Recommendations for the Use of Statin Therapy as Primary Prevention of Atherosclerotic Cardiovascular Disease in People with HIV

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These recommendations of the U.S. Department of Health and Human Services (HHS) Panel for the Use of Antiretroviral Agents in Adults and Adolescents with HIV (the Panel) have been developed in collaboration with representatives from the American College of Cardiology (ACC), American Heart Association (AHA), and the HIV Medicine Association (HIVMA). The following recommendations and supporting text have then been reviewed and endorsed by these respective organizations. These recommendations inform the use of statin therapy in primary prevention of atherosclerotic cardiovascular disease (ASCVD) in people with HIV receiving care in the United States.

Panel's Recommendations

For people with HIV who have low-to-intermediate (<20%) 10-year atherosclerotic cardiovascular disease (ASCVD) risk estimates

- Age 40–75 years
  - 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)
- Age <40 years
  - Data are insufficient to recommend for or against statin therapy as primary prevention of ASCVD in people with HIV. In the general population, lifestyle modifications are recommended for people age <40 years, 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 mellitus
• 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*

[a] HIV-related factors that may increase ASCVD risk but are not considered in traditional risk estimate tools may strengthen the rationale for initiating statin therapy in this population. Examples include prolonged duration of HIV infection, delayed antiretroviral therapy initiation, long periods of HIV viremia and/or treatment nonadherence, low current or nadir CD4 T lymphocyte cell count (e.g., <350 cells/mm^3), exposure to older antiretroviral drugs associated with cardiometabolic toxicity, and/or coinfection with hepatitis C (see text below within rationale for the Panel's recommendations).

Background

With continuous antiretroviral therapy (ART) and viral suppression, most people with HIV achieve a life expectancy close to that of people without HIV. There remains, however, a mortality gap primarily due to cardiovascular disease (CVD) and cancer. As mortality rates among people with HIV have declined, the proportion of ASCVD-related deaths has increased. When compared to people without HIV, people with HIV have about a twofold higher risk of developing ASCVD, and their age at incident ASCVD diagnosis is about a decade younger.[1-3] ASCVD risk prediction tools used for the general population tend to underestimate risk among people with HIV.[4,5] Data also suggest that the relative increase in ASCVD risk is greater among women with HIV than among age-matched men with HIV when compared with people without HIV.[6,7] Factors influencing ASCVD risk among people with HIV include both higher prevalence of traditional cardiometabolic risk factors and ongoing systemic inflammation associated with HIV,[6,8] even in individuals with viral suppression while on ART. In addition, structural barriers and health disparities in screening and treatment of ASCVD risk factors likely also contribute to excess ASCVD risk among people with HIV in the United States.[9,10]

Currently, primary ASCVD prevention strategies for people with HIV have focused on traditional risk factor modifications, such as diet, exercise, smoking cessation, blood pressure control, and lipid lowering for those with hyperlipidemia. Hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (i.e., statins) may offer advantages for people with HIV over other prevention strategies, given that statin therapy is associated with a well-described reduction in ASCVD events, as well as treatment effects on inflammatory pathways.[11-13]

To date, there are no specific recommendations for statin therapy as primary ASCVD prevention in people with HIV in the United States who do not have known ASCVD. The 2018 AHA/ACC/Multisociety Guidelines' recommendations on the use of statins as primary prevention were based on risk stratification by 10-year ASCVD risk estimates using pooled cohort risk

equations, along with clinician–patient discussions about risk,[14,15] benefits, and patient preference, given the importance of shared decision-making. Statin therapy is recommended for all people at high 10-year ASCVD risk, defined as ≥20%. For people at intermediate risk (i.e., ≥7.5% to <20%) or borderline risk (i.e., 5% to <7.5%), it is recommended to prescribe statin therapy based on risk discussions with patients as part of shared decision-making. Given that current ASCVD risk prediction tools typically underestimate risk among people with HIV, the AHA/ACC/Multisociety Guidelines identify HIV as a potential "risk enhancer" that should influence discussions on the use of statin therapy among those at borderline or intermediate risk.[15] However, to date, no formal recommendations have been issued for people with HIV at low-to-intermediate ASCVD risk (i.e., <20%). This has been in part due to the absence of randomized clinical trial data with clinical ASCVD events as endpoints among people with HIV.

