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Authors

Durstenfeld, Matthew S
Hsue, Priscilla Y

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Mechanisms and Primary Prevention of Atherosclerotic Cardiovascular Disease among People Living with HIV

Matthew S Durstenfeld[a,b], **Priscilla Y Hsue**[a,b]

[a]Division of Cardiology, UCSF at Zuckerberg San Francisco General Hospital

[b]Department of Medicine, University of California, San Francisco, California, USA

Abstract

Purpose of review—To highlight mechanisms of elevated risk of atherosclerotic cardiovascular disease (ASCVD) among people living with HIV (PLWH), discuss therapeutic strategies, and opportunities for primary prevention.

Recent findings—HIV-associated ASCVD risk is likely multifactorial and due to HIV-specific factors and traditional risk factors even in the setting of treated and suppressed HIV disease. While a growing body of evidence suggests that inflammation and immune activation are key drivers of atherogenesis, therapies designed to lower inflammation including colchicine and low-dose methotrexate have not improved secondary cardiovascular endpoints among PLWH. Statins continue to be the mainstay of management of hyperlipidemia in HIV, but the impact of newer lipid therapies including PCSK-9 inhibitors on ASCVD risk among PLWH is under investigation. Aside from the factors mentioned above, health care disparities are particularly prominent among PLWH and thus likely contribute to increased ASCVD risk.

Summary—Our understanding of mechanisms of elevated ASCVD risk in HIV continues to evolve, and the optimal treatment for CVD in HIV aside from targeting traditional risk factors remains unknown. Future studies including novel therapies to lower inflammation, control of risk factors, and implementation science are needed to ascertain optimal ways to treat and prevent ASCVD among PLWH.

Keywords

HIV infection; atherosclerotic cardiovascular disease; cardiovascular primary prevention; antiretroviral therapy; disparities

Introduction

People living with HIV (PLWH), even treated with antiretroviral therapy (ART), have elevated risk of atherosclerotic cardiovascular disease (ASCVD). Risk factors among PLWH include HIV-specific factors such as chronic inflammation and immune activation and ART-

Correspondence to: Matthew S. Durstenfeld, MD, Division of Cardiology, UCSF, Zuckerberg San Francisco General Hospital, 1001 Potrero Avenue, 5G4, San Francisco, CA 94110, USA, Telephone: 628-206-5461, matthew.durstenfeld@ucsf.edu.

Conflicts of interest

Dr. Priscilla Hsue has received honoraria from Gilead and Merck.

associated metabolic changes, traditional cardiovascular risk factors, and disparities. In this Review, we will explore mechanisms of ASCVD among PLWH and targets for prevention.

Epidemiology of HIV & Atherosclerotic Cardiovascular Disease

With early ART initiation as recommended for all PLWH, HIV infection has become a chronic disease.(1) A meta-analysis of 793,635 PLWH with 3.5 million person-years follow-up demonstrated that PLWH are twice as likely to develop CVD.(2) The global burden of HIV-associated CVD has tripled over the past 20 years, now accounting for 2.6 million disability adjusted life-years.(2) The median age of PLWH is projected to increase from 44 years in 2010 to 57 years in 2030, and the prevalence of CVD is projected to increase from 28% to 78% over that period.(3)

HIV infection is associated with premature ASCVD; namely, PLWH develop acute coronary syndromes (ACS) a decade younger than people without HIV.(4) The risk of acute myocardial infarction (AMI) among PLWH on ART is 1.4 to 2.2 times higher compared to matched controls.(2, 5–7) PLWH also have higher risk of ACS recurrence.(8) Type 2 AMI (supply-demand mismatch) occurs more frequently among PLWH as compared to Type 1 AMI (acute spontaneous plaque rupture and atherothrombosis), and the mortality among PLWH is higher after Type 2 AMI compared to Type 1 AMI.(9, 10) Even in people without HIV, there are limited data regarding optimal prevention and management of Type 2 AMI. (11, 12)

HIV-Associated Inflammation and Immune Activation

HIV infection, even treated, results in chronic inflammation and immune activation that drives atherosclerosis. The mechanisms of atherogenesis in HIV are complex, not well-understood, and beyond the scope of this Review, so we briefly highlight a few key mechanisms as shown in Figure 1.(13)

