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COMMENTARY

Primary Prevention for People Living With HIV

A Call to Action

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The 2026 ACC/AHA/Multisociety Guideline on the Management of Dyslipidemia ushers in a new era of evidence-based clinical practice, including a focus on preventing atherosclerotic cardiovascular disease (ASCVD) among people living with human immunodeficiency virus (PLHIV).[1] We commend the 2026 ACC/AHA Dyslipidemia Guideline authors for utilizing results of the REPRIEVE (Randomized Trial to Prevent Vascular Events in HIV)[2,3] to newly recommend statin therapy for all PLHIV in the United States aged 40 to 75 years, independently from traditional atherosclerotic cardiovascular disease (ASCVD) risk profile.[1]

PLHIV on effective and life-preserving combined antiretroviral therapy (c-ART)[4] face a 2-fold increased risk of ASCVD compared with individuals without HIV.[5,6] Behavioral and metabolic risk factors, together with systemic immune activation and inflammation, fuel heightened ASCVD risk among PLHIV.[7] Accordingly, REPRIEVE tested the hypothesis that among c-ART-treated PLHIV without overt dyslipidemia, treatment with pitavastatin, which lowers low-density lipoprotein cholesterol (LDL-C) levels[8] and dampens inflammation,[9] would mitigate ASCVD risk.[10] Trial results confirmed the hypothesis: Among a global cohort of 7,769 PLHIV with low-to-moderate traditional ASCVD risk followed for an average of ~5 years, 4 mg pitavastatin daily (vs placebo) reduced major adverse cardiovascular events (MACE) by 36%.[2,3] Pitavastatin therapy also reduced noncalcified coronary artery plaque volume and indices of inflammation.[11,12]

More nuanced REPRIEVE findings further reinforce the 2026 Dyslipidemia Guideline statin recommendation for all PLHIV in the United States aged 40 to 75 years. First, statin therapy effected similar relative ASCVD risk reduction across REPRIEVE participant subgroups stratified by sex, race, and baseline LDL-C.[2,3] In the overall cohort, baseline LDL-C was relatively low, as was baseline 10-year ASCVD risk score by the Pooled Cohort Equations (median: 4.5%),[2,3] such that most REPRIEVE participants would not have been recommended to receive statin therapy according to previous cholesterol treatment guidelines.[13,14] Second, most REPRIEVE participants tolerated statin therapy well. Muscle-related symptoms occurred in 2.3% of statin-treated participants vs 1.4% of those on placebo.[2,3] Statin therapy did not worsen physical function,[15] muscle quality,[16] or neurocognition,[17] and had neutral effects on major noncardiovascular disease events, including non-AIDS-defining cancers.[18] A slightly larger proportion on statin therapy (vs placebo) developed diabetes (5.3% vs 4.0%),[2,3] but diabetes development hinged primarily on antecedent metabolic risk factors, including obesity and prediabetes.[19] Moreover, statin therapy reduced the risk of MACE even among those PLHIV who developed

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diabetes while on treatment.[2,3,19] Third, among REPRIEVE participants from high-income countries (including the United States, Canada, and Spain), the Pooled Cohort Equations calculator significantly underestimated risks for women and African American men.[20] By extension, the 2026 Dyslipidemia Guideline recommendation that all PLHIV in the United States aged 40 to 75 years initiate statin therapy, rather than only those PLHIV meeting calculator-predicted ASCVD risk thresholds, will likely minimize potential for treatment bias. Finally, simple, direct statin prescribing guidelines for PLHIV may gain traction in clinical practice, compared with guidelines requiring ASCVD risk score-based stratification. Previous studies have shown strikingly low rates of statin initiation[21,22] among PLHIV in the United States with older guideline-espoused indications.

"Statin therapy effected similar relative ASCVD risk reduction across REPRIEVE participant subgroups stratified by sex, race, and baseline LDL-C. … The 2026 Dyslipidemia Guideline recommendation that all people in the United States aged 40 to 75 years living with HIV initiate statin therapy, rather than only those meeting calculator-predicted ASCVD risk thresholds, will minimize potential for treatment bias."

