statins have been implicated in small increases in the risk of diabetes. The increased risk has been associated with older age and the presence of ≥ 2 risk factors, such as hypertension or elevated fasting glucose, fasting triglycerides, or body mass index (41, 42). Pitavastatin has previously been shown to have a neutral effect on glucose levels among people with metabolic syndrome. This effect was consistent in REPRIEVE where there was no treatment effect on glucose levels (28,43). However, in REPRIEVE, there was a small increase in new-onset diabetes (6.0% in the pitavastatin group; 4.7% in the placebo group). Data are lacking on risk for new-onset diabetes with other statins among PWH, but a randomized controlled trial in PWH did demonstrate increases in insulin resistance and impaired fasting glucose levels with rosuvastatin use (44). The specific mechanisms leading to statin-associated diabetes mellitus remain unclear. Rather, it appears that a small number of individuals with diabetic susceptibility cross the threshold to incident diabetes mellitus after statin therapy. Thus, the 2018 AHA/ACC/Multisociety guidelines note that the benefits of statin therapy are

shown to outweigh the risks of new-onset diabetes mellitus, and the possibility of incident diabetes mellitus should not be a contraindication to statin therapy or indication for statin discontinuation (24).

Mild increases in liver enzymes are seen in some individuals who receive statins usually transient without clinical complications (45). Data related to any concerns of cognitive decline have been weak or contradictory and, as such, do not warrant statin avoidance or cessation (24). Before starting statins, clinicians should perform a comprehensive evaluation of musculoskeletal symptoms, an assessment of risk factors for diabetes, and a clinician–patient shared decision-making discussion focused on indications, benefits, risks, and patient concerns and preferences.

Implications for Practice in Other Settings Globally

Differences in ASCVD risk and the validity of risk prediction tools have implications when considering the application of the ARV Guidelines Panel’s recommendations on use of statin therapy in other settings globally. While the majority of PWH reside in sub-Saharan Africa and other low-to-middle income countries (LMIC), risk prediction tools and prevention strategies for ASCVD have been typically validated in high income countries (HIC) such as the U.S. and western Europe. This creates uncertainty as to whether the risk for ASCVD and benefits from statin therapy that have been established in HICs can be applied in LMICs. Importantly, the REPRIEVE population reflected global enrollment, although 52.7% was from high income countries, with 18.3% from Latin American or Caribbean, 7.6% from Southeast or East Asia, and 14.9% from Sub-Saharan Africa (27).

The relative contribution of ASCVD as the primary manifestation of CVD, or as a major cause of morbidity and mortality among PWH, may also differ between LMICs and HICs. A systematic review describing causes of morbidity and mortality within sub-Saharan Africa during the era of ART (2008-2018) found that tuberculosis was the most common cause of hospitalization or death, with infectious diseases still outnumbering other non-communicable diseases as a group (46). When considering the specific manifestations of CVD among PWH, non-ischemic causes of heart failure (HF) account for a large proportion of CVD morbidity within LMICs (47, 48). Specific to HIV endemic regions within sub-Saharan Africa, important factors influencing the spectrum of individual CVD manifestations among PWH include the younger age distribution of the population (49), the higher burden of infectious diseases with CVD complications (e.g., tuberculosis) (50), the lower burden of dyslipidemia (51), and the high prevalence hypertension and associated hypertensive heart disease and HF (53, 53). Consistent with this, data from REPRIEVE demonstrate that the rate of ASCVD events (MACE) among the placebo group was lowest within sub-Saharan Africa (1.8 per 1000 person-years), when compared with other regions in the trial.

In this context, there are limitations in applying ASCVD risk scores across regions globally. A recent study compared predicted ASCVD risk using the Framingham Risk Score (FRS, used commonly in U.S. and Canada), the Pooled Cohort Equation (PCE used by AHA/ACC/Multisociety Cholesterol Guidelines within the U.S.) and four versions of the Systematic

Coronary Risk Evaluation 2 (SCORE2; recommended by European Society of Cardiology and European Atherosclerosis Society within Europe and the only score that considers geographic risk region) (54). This study used a simulated cohort that varied risk factor prevalence, such that this theoretical population would not directly reflect the populations used to derive/validate the risk equations. The concordance across these risk algorithms ranged between 19-85%, and the proportion of the population stratified specifically to moderate risk was 32% by FRS, 39% by PCE, 45% by SCORE2 (low risk region), and 25% by SCORE2 (very high-risk region). The lack of validated risk scores for sub-Saharan Africa and other LMIC regions where the majority of PWH reside, greatly limits the ability to identify those who may benefit most from primary prevention strategies such as statin therapy. Finally, recommendations on statin use within LMICs is further complicated by public health priorities competing for a smaller pool of health care resources, both in absolute dollars, as well as when measured by the proportion of gross domestic product spent on healthcare.