Immunodeficiency with CD4+ T cell depletion and detectable viremia are associated with the highest risk of AMI and cardiovascular mortality.(14) Even with viral suppression, transcription of HIV-encoded genes induces inflammation, endothelial dysfunction, and endothelin 1 production which drive atherogenesis.(13) Elite controllers have higher rates of inflammatory markers and atherosclerosis compared to uninfected individuals.(15) Other studies have demonstrated that elite controllers and long-term non-progressors have elevated monocyte activation markers but similar levels of atherosclerosis.(16, 17) Among treated individuals, measurements of viral reservoir were independently associated with incident plaque development, providing additional evidence that HIV disease itself accelerates CVD. (18)

PLWH have elevated biomarkers of inflammation including CRP, IL-1ß, IL-6, sTNF-αR1 sTNF-αR2, monocyte activation including CCL2, soluble CD163, soluble CD14, and endothelial dysfunction (ICAM-1).(19) Inflammatory markers are associated with arterial and lymph node inflammation(20, 21) and subclinical atherosclerosis.(22) Inflammatory and coagulation biomarkers are strongly associated with mortality and cardiovascular events among PLWH.(23–29) Given the strong predictive value of IL-6 and D-dimer for non-AIDS conditions and death in treated HIV, a 25% lowering of these markers has been predicted to

reduce serious non-AIDS events and death by up to 37%.(30) Given the role of inflammation in HIV disease pathogenesis and HIV-associated ASCVD, anti-inflammatory strategies may be even more beneficial than in the general population. However, as discussed below, pathways of inflammation in HIV are complex and likely distinct from the general population and thus, one size does not fit all.

Inflammation is a therapeutic target for ASCVD even in people without HIV. In a randomized placebo-controlled trial (CANTOS) that included 10,061 patients with prior AMI and elevated CRP, a monoclonal antibody against IL-1ß, canakinumab, decreased CRP, IL-6 and cardiovascular events, but was associated with higher incidence of fatal infection. (31, 32) A single dose of canakinumab safely reduced inflammatory markers and arterial inflammation among PLWH,(33) and we are currently conducting a trial of canakinumab among PLWH with cardiovascular risk factors (NCT02272946).

The Cardiovascular Inflammation Reduction Trial randomized 4,786 people with stable atherosclerosis to low-dose methotrexate versus placebo for secondary prevention, with no difference in cardiovascular events or reduction in inflammatory markers.(34) In a randomized, placebo-controlled trial that included 176 PLWH, methotrexate did not improve endothelial function or inflammatory biomarkers,(35) although it did reduce CD8+ T cells and improve novel brachial artery ultrasound measures.(36)

In the general population, low-dose colchicine has shown promise in reducing cardiovascular events in patients with stable coronary artery disease(37) and after AMI.(38) A recent randomized, placebo-controlled trial that included 81 PLWH tested the effect of colchicine (0.6mg daily) on plasma inflammatory markers and coronary endothelial function found no difference after 8 weeks.(39) Reasons why colchicine was not effective this study include small sample size, short duration, and possibly inclusion of individuals without CAD or recent AMI.

Co-infection with cytomegalovirus may also plays a significant role in atherosclerosis among PLWH on ART(15, 40) and efforts are underway to evaluate the impact of anti-CMV strategies on inflammatory markers and CV risk in HIV (ACTG 5383, evaluation of letermovir in HIV). Gut microbial translocation is present in HIV, associated with elevated inflammatory markers, and may contribute to atherosclerosis, but attempts to target this mechanism have not consistently lowered inflammatory markers.(41)

ART-Specific Mechanisms

Initiation with ART, particularly protease inhibitor (PI) based regimens are associated with risk of AMI,(42, 43) likely through alterations in lipids, insulin resistance, and lipodystrophy, which are discussed later. Newer ART regimens may have a lower risk of AMI than older regimens, and the population-attributable risk of ASCVD from ART is low. (44) Furthermore, high ART adherence is association with partial normalization of biomarkers of inflammation and immune activation.(45) The impact of integrase inhibitors which have been associated with weight gain(46) on ASCVD risk remains unknown.(47)

Traditional Risk Factors

Traditional risk factors remain a major contributor to cardiovascular morbidity and mortality among PLWH due to high prevalence and inadequate control.(48) Notably, less than 2% of Veterans in the large VACS VC cohort (who have access to care) have optimal control of traditional risk factors.(6) Prevention of hypertension, hyperlipidemia, and smoking would prevent 40% of AMI among PLWH.(48) Nurse-led interventions are currently being tested and may provide evidence for strategies to improve management of traditional risk factors.(49)

Hypertension

Hypertension is the leading cause of cardiovascular disease worldwide including among PLWH.(50) A global meta-analysis found that 35% of PLWH on ART have hypertension compared to 30% among people without HIV and that the prevalence is increasing.(51) Initiation of ART is associated with risk of hypertension.(52, 53) People with both hypertension and HIV have 2-fold risk of AMI compared to people with only HIV or hypertension.(7, 54) Similarly, one study found that men with non-advanced HIV and hypertension had a three-fold higher death rate compared to men with HIV without hypertension.(55)

Mechanisms of hypertension specific to HIV include ART-associated lipodystrophy and renal disease, direct ART effects, immune suppression or reconstitution, gut microbial translocation, chronic inflammation, and activation of the renin-angiotensin aldosterone system (RAAS).(50)

PLWH have high plasma renin activity, possibly related to structural similarity between renin and HIV-protease, production of renin by CD4+ T cells stimulated by HIV-1, and renin-stimulated viral reproduction.(50, 56–58) Several small trials of telmisartan, an angiotensin receptor blocker and PPAR-γ agonist, showed impressive blood pressure reductions.(59–61) A study of losartan demonstrated decreased blood pressure but no improvement in inflammation or T-cell recovery.(62) Currently, there are no HIV-specific guidelines regarding screening or treatment of hypertension.

Dyslipidemia

Hyperlipidemia prevalence among PLWH is estimated to be 28–80% with hypertriglyceridemia most common.(63) First-generation PIs, NRTIs, and NNRTIs generally increase triglyceride levels and can increase LDL-C levels.(13) Newer ARTs that improve lipid profiles and surrogate markers of atherogenesis include integrase inhibitors [dolutegravir & raltegravir], C-C chemokine receptor 5 (CCR5)-co-receptor antagonists [maraviroc], and second-generation PI [atazanavir].(64, 65)

Statins effectively lower LDL-C among PLWH and are the first line pharmacologic treatment for hyperlipidemia.(66) A small trial demonstrated that atorvastatin reduces non-calcified plaque volume and high-risk plaques among PLWH at 1 year.(67) Until the results from REPRIEVE (NCT02344290), a large multicenter randomized-controlled trial of

pitavastatin versus placebo among PLWH at low to moderate ASCVD risk, there are no trials of statins powered for clinical events among PLWH.(68)

The 2018 ACC/AHA Cholesterol Guidelines include HIV as a risk-enhancing feature that prompts statin initiation among adults age 40–75 without diabetes with a 10-year risk of 7.5–19.9% of ASCVD using the pooled cohort equations.(69) The European AIDS Clinical Society Guidelines recommend a target LDL-C <2.0 mmol/L for PLWH with established ASCVD, type 2 diabetes, or 10-year risk ≥10% for primary prevention, and a target <1.4 mmol/L for secondary prevention.(70) An estimated 50% of PLWH qualify for statins, yet many are not prescribed statins.(71) Switching to an integrase-inhibitor based ART regimen may improve lipids at a small risk of virologic failure,(72, 73) but rosuvastatin initiation improves lipids more without that risk.(74) Drug-drug interactions are an important consideration, but atorvastatin and rosuvastatin have only modest interactions with most ART regimens.(75, 76)

PLWH achieve less LDL-C lowering than expected on statin therapy(77) with minimal evident short-term vascular benefit.(78) PLWH intolerant of statins or with insufficient LDL-C lowering response may be treated with ezetimibe, which is safe but less effective.(79) Proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors are highly effective at lowering LDL-C, but expensive. The BEIJERINCK trial randomized 464 PLWH to evolocumab versus placebo; it reduced LDL-C by 56.9% from baseline to 24 weeks compared to placebo among PLWH and was well-tolerated.(80) The EPIC-HIV trial (NCT03207945), by our group, is examining whether PCSK-9 inhibition with alirocumab improves arterial inflammation and endothelial function. Bempedoic acid, which lowers LDL-C among people without HIV treated with statins (81) and among people intolerant of statins,(82) has not been studied among PLWH.

Hypertriglyceridemia, although common among PLWH, does not independently predict ASCVD events, so treatment of hypertriglyceridemia among PLWH remains uncertain.(1) Icosapent ethyl may be a promising treatment not yet studied among PLWH. Among people without HIV, icosapent ethyl compared to mineral-oil placebo lowered triglycerides,(83) reduced ischemic events(84) and decreased inflammatory markers among those with elevated high sensitivity C-reactive protein.(85) In contrast, marine n-3 fatty acids (combined eicosapentaenoic acid and docosahexaenoic acid) did not reduce major cardiovascular events in two large trials among people without HIV(86, 87) or improve inflammatory markers among PLWH.(88)

Lipodystrophy, Diabetes, Metabolic Syndrome, and Chronic Kidney Disease

Older ART regimens increase risk of lipodystrophy, diabetes, and the metabolic syndrome, but there are mixed data regarding risk of diabetes with newer ART regimens.(89, 90) Lipodystrophy is a syndrome of central adiposity from dorsocervical fat accumulation, increased or preserved visceral fat and peripheral fat loss in some patients taking older protease inhibitors and NRTIs [didanosine and stavudine].(41) Lipodystrophy is associated with the metabolic syndrome, which is associated with cardiovascular events and mortality among PLWH.(91) Chronic kidney disease is highly associated with cardiovascular risk.(92)

Smoking

Smoking is highly prevalent among PLWH. One study from Denmark found that PLWH were twice as likely to smoke as people without HIV, and the population-attributable risk of death from smoking was 61.5% among PLWH compared to 34.2% among those without HIV.(93) Similarly, a study in California found that 43.3% of PLWH had a smoking history compared to 29.0% of controls.(5) Smoking cessation nearly halves the incident rate ratio of AMI compared after 3 years of abstinence.(94) Behavioral interventions increase abstinence rates by 50% among PLWH,(95) and pharmacologic smoking cessation tools including nicotine replacement, buproprion, and varenicline have similar safety and efficacy among PLWH.(96)

Diet, Physical Activity, Alcohol and Other Substance Use

Diet, physical activity, unhealthy alcohol use and other substance use are important contributing factors in the development of ASCVD among PLWH not covered in this Review.

Disparities

PLWH are a vulnerable group and face significant stigma. In the US, historically marginalized racial and ethnic groups including African Americans have much higher rates of HIV infection and lower rates of viral control; African Americans make up 41% of PLWH in the US and 41% of new HIV diagnoses despite only making up 13% of the population.(97) Neighborhood poverty is also associated with unsuppressed viral load.(98)

African Americans with HIV have a higher prevalence of ASCVD risk factors than non-African Americans with HIV.(99) Racial disparities in care further impact treatment of ASCVD risk factors among PLWH. Black veterans living with HIV are less likely to have hypertension, diabetes, and lipids controlled than white veterans.(100) Racism is causally related to cardiovascular disease,(101) and perceived discrimination based on sexual orientation and gender identity also contribute.(102, 103) These disparities translate into increased odds of CVD hospitalizations (OR 1.45, 95% CI 1.39–1.51) among African American PLWH compared to white PLWH, for example, but are less studied among other socially stigmatized groups.(104)

Sex and gender differences also modify risk among PLWH. Most research on ASCVD among PLWH has focused on men, but women have a higher excess risk of cardiovascular disease (relative risk of 3.0 for women compared to 1.4 for men).(54) Sex-related differences in monocyte activation are associated with noncalcified plaque.(105) Intersectionality of marginalized identities may further exacerbate cardiovascular risk through activation of stress pathways.(106),(107)

The majority of PLWH (25.6 million out of 37.9 million) live in sub-Saharan Africa. The burden of cardiovascular disease attributable to HIV is highest in sub-Saharan Africa and Asia Pacific.(2) Access to newer ART regimens and prevalence of traditional ASCVD risk factors varies by geography, with lower smoking rates and dyslipidemia but more hypertension in sub-Saharan Africa compared to Europe and North America.(108) Different

approaches need to be studied in a global context to reduce risk of ASCVD among PLWH.(109) If new therapies are effective, cost-effectiveness and global access need to be prioritized.

Risk Stratification for Primary Prevention

The paradigm for primary prevention of ASCVD is matching treatment intensity with estimated risk. Current guidelines favor the pooled cohort equations, which underestimate risk of ASCVD among PLWH, with poor discrimination and calibration similar to the Framingham Heart Study ASCVCD.(110) The D:A:D models provide HIV-specific risk estimators but were derived in white European cohorts.(111) The risk stratification and management algorithm developed by the AHA Scientific Statement committee in 2019 is presented in Figure 2.(1) There are insufficient data to recommend routine measurement of subclinical atherosclerosis through assessment of coronary artery calcification, arterial plaque, or ankle-brachial indices, but they may help with risk stratification among PLWH.(1, 112) Proteomics or imaging-based approaches may improve risk stratification in the future.

Lack of HIV-Specific Management Recommendations

There are few HIV-specific recommendations for ACSVD prevention.(1) No prospective primary prevention trials powered for clinical events of common therapies such as statins and aspirin have yet been completed in HIV. As the pendulum has shifted away from aspirin for primary prevention in the general population, the net benefit of aspirin for primary prevention among PLWH is uncertain. Nonetheless, PLWH are prescribed aspirin and statins less than people without HIV, which may contribute to excess risk.(113)

Conclusion

HIV is a major risk factor for ASCVD due to HIV-associated mechanisms and excess traditional risk factors. Additional investigations are needed to identify therapeutic targets and test interventions particularly related to HIV-specific mechanisms such as immune activation and chronic inflammation, and the impact of HIV-curative strategies on CV risk. In addition, how to best improve management of traditional risk factors and address disparities among PLWH at risk for ASCVD remains an important area for future work.

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Abbreviations

PLWH	People living with HIV
ASCVD	atherosclerotic cardiovascular disease
CVD	cardiovascular disease

ART	antiretroviral therapy
ACS	acute coronary syndrome
AMI	acute myocardial infarction
RAAS	renin-angiotensin aldosterone system
LDL-C	low density lipoprotein cholesterol
PIs	protease inhibitors
NRTIs	nucleoside reverse transcriptase inhibitors
NNRTIs	non-nucleoside reverse transcriptase inhibitor
PCSK-9	Proprotein convertase subtilisin/kexin type 9

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Key Points:

- Inflammation and immune activation are key drivers of elevated ASCVD risk among PLWH, but impact of anti-inflammatory therapies on CV risk in HIV and clinical endpoints in HIV remains unknown.
- Statins continue to be the mainstay of management of hyperlipidemia; PCSK-9 inhibitors effectively lower LDL-C among PLWH. Whether or not attainment of lower clinical cutpoints for LDL will translate into improvement clinical outcomes or reduction in incident CVD in HIV remains unknown.
- There is emerging evidence that disparities are present in HIV-associated ASCVD risk factors and may contribute to increased risk in ASCVD.

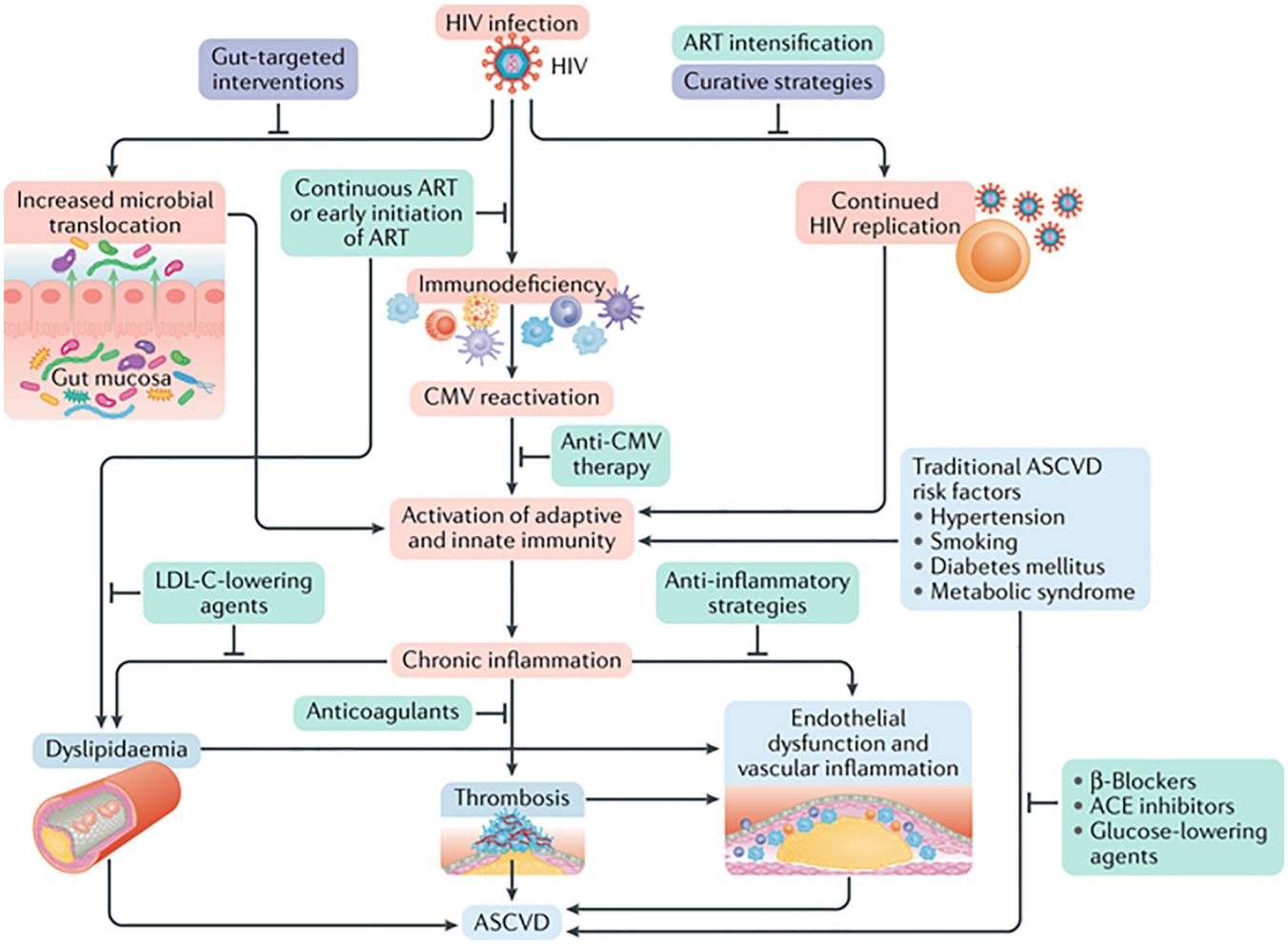

Fig 1. Mechanisms of Atherosclerotic Cardiovascular Disease among People Living with HIV

Mechanisms of ASCVD include HIV infection itself, and the resulting increased microbial translocation, immunodeficiency, Cytomegalovirus (CMV) reactivation, chronic inflammation and immune activation, dyslipidemia, and traditional risk factors. Pathophysiologic mechanisms are highlighted in red, potential therapeutic targets with supporting evidence in green, and potential future areas of investigation are in purple. Reproduced with permission from Springer Nature.

Source: Hsue PY, Waters DD. HIV infection and coronary heart disease: mechanisms and management. *Nature Reviews Cardiology.* 2019;16(12):745–759.(13)

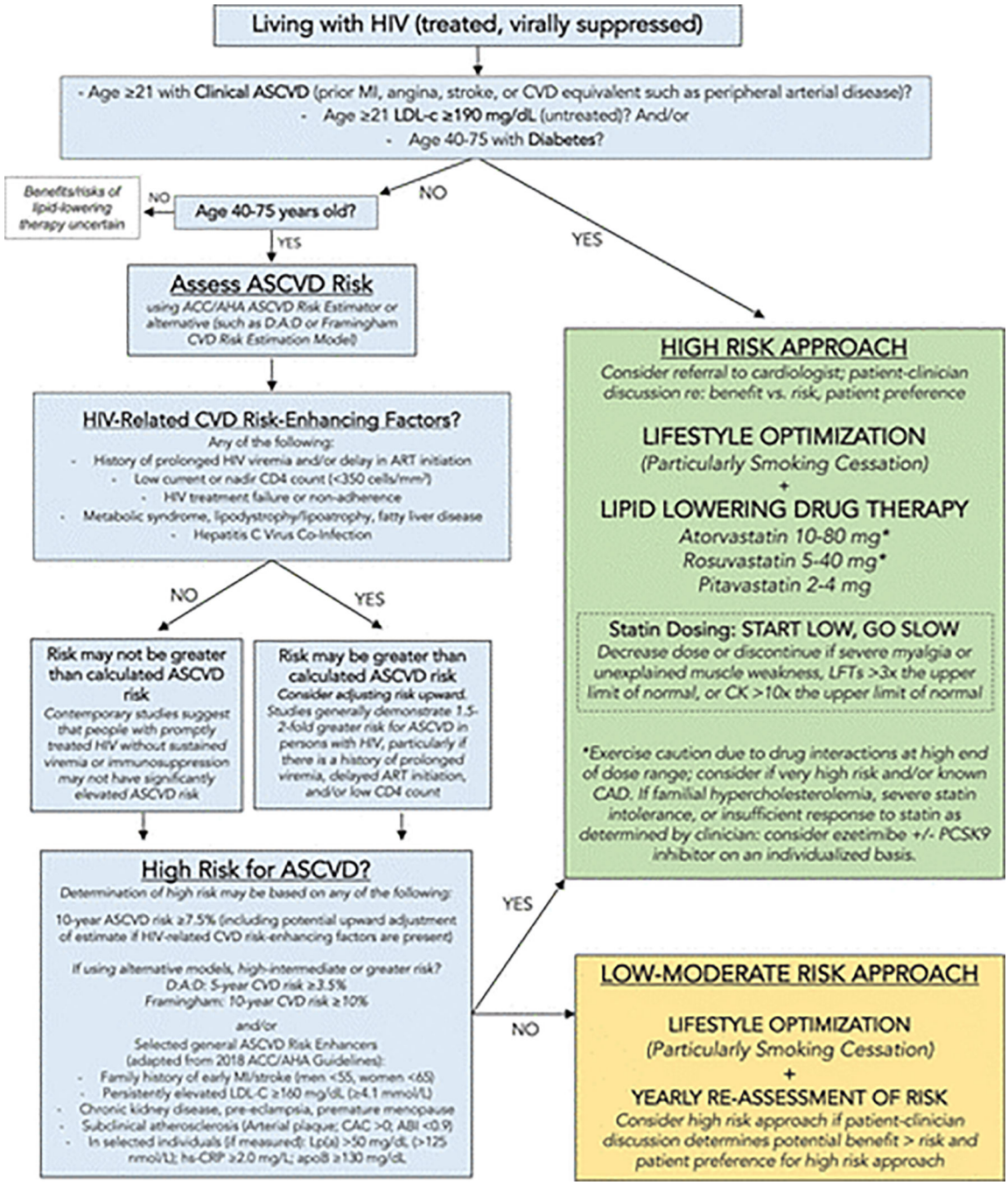

Fig 2. Primary Prevention Management Algorithm for ASCVD Primary Prevention among People Living with treated HIV

This is the 2019 American Heart Association Scientific Statement pragmatic algorithm summarizing recommendations for management of people with treated HIV to prevent ASCVD. For people with uncontrolled HIV, the priority is appropriate HIV therapy to achieve viral suppression. ABI indicates ankle-brachial index; ACC/AHA, American College of Cardiology/American Heart Association; apoB, apolipoprotein B; ART, antiretroviral therapy; CAC, coronary artery calcium; CAD, coronary artery disease; CK, creatine kinase; CVD, cardiovascular disease; D:A:D, Data Collection on Adverse Events of

Anti-HIV Drugs; hs-CRP, high sensitivity C-reactive protein; LFT, liver function test; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein A; and PCSK9, proprotein convertase subtilisin-kexin type 9. Reproduced with permission from the American Heart Association.

Source: Feinstein MJ, Hsue PY, Benjamin LA, et al. Characteristics, Prevention, and Management of Cardiovascular Disease in People Living With HIV: A Scientific Statement From the American Heart Association. *Circulation.* 2019;140(2):e98-e124. (1)