The 2026 Dyslipidemia Guideline introduces LDL-C treatment targets inversely proportional to perceived ASCVD risk. For example, individuals with a PREVENT calculator-derived 10-year ASCVD risk of 3%-5% are recommended to achieve an LDL-C <100 mg/dL (<2.6 mmol/L), with lower targets suggested for individuals with higher calculated risk. Evidence supporting LDL-C treatment targets in the general population abound. For example, meta-regression of data from 312,175 individuals in ASCVD prevention trials testing various lipid-lowering agents revealed a strong association between lower achieved LDL-C and lower event rates.[23] Analogously, analyses of REPRIEVE data indirectly support a target LDL-C <100 mg/dL (<2.6 mmol/L) for PLHIV aged 40 to 75 years. Among the REPRIEVE cohort, despite relatively low baseline median LDL-C (108 mg/dL [2.8 mmol/L]), an achieved 30% lower time-updated LDL-C was associated with a 20% lower primary MACE risk.[24] Forthcoming studies may usefully interrogate optimal LDL-C targets for c-ART-treated PLHIV. Such work should acknowledge population-specific underestimation of ASCVD risk by the PREVENT calculator[25,26] and account for population-specific risks related to systemic immune activation, inflammation, and demonstrated coronary vascular pathology. Regarding the latter, the 2026 Dyslipidemia Guideline emphasizes that among PLHIV, coronary computed tomography (CT) may be useful to detect noncalcified plaque. In REPRIEVE, 20.8% of U.S. substudy participants with a coronary artery calcium score of 0 exhibited plaque on coronary CT.[27] Importantly, among PLHIV,[28,29] and especially among women living with HIV,[30] coronary microvascular dysfunction may represent a pathway to heightened ASCVD risk missed both by noncontrast CT and coronary CT.

REPRIEVE tested cardioprotective effects of pitavastatin, a moderate-intensity statin, which, based on primary metabolism via glucuronidation, does not interact with c-ART;[10] however, REPRIEVE findings suggest that higher-intensity statin therapy, potentially even coupled with adjunctive therapies, may be needed to help subgroups of PLHIV achieve 2026 Dyslipidemia Guideline-recommended LDL-C targets. The percentages of statin-treated REPRIEVE participants who achieved LDL-C <100 mg/dL (<2.6 mmol/L) were 82% overall and 62% among those with baseline LDL-C ≥130 mg/dL (≥3.4 mmol/L).[24] Regarding adjunctive therapies, treatment with the proprotein convertase subtilisin/kexin type 9 inhibitor evolocumab has been shown to reduce LDL-C by ~60% among dyslipidemic PLHIV, most of whom were already on maximally tolerated statin doses.[31] Meanwhile, treatment with ezetimibe effects more modest reductions in LDL-C among statin-treated PWH and is well tolerated.[32] Of note, the Dyslipidemia Guideline statin recommendations for PLHIV are class-based, not specific to pitavastatin per se. The Dyslipidemia Guideline appropriately emphasizes the need for anticipating and avoiding drug-drug interactions between select statins (other than pitavastatin) and antiretroviral therapeutics. Providers should be aware that protease inhibitors slow the metabolism of select statins, boosting levels. In this regard, simvastatin and lovastatin are not to be used among PLHIV on protease inhibitors. Additional statin-antiretroviral therapeutic interactions are summarized in Table 22 of the 2026 Dyslipidemia Guideline[1] and warrant scenario-specific verification, potentially through reference to the University of Liverpool HIV Drug Interactions Checker and relevant drug package inserts.

Although excellent statin safety data in REPRIEVE imply that effective statin prescribing can occur in infectious diseases and HIV or in primary care clinic settings, the 2026 Dyslipidemia Guideline points out that cardiometabolic health specialist consultation may benefit PLHIV. Comprehensive cardiometabolic health care would entail attention not only to lipid lowering, but also to lifestyle counseling, screening for and adequately treating hypertension, and, potentially, offering either glucagon-like peptide 1 receptor agonist or sodium-glucose transport 2 inhibitors therapy to address salient comorbidities. Highlighting the need for enhanced cardiometabolic care among PLHIV, <1% of REPRIEVE participants at baseline had achieved ideal lifestyle behaviors and cardiovascular risk management.[33] It will be important to assess the comparative effectiveness of coordinated care delivery approaches. Coordinated care may also reinforce the importance of c-ART adherence, given that low-level viremia represents a modifiable ASCVD risk factor.[34] Future comprehensive cardiometabolic care approaches may ultimately include targeted immune-modulatory therapies, added to statin therapy. Indeed, among pitavastatin-treated REPRIEVE participants, residual immune activation or inflammation persisted, in association with MACE.[35,36]

The Dyslipidemia Guideline applies clinical trial findings to affect a significant change in cardiometabolic preventive care recommendations for PLHIV in the U.S. Forthcoming research advances will inform population-specific ASCVD risk assessment, optimization of LDL-C targets, the effects of statin monotherapy vs combinatorial lipid-lowering therapy, risks and benefits of add-on immunomodulatory therapies, and the optimization of health care delivery strategies. We must also critically assess whether PLHIV <40 years old may benefit from statin therapy, particularly those individuals with lifelong exposure to HIV and c-ART.

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