Ongoing Clinical Questions and Priorities

Given the limitations of the PCE both domestically and internationally, as outlined above, there have been efforts to continue to refine CVD risk estimates across all populations, including people with HIV. The 2018 AHA/ACC Multi-society Guidelines note that other markers can help inform individual risk, including inflammatory markers such as high-sensitivity C-reactive protein (hs-CRP) (24). Additional analyses in REPRIEVE will inform whether inflammatory biomarkers, hs-CRP and IL-6, measured at entry are able to identify participants who had a greater treatment effect from pitavastatin. In this context, it should be noted that the REPRIEVE population had relatively low ASCVD risk by traditional risk factors and limited changes in hs-CRP with pitavastatin (55). One additional biomarker that may reflect residual inflammatory risk is Lipoprotein(a) [Lp(a)], which has been associated with greater peri-coronary inflammation among PWH compared to people without HIV (56). Further analyses and additional research is needed to inform whether Lp(a) or other novel inflammatory markers have a role in risk stratification for PWH.

Work is also ongoing to develop novel algorithms that will improve risk prediction. As mentioned above, there are several risk scores that are designed to refine estimates based on global region, such as the SCORE2. Ideally, any risk score would be independent of sex and race and include a younger demographic, which would allow broader generalizability. Through a science advisory group, the AHA recently developed the Predicting Risk of CVD EVENTS (PREVENT) equation to improve the estimated risk of ASCVD and heart failure separately, as well as a total CVD composite. Using more contemporary epidemiological data, the PREVENT equation has been validated and enables 10- and 30-year risk estimates for total CVD, including HF, for a U.S. cohort aged 30-79 years of age, independent of race (57, 58). The score includes the variables of sex, age, cholesterol and treatment, body mass index, systolic blood pressure and treatment, renal function, diabetes, smoking, as well as optional models that also incorporate urinary albumin-creatinine ratio and social deprivation index as a marker of social determinants of health. Further research is needed to understand how this tool performs among PWH. In addition, research into implementation strategies, including those with a focus on removing barriers to care, will need to be performed.

Other future research questions to be addressed in the prevention of ASCVD among PWH include the use of lipid modifying agents beyond statins, such as proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, ezetimibe, inclisiran, bempedoic acid and other agents under investigation. A recent study examined the use of evolucumab, a PCSK9 inhibitor, in PWH and dyslipidemia, which reduced LDL-C by 56.9% compared to placebo at 24 weeks (59). While promising, additional confirmatory studies and clinical outcome data are needed for PCSK9 inhibitors and other novel classes of treatment.

Another important area needing further evidence and guidance is the role of Type II versus Type I MIs in PWH who are under 40 given the high prevalence of Type II MI in this subset, and the fact that statins may have limited role for prevention of Type II MI (60).

Conclusion

REPREIVE was a practice changing clinical trial that, when combined with guidelines for the general population, informed recommendations on use of statin therapy as primary prevention among people with HIV at low-to-intermediate ASCVD risk. The ARV Guidelines Panel issued a strong recommendation for initiating statin therapy among people with 10-year ASCVD risk score $\geq 5\%$, where the absolute benefit from statins in REPRIEVE was greater. For PWH with 10-year ASCVD risk score $< 5\%$, the ARV Guidelines Panel favored statin therapy but also recommended that patient-clinician risk discussions consider the presence or absence of additional HIV-related factors that can increase ASCVD risk but are not included within traditional risk assessment equations. There remain important clinical questions in the management of CVD risk among PWH, including further improvements in risk stratification, as well as additional ASCVD prevention strategies focused on reducing residual risk associated with inflammation. It is important to remember that optimizing lifestyle factors (including smoking cessation, diet, and exercise) remains paramount regardless of statin use. Finally, future research is needed to better understand the absolute risk of ASCVD and other non-ischemic CVD manifestations among PWH specifically within regions where the majority of the HIV epidemic exists globally.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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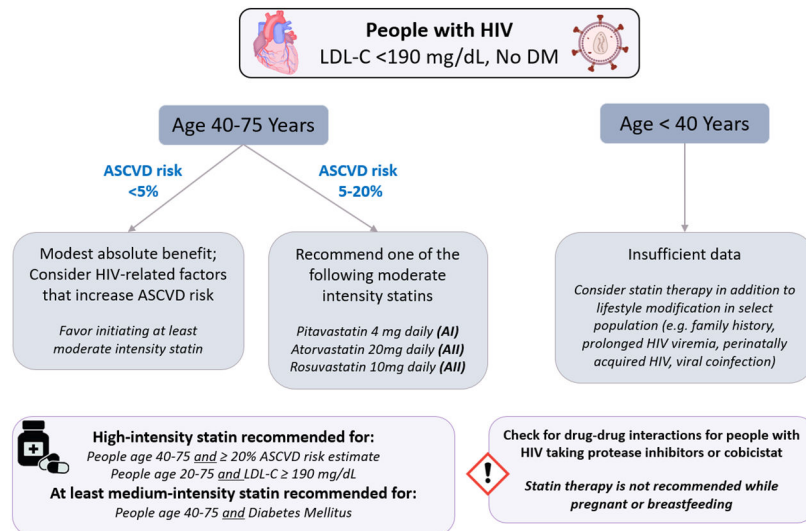
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Central Figure:

Recommendations for Statin Therapy as Primary Prevention Among Persons with HIV from the U.S. Department of Health and Human Services Panel for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Adapted with modifications from the ACC.org with permission from <https://www.acc.org/Latest-in-Cardiology/Articles/2024/08/01/01/42/For-the-FITs-Closing-the-Mortality-Gap-For-People-Living-With-HIV-Updated-Recommendations-For-Statins-For-Primary-Prevention-of-ASCVD>.

Table 1:
Panel's Recommendations for Statin Therapy for Primary Prevention for People Living with HIV.

For PWH Age 40–75 Year Who Have Low-to-Intermediate (<20%) 10-Year Atherosclerotic Cardiovascular Disease (ASCVD) Risk Estimates	
•	When 10-year ASCVD risk estimates are 5% to <20%, the Panel for the Use of Antiretroviral Agents in Adults and Adolescents with HIV (the Panel) recommends initiating at least moderate-intensity statin therapy (AI).
–	Recommended options for moderate-intensity statin therapy include the following:
◆	Pitavastatin 4 mg once daily (AI)
◆	Atorvastatin 20 mg once daily (AII)
◆	Rosuvastatin 10 mg once daily (AII)
•	When 10-year ASCVD risk estimates are <5%, the Panel favors initiating at least moderate-intensity statin therapy (CI). The absolute benefit from statin therapy is modest in this population; therefore, the decision to initiate a statin should take into account the presence or absence of HIV-related factors that can increase ASCVD risk. ^a
–	Same options for moderate-intensity statin therapy as recommended for 10-year ASCVD risk estimates of 5% to <20% (see above)
For PWH Age < 40 Years	
•	Data are insufficient to recommend for or against statin therapy as primary prevention of ASCVD in PWH in this age group. In the general population, lifestyle modifications are recommended, with statin therapy considered only in select populations (see American Heart Association (AHA)/American College of Cardiology (ACC)/Multisociety Guidelines).
Key Recommendations for the General Population (Including People With HIV) Based on AHA/ACC/Multisociety Guidelines	
For People Age 40–75 Years Who Have High (≥20%) 10-Year ASCVD Risk Estimates	
•	Initiate high-intensity statin therapy.
For People Age 20–75 Years Who Have Low-Density Lipoprotein Cholesterol (LDL-C) ≥190 mg/dL	
•	Initiate high-intensity statin therapy at maximum tolerated dose.
For People Age 40–75 Years With Diabetes Mellitu	
•	Initiate at least moderate-intensity statin therapy. Perform further risk assessment to consider using a high-intensity statin.
Key Considerations	
•	Coadministration of certain statins and antiretroviral drugs may result in significant drug–drug interactions. In some cases, the interaction may require statin dose adjustment, switching to another statin, or increased monitoring for statin-related adverse effects (see the Drug–Drug Interaction section below for details).
•	Initiation of statin therapy should be deferred in pregnant individuals at low-to-intermediate ASCVD risk until after pregnancy, and statin therapy should be discontinued if a person with HIV becomes pregnant. Breastfeeding is not recommended while a person is on statin therapy.
Rating of Recommendations: A = Strong; B = Moderate; C = Weak	
Rating of Evidence: I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials, observational cohort studies with long-term clinical outcomes, relative bioavailability/bioequivalence studies, or regimen comparisons from randomized switch studies; III = Expert opinion	