Recent findings from Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE), a large randomized controlled trial among people with HIV who were aged 40 to 75 years and were receiving ART, showed that when compared to placebo, pitavastatin 4 mg daily was associated with a 35% reduction in major adverse cardiovascular events (MACE) over a median follow-up duration of 5 years.[16] In REPRIEVE, the absolute risk reduction was substantially greater for people with ASCVD risk estimates of ≥5% compared to lower risk at <5%. Incident diabetes (incident rate ratio [IRR] 1.35; 95% confidence interval [CI], 1.09–1.66) and muscle-related symptoms (IRR 1.74; 95% CI, 1.24–2.45) were also higher with pitavastatin treatment. Results from REPRIEVE provide evidence that addresses a current knowledge gap on the use of statin therapy as primary prevention among people with HIV who are on ART and at low-to-intermediate ASCVD risk (i.e., <20%).

Rationale for the Panel's Recommendations for People with HIV Who Are Ages 40 to 75 Years at Low-to-Intermediate (<20%) 10-Year ASCVD Risk

Primary Study Results from the REPRIEVE Trial

The rationale for the Panel's recommendations is based on results from REPRIEVE, a Phase 3 global randomized controlled trial of oral daily pitavastatin 4 mg versus placebo in preventing ASCVD in people with HIV who were aged 40 to 75 years and at low-to-intermediate risk based on 10-year ASCVD risk estimates.[16] A total of 7,769 people with HIV who were receiving ART enrolled in the trial. People with known ASCVD were excluded, and further eligibility criteria were based on low-density lipoprotein cholesterol (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 MACE, defined as a composite of CVD death; myocardial infarction; hospitalization for unstable angina; stroke; transient ischemic attack; peripheral arterial ischemia; revascularization of coronary, carotid, or peripheral artery; or death of undetermined cause. Study participants were 31% female, 53% from high-income countries, 41% Black, and 35% White, with a median age of 50 years (interquartile range [IQR] 45–55), a median 10-year ASCVD risk of 4.5% (IQR 2.1–7.0), a median current CD4 T lymphocyte (CD4) cell count of 621 cells/mm^3 (IQR 448–827), a prior CD4 nadir <200 cells/mm^3 among 49%, and HIV RNA below the lower limit of quantification among 88%.

Compared to placebo, pitavastatin was associated with a 35% reduction in MACE (hazard ratio 0.65; 95% CI, 0.48–0.90), with event rates of 7.32 and 4.81 per 1,000 people-years, respectively. A similar treatment effect was present across the individual components of MACE. Median levels of LDL-C at baseline and month 12 were 107 mg/dL and 74 mg/dL in the pitavastatin group and 106 mg/dL and 105 mg/dL in the placebo group, respectively. During the study, a statin was initiated as part of clinical care in 5.7% of the pitavastatin group and 9.6% of the placebo group, leading to premature

discontinuation of the blinded study drug. Adverse event rates for muscle-related symptoms were higher in the pitavastatin group (2.3%) compared to placebo (1.4%), as were rates of incident diabetes mellitus (5.3% vs. 4.0%, respectively).

In summary, the overall findings from REPRIEVE, combined with the observation that equations based on traditional risk factors underestimate ASCVD risk among people with HIV, informed the Panel's decision to recommend the use of at least moderate-intensity statin therapy as primary prevention among people with HIV of age 40 to 75 years.[4,5]

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

To inform whether some participants demonstrated greater benefit from pitavastatin, subgroup analyses were performed in REPRIEVE.[16] Relative risk reductions across subgroups defined by key demographic and clinical characteristics did not demonstrate a clear interaction with the treatment effect. However, when incident MACE was stratified by 10-year ASCVD risk score, the absolute reduction in events was greatest for people with ASCVD risk ≥5%. The estimated number needed to treat over 5 years (NNT_5) to avoid incident MACE events with pitavastatin treatment are reported below. Of note, the NNT_5 for people with ASCVD risk ≥5% was one-quarter to one-third that for those with ASCVD risk <5%. These data motivated the Panel's decision to issue a stronger recommendation for initiating statin therapy among those with ASCVD risk ≥5%. It should be noted that some of these NNT_5 for subgroups defined by ASCVD risk are estimated based on low numbers of events and should be interpreted with caution.

Table 1: Number Needed to Treat over 5 Years Based on REPRIEVE

	Population	N	NNT_5
10-Year Atherosclerotic Cardiovascular Disease Risk Score	>10%	563	35
	5–10%	2,995	53
	2.5% to <5.0%	2,055	149
	0% to <2.5%	2,156	199
Overall		7,769	106

Key: NNT_5 = number needed to treat over 5 years

The greater the 10-year ASCVD risk estimate, the more favorable the decision to initiate statin therapy. The relationship between a higher absolute benefit from statin therapy (i.e., lower NNT_5) with higher baseline ASCVD risk estimates is well described. This relationship should be used to inform shared decision-making discussions with patients on the use of statins.[15] 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 include the increased risk of diabetes and muscle-related symptoms reported in REPRIEVE, as well as rates of other adverse events associated with statin therapy (see Common Adverse Events with Statin Therapy below). For people at low (<5%) 10-year ASCVD risk, where the absolute benefit from statin therapy is more modest, it is particularly important to weigh potential benefits for the individual against risks.

The findings from REPRIEVE related to the higher absolute benefit of statin therapy among those with greater ASCVD risk informed the Panel's decision to recommend the use of at least moderate-intensity statin therapy with a strong recommendation for those with ASCVD risk score ≥5% **(AI).**

Among participants with low estimated ASCVD risk (<5%), HIV-related factors that are not considered in traditional ASCVD risk factor equations may be important to consider. 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 and/or delayed ART initiation, low current or nadir CD4 count (<350 cells/mm^3), HIV treatment failure or nonadherence, and lipodystrophy/lipoatrophy, as well as metabolic syndrome, fatty liver disease, and coinfection with hepatitis C.[17] Additional HIV-related factors associated with greater ASCVD risk may include, but are not limited to, longer total duration of HIV infection and exposure to older antiretroviral (ARV) drugs with cardiometabolic toxicity. Conversely, people diagnosed with HIV who initiated ART with contemporary regimens at higher CD4 counts (e.g., >500 cells/mm^3) are likely to be at lower absolute ASCVD risk. Finally, non-HIV risk factors that may favor initiating statin therapy are discussed within the AHA/ACC/Multisociety Guidelines.[15] In this context, discussions with patients that weigh individual HIV-related factors along with the potential benefits and risks of statins are particularly important for people at low (<5%) 10-year ASCVD risk where the NNT_5 for benefit is substantially higher. In summary, 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.

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.

Rationale for the Panel's Recommendations for People with HIV Who Are Ages <40 Years at Low-to-Intermediate (<20%) 10-Year ASCVD Risk

REPRIEVE did not enroll people with HIV under 40 years of age. In the general population, lifestyle modifications targeting traditional risk factors (e.g., diet, exercise, smoking cessation, and blood pressure control) are recommended for people under 40 years of age.[15] Still, some of these individuals also may benefit from statin therapy, and recommendations for the general population suggest risk factors such as familial hypercholesterolemia or family history of premature ASCVD may favor statin therapy. 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 people with HIV may be at increased ASCVD risk—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.

Rationale for Recommendations on Statin Therapy for People with HIV Who Are Ages 40 to 75 Years **at High (≥20%) 10**-Year ASCVD Risk or Ages 20 to 75 Years with LDL-**C ≥190** mg/dL

The 2018 ACC/AHA/Multisociety Guidelines recommends the use of statins as primary prevention for all people at high risk, defined as ages 40 to 75 years with a 10-year ASCVD risk estimate of ≥20%, as well as those ages 20 to 75 years with an LDL-C ≥190 mg/dL.[15] In this context, an LDL-C reduction of ≥50% should be achieved, which will typically require high-intensity statin therapy (see the Intensity of Statin Therapy table below).

Rationale for Recommendations on Statin Therapy for People with HIV Who Are Ages 40 to 75 Years with Diabetes Mellitus

The 2018 ACC/AHA/Multisociety Guidelines recommends that for people with diabetes mellitus, at least a moderate-intensity statin is recommended with additional risk assessment to inform consideration of initiating a high-intensity statin. These general population guidelines are based on high-quality randomized trial data and should inform the management of people with HIV who meet these criteria.[15]

Rationale for the Panel's Recommendation on Choice and Dose of Statin

Recommendations for Which Statin to Use for Primary Prevention

In REPRIEVE, pitavastatin was chosen in part due to less drug–drug interaction potential with certain ARV medications used in people with HIV compared with other statins.[18] While there are no clinical outcome comparative effectiveness trials of different statins among people with HIV, additional studies 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. Pitavastatin, atorvastatin, and rosuvastatin are all associated with greater reductions in LDL-C among people with HIV 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 and monocyte and T-cell immune activation biomarkers among people with HIV.[19-21] Finally, in two separate Phase 2 placebo-controlled randomized trials of statin therapy in people with HIV, atorvastatin (initiated at 20 mg daily) was associated with reductions in coronary noncalcified plaque by CT angiography, and rosuvastatin (10 mg daily) was associated with slower progression of common carotid artery intima-media thickness.[22,23] Cumulatively, these data among people with HIV motivated the Panel's recommendation for use of at least moderate-intensity statins to include pitavastatin 4 mg daily, atorvastatin 20 mg daily, or rosuvastatin 10 mg daily, with the level of evidence differing between statins.

Considerations for Dosing of Statin Therapy

As outlined above, the recommendation for which statin agent to select and the intensity of therapy is based on the patient's overall risk profile. As outlined in the 2018 AHA/ACC/Multisociety Guideline on the Management of Blood Cholesterol, statin intensity consists of three categories—high, moderate, and low—based on the LDL-C lowering effect.[15] Table 2 below outlines the statin agent and dose that qualify for each intensity, as well as the anticipated LDL-C lowering effect. More specifically, for every 39 mg/dL reduction in LDL-C, there is approximately a >20% reduction in ASCVD events and 10% reduction in all-cause mortality.[24] However, it should also be noted that the magnitude of LDL-C lowering is variable in clinical practice.

Table 2. Intensity of Statin Therapy

	High Intensity	Moderate Intensity	Low Intensity
LDL-C Lowering	≥50%	30% to **49%**	<30%
	Atorvastatin[a] 40–80 mg Rosuvastatin[a] 20–40 mg	**Pitavastatin 4 mg (AI)**[b] **Atorvastatin 20 mg (AII)**[a,b] **Rosuvastatin 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	Pravastatin 10–20 mg Simvastatin[c] 10 mg Fluvastatin 20–40 mg Lovastatin[c] 20 mg

[a] Atorvastatin and rosuvastatin have drug–drug interactions with ritonavir- and cobicistat-boosted ARVs; see Drug–Drug Interactions Between Statin Therapies and Antiretroviral Medications below.

[b] Bolded statins are included in the Panel's recommendations; see Rationale for the Panel's Recommendation on Choice and Dose of Statin above for rationale.

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

Key: LDL-C = low-density lipoprotein cholesterol

Drug–Drug Interactions Between Statin Therapies and Antiretroviral Medications

Drug–drug interaction potential varies among the statins based on susceptibility to cytochrome P450 (CYP) 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).

Ritonavir (RTV)- and cobicistat (COBI)-boosted ARVs are particularly prone to drug–drug interactions with statins. When RTV- or COBI-boosted ARVs are coadministered with atorvastatin or rosuvastatin, statin dose reduction, a switch to an alternative statin, or increased monitoring for statin-related adverse effects may be required. Lovastatin and simvastatin are **contraindicated** with ARVs requiring pharmacokinetic boosting with COBI or RTV.

In general, some degree of drug–drug interactions may be expected between certain statins and protease inhibitors, COBI-boosted elvitegravir, older non-nucleoside reverse transcriptase inhibitors, fostemsavir, and lenacapavir. The magnitude of the interaction and management strategy vary based on the individual statin and ARV combination. For more information on drug–drug interactions between pitavastatin, atorvastatin, and rosuvastatin and ARV drugs, see Table 3 below. Interactions between other statins and ARV drugs can be found in the Drug Interaction tables (Tables 23, 24a, 24b, 24c, 24d, 24e, 24f, 24g, 25a, 25b).

Table 3. Concomitant Use of Antiretroviral Drugs and Statins Recommended by the Panel as Primary ASCVD Prevention

This table includes recommendations for pitavastatin, atorvastatin, and rosuvastatin when used with different ARV drugs based on their drug–drug interaction potential. Because all statins can be used with nucleoside reverse transcriptase inhibitors (NRTIs) without dosage adjustment, NRTIs are not listed in this table. Drug interaction information for statins not listed in this table can be found in Tables 24a, 24b, 24d, 24f, and 24g of the Adult and Adolescent Antiretroviral Guidelines.

Panel Recommended Statins and Doses	ARV Drugs	Recommendations
Pitavastatin 4 mg once daily (AI)	INSTI: BIC, CAB, DTG, RAL NNRTI: DOR, EFV, ETR, RPV 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; monitor for AEs.
Atorvastatin 20 mg once daily (AII)	INSTI: BIC, CAB, DTG, RAL NNRTI: DOR, RPV Other: LEN, MVC	No dosage adjustment
	INSTI: EVG/c PI: DRV/c, DRV/r	↑ atorvastatin concentrations observed. Do not exceed 20 mg per day[a]; monitor for AEs.
	NNRTI: EFV, ETR	↓ atorvastatin concentrations observed
	PI: ATV/c	Do not coadminister.
	PI: ATV, ATV/r Other: FTR	↑ atorvastatin concentrations observed or possible. Monitor for AEs.
Rosuvastatin 10 mg once daily (AII)	INSTI: BIC, CAB, DTG, RAL NNRTI: DOR, EFV, ETR, RPV Other: LEN, MVC	No dosage adjustment
	INSTI: EVG/c PI: DRV/r Other: FTR	↑ rosuvastatin concentrations observed. Monitor for AEs.
	PI: DRV/c	↑ rosuvastatin concentrations observed. Do not exceed 20 mg per day[a]; monitor for AEs.

Table 3. Concomitant Use of Antiretroviral Drugs and Statins Recommended by the Panel as Primary ASCVD Prevention

	PI: ATV, ATV/r, ATV/c	↑ rosuvastatin concentrations observed or expected. Do not exceed 10 mg per day[a]; monitor for AEs.

[a] Based on recommendations from the FDA product label.

Key: AE = adverse effects; 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; FDA = U.S. Food and Drug Administration; 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

Common Adverse Effects with Statin Therapy

Statin therapy is well tolerated and safe; however, some side effects have been observed. The 2018 AHA/ACC/Multisociety Guidelines introduced the terminology *statin-associated side effects*, as opposed to *statin intolerance*, when these adverse effects occur.[15] The reason for this nomenclature is due to the fact that the majority of patients are able to tolerate statin re-challenge with an alternative statin agent or regimen. The most frequent adverse events are statin-associated muscle symptoms, with reported occurrence rates of 5% to 25% of patients.[25]

All statins have been implicated in small increases in both relative and absolute risk of diabetes. The increased risk of diabetes with statin use has been associated with older age and the presence of ≥2 risk factors, such as elevated baseline fasting glucose level, elevated fasting triglycerides, elevated body mass index, or history of hypertension.[26,27] Pitavastatin previously has been shown to have a neutral effect on glucose levels among patients with metabolic syndrome, and this effect was consistent in REPRIEVE where there was no difference in glucose levels between pitavastatin and placebo groups over follow-up (median levels at month 72 were 91 mg/dL and 90 mg/dL, respectively).[28] However, in REPRIEVE, there was a small increase in new-onset diabetes (5.3% in the pitavastatin group; 4.0% in the placebo group). Data are lacking on the risk for new-onset diabetes with other statins, specifically among people with HIV. However, in a randomized controlled trial of rosuvastatin in HIV, increases in insulin resistance and impaired fasting glucose levels were seen with rosuvastatin use.[29]

Mild increases in liver enzymes are seen in some individuals, though these are usually transient without clinical complications. However, the overall clinical benefits with statin use outweigh the overall risks of adverse effects, especially for people with greater estimated 10-year ASCVD risk.[30] Data related to any concerns of cognitive decline have been weak or contradictory and, as such, do not warrant statin avoidance or cessation.[15] Anytime statins are initiated, 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. When mild adverse events occur, close clinical follow-up is important.

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