Table 2. Number Needed to Treat Over 5 Years (NNT₅) Based on REPRIEVE (29)

		N	NNT ₅ ^a
10-Year Atherosclerotic Cardiovascular Disease Risk Score	>10%	563 (7%)	34
	5–10%	2,995 (39%)	53
	2.5% to <5.0%	2,055 (26%)	130
	0% to <2.5%	2,156 (28%)	187
Overall		7,769 (100%)	100

Key: NNT₅ = number needed to treat over 5 years

Table 3. Intensity of Statin Therapy (28, 29)

	High Intensity	Moderate Intensity	Low Intensity
Estimated LDL-C Lowering	≥50%	30% to 49%	<30%
	Atorvastatin ^a 40–80 mg Rosuvastatin ^a 20–40 mg	Pitavastatin 1-4 mg (AI)^b Atorvastatin 10-20 mg (AII)^{a,b} Rosuvastatin 5-10 mg (AII)^{a,b} Fluvastatin XL 80 mg Fluvastatin 40 mg twice daily Lovastatin ^c 40–80 mg Pravastatin 40–80 mg Simvastatin ^c 20–40 mg	Fluvastatin 20–40 mg Lovastatin ^c 20 mg Pravastatin 10–20 mg Simvastatin ^c 10 mg

^a Atorvastatin and rosuvastatin have drug–drug interactions with ritonavir- and cobicistat-boosted ARVs; see Table 4.

^b Bolded statins are included in the ARV Guidelines Panel’s recommendations.

^c Simvastatin and lovastatin are contraindicated with ritonavir- and cobicistat-boosted ARVs.

Key: LDL-C = low-density lipoprotein cholesterol

Table 4. Concomitant Use of Antiretroviral Drugs and Statins Recommended by the ARV Guidelines Panel as Primary ASCVD Prevention

This table includes recommendations for pitavastatin, atorvastatin, and rosuvastatin when used with different ARV drugs based on potential drug–drug interactions.

Panel Recommended Statins and Doses	ARV Drugs	Recommendations
Pitavastatin 4 mg once daily (	INSTI: BIC, CAB, DTG, RAL NNRTI: DOR, EFV, ETR, RPV NRTI: 3TC, ABC, FTC, TAF, TDF PI/r: ATV/r, DRV/r Other: LEN, MVC	No dosage adjustment
	INSTI: EVG/c PI/c: ATV/c, DRV/c Other: FTR	No data; use standard dose and monitor for AEs.
Atorvastatin 20 mg once daily	INSTI: BIC, CAB, DTG, RAL NNRTI: DOR, RPV NRTI: 3TC, ABC, FTC, TAF, TDF Other: LEN, MVC	No dosage adjustment
	INSTI: EVG/c PI: DRV/c, DRV/r	Increase atorvastatin concentrations observed. Do not exceed 20 mg per day ^a ; monitor for AEs.
	NNRTI: EFV, ETR	Decrease atorvastatin concentrations observed
	PI: ATV/c	Do not coadminister.
	PI: ATV, ATV/r Other: FTR	Increase atorvastatin concentrations observed or possible. Monitor for AEs.
Rosuvastatin 10 mg once daily	INSTI: BIC, CAB, DTG, RAL NNRTI: DOR, EFV, ETR, RPV NRTI: 3TC, ABC, FTC, TAF, TDF Other: LEN, MVC	No dosage adjustment
	INSTI: EVG/c PI: DRV/r Other: FTR	Increase rosuvastatin concentrations observed. Monitor for AEs.
	PI: DRV/c	Increase rosuvastatin concentrations observed. Do not exceed 20 mg per day ^a ; monitor for AEs.
	PI: ATV, ATV/r, ATV/c	Increase rosuvastatin concentrations observed or expected. Do not exceed 10 mg per day ^a ; monitor for AEs.

^aBased on recommendations from the U.S. Food and Drug Administration product label.

Key: 3TC = lamivudine; ABC = abacavir; AE = adverse effect; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BIC = bictegravir; CAB = cabotegravir; DOR = doravirine; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG/c = elvitegravir/cobicistat; FTC = emtricitabine; FTR = fostemsavir; INSTI = integrase strand transfer inhibitor; LEN = lenacapavir; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; PI/c = cobicistat-boosted protease inhibitor; PI/r = ritonavir-boosted protease inhibitor; RAL = raltegravir; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate