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Evolving mechanisms and presentations of cardiovascular disease in people with HIV: implications for management

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SUMMARY People with HIV (PWH) are at elevated risk for cardiovascular diseases (CVDs), including myocardial infarction, heart failure, and sudden cardiac death, among other CVD manifestations. Chronic immune dysregulation resulting in persistent inflammation is common among PWH, particularly those with sustained viremia and impaired CD4+ T cell recovery. This inflammatory milieu is a major contributor to CVDs among PWH, in concert with common comorbidities (such as dyslipidemia and smoking) and, to a lesser extent, off-target effects of antiretroviral therapy. In this review, we discuss the clinical and mechanistic evidence surrounding heightened CVD risks among PWH, implications for specific CVD manifestations, and practical guidance for management in the setting of evolving data.

KEYWORDS human immunodeficiency virus, inflammation, cardiovascular disease

INTRODUCTION TO HIV-ASSOCIATED CARDIOVASCULAR DISEASES: SCOPE AND CONTEXT

As immediate and continuous antiretroviral therapy (ART) has become the standard of care for people with HIV (PWH), life expectancies among PWH with access to treatment have increased dramatically (1, 2). Concomitant with this increased life expectancy is the emerging epidemic of aging-associated multimorbidity among PWH (3). Cardiovascular diseases (CVDs)—which include coronary artery disease and myocardial infarction (MI), heart failure (HF), arrhythmia and sudden cardiac death, and

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pulmonary arterial hypertension (PAH), among others—are among the chief drivers of this HIV-associated multimorbidity (4–6). The burden of CVD morbidity and mortality among PWH is substantial in both relative and absolute terms. People with HIV have significantly higher risks for various CVDs compared with HIV-uninfected individuals; these include 1.5× or higher relative risks for MI, HF, stroke, pulmonary arterial hypertension, and sudden cardiac death (7–16). In absolute terms, disability-adjusted life years from HIV-associated cardiovascular disease increased from 0.74 million in 1990 to 2.57 million in 2015, while CVD-related mortality (as a proportion of overall causes of death among PWH) more than doubled (17). Several factors contribute to the growing and excess burden of CVD among PWH, ranging from chronic immune dysregulation and unresolving inflammation, coinciding "traditional" cardiovascular risk factors such as cigarette smoking and dyslipidemia, and off-target effects of certain antiretrovirals, among other factors (5). In this review, we will discuss the pathogenesis and scope of HIV-associated CVDs, with the goal of elucidating immunologic, clinical, and social and environmental factors that shape emerging CVD risks among PWH. We will also provide practical guidance on CVD prevention and management for PWH based on existing and emerging data.

PERSISTENT INFLAMMATION IN HIV: A NIDUS FOR CARDIOVASCULAR DISEASES

HIV is a retrovirus which infects and destroys immune cells, fundamentally altering host immune responses in a way that persists even after viral suppression to undetectable levels (18, 19). The natural history of HIV typically includes an acute phase of viral replication, a chronic phase of immune activation and continued viral replication, and, left untreated, an eventual decline in CD4+ T cells (referred to hereafter as "CD4 cells" or "CD4" when discussing levels) leading to AIDS (20), marked by opportunistic infections and high mortality (18, 21). Heterogeneity exists in viral suppression and progression of CD4 decline among untreated PWH: long-term nonprogressors remain asymptomatic with higher (>500 cells/mm^3) CD4 counts even without ART (22–24), while others (often termed "elite controllers") can suppress HIV replication to undetectable levels without ART (22). Nevertheless, these individuals comprise a small minority [<1%, by some estimates (25)] of PWH, as the vast majority experience some degree of viremia and continued CD4 cell decline when untreated. Importantly, CD4 cells are not the only targets of HIV, as macrophages are also targets and express surface markers, including CCR5 and CXCR4, through which HIV entry may occur via the viral envelope protein, gp120 (26, 27).

The natural history of HIV fundamentally changed with the genesis and widespread uptake of ART, which suppresses viral replication and limits CD4 decline (19). Landmark clinical trials demonstrating benefits of continuous (28) and early (29) ART, coupled with subsequent observational and interventional studies of rapid ART initiation in various settings (30–34), helped establish the current consensus approach of initiating ART as soon as possible after diagnosis (35), ideally within 7 days. The clinical trial-demonstrated benefits of early/immediate ART have also been mirrored in surveillance data: although mortality among PWH remains higher than the general population overall, mortality for PWH with minimal CD4 decline, and consistently undetectable viral loads on ART approaches that of the general population in some settings (6, 36–39).

Yet, despite effective viral suppression and CD4 stabilization/recovery on ART, residual immunologic changes favoring a persistently inflammatory phenotype remain for many PWH. PWH on ART with modest CD4 recovery still experience a functional regulatory T cell (T_{reg}) deficit (40, 41), with related impairment in homeostatic/regulatory immune responses and a shift toward more inflammatory immune repertoires. Furthermore, even with modest CD4 recovery in absolute terms, comparative expansion of the CD8+ T cell (referred to hereafter as "CD8 cell" or "CD8" when discussing counts) repertoire is common in PWH; this results from initial increases in CD8 cells coupled with CD4 decline during untreated infection, followed by variable CD4 recovery and CD8 decline after ART

initiation (42, 43). Ultimately, despite the effectiveness of ART in aiding CD4 recovery, blunting exuberant CD8 expansion, and normalizing some markers of T cell-associated inflammation (44), a net inflammatory shift in immune cell repertoire persists. Even PWH who achieve undetectable viremia and CD4 recovery to >500 cells/mm^3 have permanently altered T cell phenotypes, with a majority of such patients continuing to have "inverted" CD4/CD8 ratios less than 1 (45). This inverted CD4/CD8 ratio—so called because CD4/CD8 ratios are commonly 1.5–2.5 in the general population (46, 47)—reflects a general shift toward a T cell repertoire marked by excess activation as well as, ultimately, exhaustion and senescence among PWH (48–53). Concomitant with this shift in T cell phenotype is a shift toward activated, inflammatory monocytes and macrophages among PWH (54, 55), which does not normalize with ART (44).

These shifts in host immune repertoire dovetail with increased gut microbial translocation and reactivation of latent viruses [including but not limited to cytomegalovirus (CMV)] to contribute to a net inflammatory state among PWH, even in the setting of sustained viral suppression (40, 56–59). Unsurprisingly, PWH have elevated circulating markers of immune activation and inflammation compared with HIV-uninfected individuals, including but not limited to interleukin-6 (IL-6), high-sensitivity C-reactive protein (hsCRP), soluble CD14 and CD163 (sCD14 and sCD163), and lipopolysaccharide; importantly, several of these markers independently associate with CVD and overall mortality among PWH (44, 60–64). Next, we will discuss the biology and scope of CVDs in PWH, with particular attention to ways in which chronic HIV-related immune dysregulation and inflammation contribute.

ATHERO-THROMBOTIC DISEASE IN HIV

Cholesterol, chronic inflammation, comorbidity, and clots: biological underpinnings of HIV-associated atherosclerosis and thrombosis

Inflammation is a cause and byproduct of atherosclerosis, thrombosis, and myocardial dysfunction and plays central roles in resulting clinical presentations, including MI, stroke, HF, and sudden cardiac death (65–89). Atherosclerosis broadly results from accumulation of plaque due to excess retained lipids within the arterial wall, net-inflammatory immune response to these retained products, and vascular injury (hemodynamic and otherwise) (90–93). Eventually, this plaque may erode or rupture, leading to thrombus formation and possible occlusion of the artery (70, 76, 78). Coronary artery occlusion, in turn, results in ischemia, acute MI, and/or sudden cardiac death (94, 95). The pathogenesis of HIV-associated atherosclerosis is incompletely described, and data are based mainly on clinical studies and a limited number of experimental studies. It is likely that HIV-mediated inflammation and dyslipidemia contribute to the severity of HIV-associated atherosclerosis, while the pathogenesis itself is largely the same as in uninfected individuals. The first step of atherogenesis remains the same: endothelial dysfunction which leads to immune activation (96, 97). This inflammation in the endothelium, which is largely mediated by IL-6 and monocyte chemoattractant protein-1 (MCP-1), two proteins commonly upregulated in HIV infection (97, 98), leads to the recruitment, migration, and transformation of macrophages into foam cells (96–98). Macrophages both harbor the HIV virus and are impacted by the HIV Nef protein which impairs cholesterol efflux from the cell (99), possibly accelerating foam cell formation and influencing HIV atherogenesis. Oxidative stress, activation of the NLRP3 inflammasome, and endoplasmic reticulum (ER) stress also contribute to atherogenesis (96–98). ER stress may be especially impacted by HIV infection due to the associated dyslipidemia and release of HIV proteins, such as gp120, which trigger the ER stress response and associated macrophage apoptosis (96, 98).

Dysregulated lipid profiles are common in PWH and often characterized by decreased high-density lipoprotein cholesterol (HDL-c) levels and elevated triglyceride levels in both treated and untreated PWH (100). HIV disrupts the function of HDL (5) (101, 102), and ART does not revert HDL levels back to pre-infection baseline (101), an important consideration, given the well-described atheroprotective role of functional HDL (103).

Effects of ART on lipids also vary by class and specific drug. Protease inhibitors (PIs; particularly earlier generation protease inhibitors) increase total cholesterol, low-density lipoprotein cholesterol (LDL-C), and triglyceride levels, whereas effects of nucleoside and non-nucleoside reverse transcriptase inhibitors (NRTIs and NNRTIs) are more variable (104–106). For instance, a recent study of over 6,000 PWH switching from tenofovir disoproxil fumarate (TDF) to tenofovir alafenamide (TAF) demonstrated significant increases in LDL-C and triglyceride levels over approximately 1 year (107). Integrase inhibitors appear to be largely lipid neutral compared with other antiretrovirals aside from protease inhibitors (108), but data are limited. In addition to changes in circulating lipids, fat distribution likewise changes both as a result of HIV and ART, resulting in redistribution syndromes marked by inflammatory visceral adiposity and varying degrees of peripheral lipodystrophy (109, 110).

Given the well-described interplay between innate immune activation and thrombosis (78–82), it is not surprising that PWH exhibit both hyper-inflammatory and hyper-thrombotic profiles. Monocyte activation persists after viral suppression on ART, with hyper-inflammatory tissue factor-expressing monocytes identified as particularly harmful promoters of a thrombo-inflammatory milieu among PWH (111, 112); markers of both monocyte activation and thrombosis have likewise been associated with CVD and death in PWH (61, 113). Although markers of thrombo-inflammation appear elevated among PWH, more research is needed to delineate underlying HIV- and ART-relevant contributors as well as potential strategies to ameliorate HIV-related thrombo-inflammation (114).

In addition to dyslipidemia and pro-thrombotic features, as well as chronic immune dysregulation, concomitant cardiovascular risk factors contribute to atherogenesis and thrombosis in PWH. The global prevalence of hypertension in PWH is approximately 20%–25%, with some variability depending on setting (e.g., North America or sub-Saharan Africa) (115–121). A complex interplay between unresolving inflammation, dyslipidemia (and associated atherosclerosis), and chronic kidney disease all may contribute to hypertension among PWH (122–125). In addition, men with HIV on ART were found to have a fourfold increase in developing diabetes mellitus (DM) compared to men without HIV in the Multicenter AIDS Cohort Study (126). Furthermore, studies of women with HIV observed a higher risk for developing DM among women with HIV compared with men with HIV, suggesting a sex-specific risk for type 2 diabetes and HIV infection (127). This elevated DM risk among people with HIV has clear implications for cardiovascular diseases; in PWH, the risk of MI is more than doubled for those with DM than for those without DM (128). It is important to note, however, that the observed elevated risk of DM among men and women with HIV compared with people without HIV has not been universal across cohorts and may depend on both HIV and control populations studied, as several cross-sectional studies observed similar prevalence of DM for people with HIV on ART and the general population (129–131).

Cigarette smoking is especially common among PWH and strongly associated with athero-thrombotic complications such as MI and stroke. Although the prevalence of current smoking in US adults declined from 20.6% to 16.8% between 2009 and 2014, these numbers were 37.6%–33.6% for PWH (132). In men with HIV, current cigarette smoking was positively associated with subclinical atherosclerosis and increased risk for MI (133). Compared to men with HIV who do not smoke, those who do smoke are estimated to have twice the risk of having a major cardiovascular event (134). Alcohol use is also common in PWH, and hazardous drinking, defined as binge drinking or more than 14 drinks per week, is associated with an increased incidence of CVD in men with HIV as determined by the Veterans Aging Cohort Study (VACS) (135). This association between hazardous drinking alcohol abuse or dependence and CVD persists after accounting for traditional CVD risk factors, CD4 count, and adherence to ART (135). Moderate drinking and other substance use, including cocaine, did not significantly increase the risk for developing HF in the VACS analysis (13). A conceptual model of HIV-associated immune dysregulation and coinciding contributors to CVD risk is included in Fig. 1.

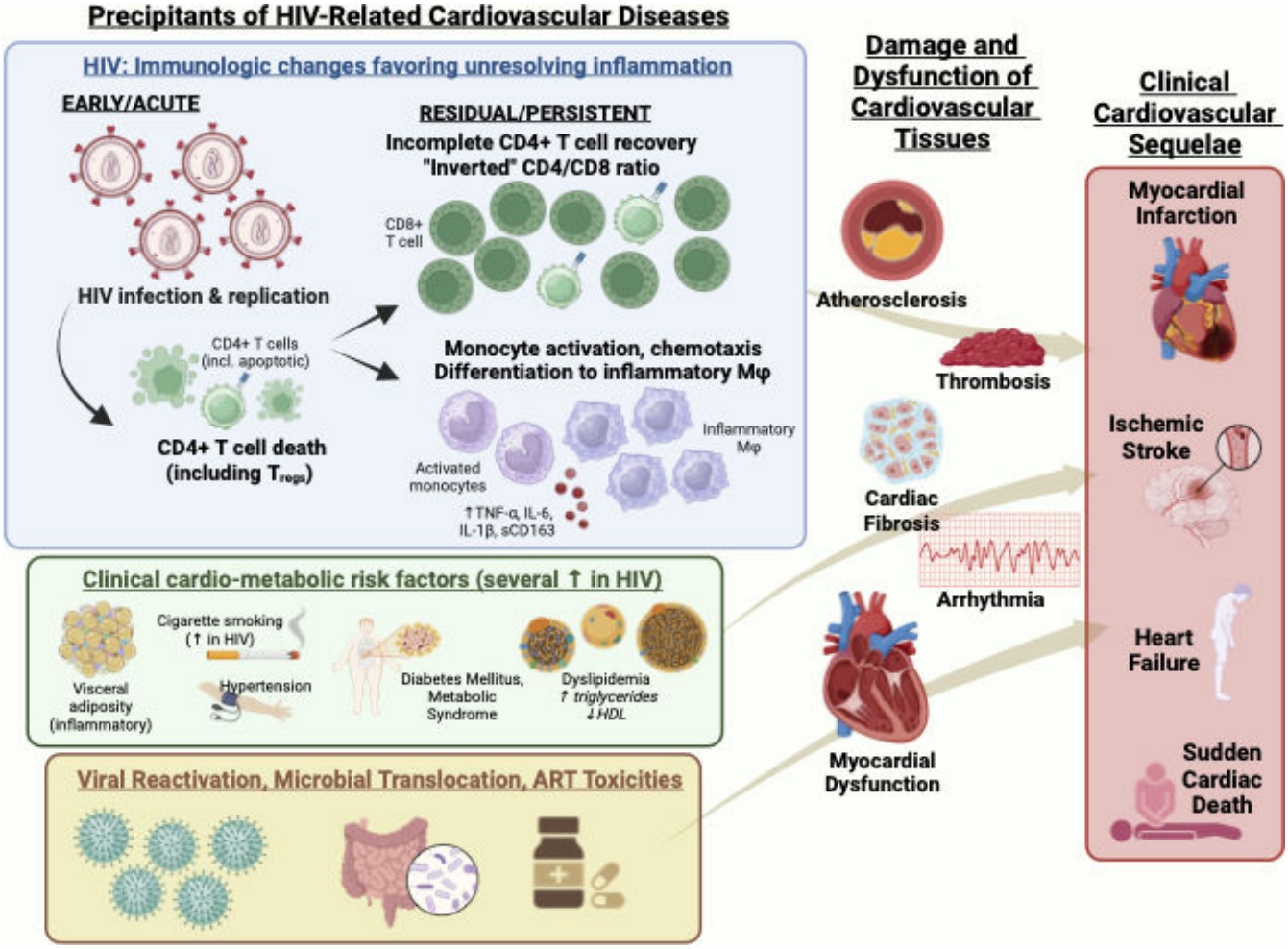

FIG 1 Immunologic and clinical contributors to HIV-associated cardiovascular diseases.

Subclinical arterial disease

Given this inflammatory and metabolically dysregulated milieu, it is not surprising that PWH exhibit a higher prevalence of subclinical arterial disease as well as a more inflammatory arterial disease phenotype compared with HIV-uninfected controls. Compared with HIV-uninfected individuals, PWH have a higher prevalence and greater extent of noncalcified, high-risk coronary plaque and increased coronary artery adverse remodeling—clinically validated markers of increased MI risk that correlate with monocyte activation markers (136–142). Interestingly, a recent analysis investigating associations of a large panel of inflammation-associated proteins with calcified and overall coronary plaque [as determined by computed tomography (CT)] suggested unique potential pathways underlying noncalcified versus calcified plaque presence in PWH (143).

Data investigating associations of systemic and vascular inflammation with coronary plaque among PWH are not limited to studies of blood-based biomarkers. Indeed, one study investigating coronary plaque via CT among 41 PWH also employed functional positron emission tomography (PET) imaging of the aorta to measure inflammation and revealed a significant association between aortic inflammation and high-risk coronary plaque (140). While this association was observed within PWH, data vary on whether PWH have significantly more arterial inflammation than HIV-uninfected controls. One study of 153 young to middle-aged adult (aged 18–40) PWH and 153 age- and gender-matched controls revealed higher target-to-background ratio—a marker of arterial

inflammation on PET—as well as high-sensitivity C-reactive protein among PWH (144). Meanwhile, a smaller study of 26 PWH and 25 HIV-uninfected controls revealed no difference in arterial inflammation measured by PET, although controls were 9 years younger (on average) than PWH in this study (145).

In addition to CT-based measurements of coronary plaque, numerous studies have investigated carotid intima-media thickness and plaque on ultrasound—direct markers of carotid disease and proxy markers of systemic and coronary arterial disease—in PWH and controls. These likewise demonstrated a higher prevalence of carotid intima-media thickness, plaque, and high-risk features among PWH, as well as associations between elevated indices of inflammation and arterial disease in PWH (141, 146–148). A recent systematic review of studies investigating subclinical cardiovascular imaging among PWH, which included several of the above-mentioned studies as well as others with variable risk of bias, revealed generally higher indices of subclinical arterial plaque and inflammation among PWH versus HIV-uninfected controls (149). Importantly, a high degree of heterogeneity across studies was noted, highlighting the non-uniformity of populations of PWH as well as controls that may be selected for such studies as well as the potential impact of variable control selection on findings related to HIV-associated subclinical disease burden (150).

Clinical presentation and HIV-specific CVD risk enhancers

Clinically, PWH have approximately 1.5- to 2-fold higher risks for MI compared with HIV-uninfected individuals, a risk that persists after accounting for common risk factors and confounders. These elevated MI risks were noted in the early ART era and have persisted; furthermore, a biologic gradient exists whereby lower CD4 count is strongly associated with MI among PWH (151–157). Additionally, higher viral loads are associated with endothelial dysfunction, inflammation, and the pathogenesis of atherosclerosis (158–161). Such associations of viremia and CD4 decline with MI risk likely reflect putative mechanisms discussed above, ranging from net-activated/inflammatory T cell and monocyte repertoires to concomitant dyslipidemia and thrombosis (5). Interestingly, HIV-associated excess MI (and overall CVD) risk may be especially high among women with HIV (156, 162), although underlying mechanisms are incompletely defined, as are CVD risks in transgender and non-binary PWH. In addition to MI, ischemic stroke also appears to be more common among PWH than in the general population (8, 163, 164), although this comparative excess risk has not been universally observed across cohorts (165).

Yet, for PWH and providers engaged in their care, broad comparisons of MI or stroke risk by HIV serostatus are less practically informative than understanding HIV-specific factors that may be driving CVD risk at an individual level (150). Among PWH, sequelae of uncontrolled virus and immune progression—in particular, low (<200 or even <350 cells/mm^3) CD4 and histories of prolonged viremia—have been consistently associated with higher MI (151–157) and stroke risk (8, 163–165) and are thus considered HIV-specific CVD risk enhancers (5). The HIV Outpatient Cohort Study found that recent (as opposed to nadir) CD4 counts of <500 cells/mm^3 were associated with a 20% attributable risk for incident CVD and could be considered as an independent risk factor for CVD (153). Additionally, a lower CD4/CD8 ratio is independently associated with an increased risk for coronary atherosclerosis (166). Other HIV-specific CVD risk enhancers, which have likewise been associated with heightened CVD risk among PWH and reflect inflammatory pathophysiologies discussed above, include co-infection with hepatitis C virus and HIV-associated metabolic sequelae such as lipodystrophy (5). Most PWH (90% or higher in some cohorts) are co-infected with CMV (167). CMV co-infection exacerbates non-AIDS comorbidities, especially CVD and cerebrovascular events (167, 168). In HIV-uninfected CMV-infected populations, the Sacramento Area Latino Study on Aging found an association between CMV IgG levels and ischemic heart disease and increased carotid artery stiffness (169). In PWH, CMV IgG levels do not necessarily correlate with CMV replication, highlighting the important role of immune activation (169). Approximately

10% of CD4 and CD8 cells are targeted toward CMV in infected individuals, and this percentage may increase as the individual ages (169). It is hypothesized that this robust response toward CMV infection may decrease the available immune cells to respond to other infections, further stressing the immune system in PWH.

Now what? practical insights for prevention and management

For CVD primary prevention—prevention of CVD before its overt clinical onset—assessment of absolute risks is required to inform the net clinical benefit [absolute risk reduction minus absolute adverse event rate (170)] of potential CVD preventive interventions. For example, if medication A was expected to broadly achieve a relative reduction in CVD events by one-third in most populations, patient X with a 10-year predicted CVD risk of 30% would be expected to achieve a 10% absolute reduction in CVD risk (down to 20%) with medication A; for patient Y with a 10-year predicted risk of only 3%, this absolute risk reduction would be only 1%. Therefore, if medication A confers a consistent 2-5% absolute risk for serious adverse effects, the net clinical benefit of medication A would be more readily justified in patient X than patient Y, for whom adverse effects would be more likely than preventing a CVD event.

In this context, there has been considerable interest in precisely estimating CVD risk among PWH. Unfortunately, general population and HIV-specific CVD risk estimators exhibit modest at-best predictive utility in assessing CVD risk for PWH (171–174), with particularly poor performance in women, Black individuals, and younger populations (175). In the absence of optimally calibrated CVD risk estimation tools for PWH, a reasonable interim approach is to use an existing CVD population risk estimator (e.g., the American Heart Association/American College of Cardiology pooled cohort equations or Framingham Risk Score, among others), with the understanding that in the presence of HIV-specific risk enhancers, an individual's actual CVD risk is likely 1.5-fold or more higher than predicted (5). As discussed above, HIV-related risk enhancers include clinical features such as low current or nadir CD4 count (<200 or <350 cells/mm^3), history of prolonged viremia and/or treatment failure, and co-infection with hepatitis C virus, among others. Whether circulating inflammatory markers such as interleukin-6 or soluble CD163 meaningfully improve risk stratification remains to be determined.

A separate question relates to the role of subclinical atherosclerotic cardiovascular disease (ASCVD) imaging—for instance, coronary artery calcium (CAC) screening—for further risk stratification in PWH. In the general population, CAC screening is a widely accepted, relatively inexpensive, and low-radiation way to evaluate calcified coronary plaque burden (which generally, though imperfectly, correlates with overall plaque burden) and thus stratify individuals' risk for progression to clinical ASCVD such as MI (176). Several investigations adding CAC scores to clinical risk prediction models have revealed CAC to be an important—in some cases, the most important—predictor of progression to clinical events, supporting its widespread use for risk stratification (176–178). While these general population data argue in favor of potential value for CVD risk stratification in PWH, there are some caveats. As discussed above, subclinical arterial disease may present with a somewhat different phenotype in PWH than in HIV-uninfected persons, with PWH having a comparative predilection for noncalcified plaque. Given these data, CAC screening in PWH may be useful insofar as observation of significant CAC [e.g., absolute CAC score >400 Agatston units, and/or at a high percentile compared to what would be age- and demographically expected based on normative cohort data (179)] is clearly indicative of plaque burden and places that individual in a higher risk group than would have been expected pretest. Meanwhile, a lower-than-expected CAC score or zero CAC, while somewhat reassuring, may not be quite as reassuring in PWH, given noncalcified plaque may still be present.

The predicted CVD risk for PWH can inform providers regarding expected net clinical benefits of established CVD preventive therapies—in particular, lipid-lowering therapies such as statins. To this end, the recently completed randomized trial to prevent vascular events in HIV (REPRIEVE), which demonstrated a higher-than-expected 35% risk

reduction in major cardiac events for PWH randomized to a moderate intensity statin (pitavastatin) and similarly low serious adverse event rates as in the general population, provides timely data to inform these individual-level risk/benefit considerations (180). Non-statin lipid-lowering therapies are also under investigation in PWH, with a recent trial of a proprotein convertase subtilisin/kexin type 9-inhibiting monoclonal antibody demonstrating lipid-lowering efficacy and a tolerable side effect profile in PWH (181). The Evolocumab Effect on LDL-C Lowering in Subjects with Human Immunodeficiency Virus and Increased Cardiovascular Risk (BEIJERINCK) trial also found monthly evolocumab injections significantly reduced LDL-C levels in PWH with high cardiovascular risk. The LDL-lowering effects of omega-3 fish oil and fenofibrate in PWH still require more elucidation, with two small studies showing insignificant differences and mild improvement for each respective therapy (182, 183). An overview of clinical trials evaluating cardiovascular endpoints in PWH is provided in Table 1.

Fewer data exist to inform on other antithrombotic and anti-inflammatory therapies for CVD prevention in PWH. Aspirin exhibited muted antiplatelet effects in PWH compared with alternative antiplatelet agents, such as clopidogrel (188–190), but the clinical relevance of these findings and comparative risk versus benefit of antiplatelet for primary prevention of CVD in PWH remain to be seen. Similarly, the role for targeted anti-inflammatory therapies, such as canakinumab, for CVD prevention remains unclear in PWH but is under investigation (191). The Antiinflamatory Therapy with Canakinumab for Atherosclerotic Disease (CANTOS) trial showed that canakinumab, a monoclonal antibody, treatment was helpful in reducing major adverse cardiovascular events in patients without HIV who achieved hsCRP levels less than 2 mg/L with the first dose (192–194). Canakinumab has major effects on inflammation as shown by circulating inflammatory markers but very little effect on lipid levels, especially LDL (192, 193). However, the study did not include PLWH, leaving limited anti-inflammatory recommendations for this population. Similarly, the Colchicine Cardiovascular Outcomes Trial (COLCOT) and the second low-dose colchicine trial (LODOCO2) found that 0.5 mg of colchicine daily significantly decreased the risk of cardiovascular events in patients with recent MI and patients with chronic coronary disease, respectively (195, 196). Neither trial collected data on PWH. An overview of clinical trials evaluating inflammation-targeted therapies in the general population is provided in Table 2.

Multiple studies have shown that low-to-moderate dose methotrexate treatment in patients with rheumatoid arthritis lowered their CVD risk by modulating inflammation (198–202), but a recent study of low-dose methotrexate showed that the drug had no significant effect on endothelial function or inflammatory markers in PWH (203). The treatment did significantly lower CD8 cells, and a subsequent study showed that the methotrexate inhibited T cell proliferation (5, 203, 204). Ultimately, while there is ongoing research on anti-inflammatory therapies and cardiovascular risk, there is an absence of data applying to PWH.

PWH also warrant different secondary prevention considerations. Although PWH have similar rates of complication following percutaneous coronary intervention compared with HIV-uninfected individuals (205), they are less likely to undergo percutaneous coronary intervention following MI. This gap in indicated coronary interventions may be especially pronounced among women (206, 207). Rates of appropriate, indicated lipid-lowering and antiplatelet therapy following athero-thrombotic CVD events (in particular, MI) likewise lag for PWH compared with HIV-uninfected individuals (208–210). Given suboptimal post-MI care and a high burden of mortality post-MI among PWH (211), HIV care providers must remain vigilant to ensure patients with existing CVD receive appropriate, indicated therapies to prevent recurrent events.

ART-specific considerations in ASCVD: past, present, and future

ART has transformed the natural history of HIV, and evolutions in ART have likewise impacted the natural history of HIV-associated aging and comorbidity. Several

TABLE 1 Randomized controlled trials evaluating cardiovascular endpoints in people with HIV

Trial	Number of participants	Intervention/observation	Primary outcome and effect size	Secondary endpoints
OPERA Cohort (2018)	6,451 PWH, at least 18 years of age, with at least 4 weeks of TDF use and direct switch from TDF to TAF between 5 September 2015 and 31 March 2018	Switched from TDF to TAF, 4,328 PWH maintained their other agents	LDL-C increased by 1.40 mg/dL/mo over first 3 months on TAF and 0.33 mg/dL/mo between 3 and 9 months before plateauing. TG increased by 3.52 mg/dL/mo over first 3 months on TAF and 0.91 mg/mL/mo between 3 and 9 months.	Weight increased 0.25 kg/mo over first 3 months and 0.10 kg/mo between 3 and 9 months.
Swiss HIV Cohort (2021) TDF versus TAF (184)	4,375 PWH who received TDF-containing ART for at least 6 months	Switch therapy to TAF or continue TDF-based regimen	Switching to TAF was associated with adjusted mean weight increase of 1.7 kg after 18 months compared to 0.7 kg in the TDF group. 13.8% of the TAF group became overweight/obese compared to 8.4% of the TDF group.	Switching to TAF led to an increased adjusted mean total cholesterol of 9.5 mg/dL, HDL-C of 1.9 mg/dL, LDL-C of 4.7 mg/dL, and TG of 16.1 mg/dL after 19 months.
SMART[a] (2009) (6, 185, 186)	5,472 PWH with CD4 counts >350 cells/μL	Intermittent ART until CD4 count <250 cells/ μL or continuous ART	The opportunistic disease/death hazard ratio (HR) was 3.5 for the drug conservation (DC) versus viral suppression (VS) groups.	The hazard ratio for serious non-AIDS events was 7.0 for the DC versus VS groups.
START(29)	4,658 PWH with a starting CD4 count of >500 cells/mm^3	Immediate initiation of ART or deferred treatment until CD4 count fell to 350 cells/mm^3 or development of AIDS	Primary outcome of composite of serious AIDS-related event and serious non-AIDS-related event. 1.8% of the immediate initiation group compared to 4.1% of the deferred initiation group reached the primary endpoint. Hazard ratio of 0.43.	Secondary endpoints included serious AIDS-related events, serious non-AIDS-related events, death from any cause, grade 4 events, and unscheduled hospitalizations for reasons other than AIDS. HR of 0.28 for serious AIDS-related event, 0.61 for serious non-AIDS-related events, and 0.58 for death from any cause.
BEIJERNIK(181)	464 PWH with hypercholesterolemia/mixed hyperlipidemia on statin therapy	Monthly subcutaneous injection of evolocumab 420 mg or placebo	Primary endpoint of percent change in LDL-C. Placebo-corrected mean percent change in LDL-C of −56.9% with evolocumab treatment.	Secondary endpoints of LDL-C <70 mg/dL and percent change in other plasma lipids and lipoprotein levels. LDL-C level <70 mg/dL achieved in 73.3% in evolocumab group compared to 7.9% in placebo group.
REPRIEVE (2023) (143, 187)	7,769 PWH between the ages of 40 and 75 years with low-to-moderate CVD risk on ART	4 mg of daily pitavastatin calcium or placebo	Daily statin use lowered risk of major adverse cardiovascular events by 35% compared to placebo group. Major adverse cardiovascular event defined as composite of cardiovascular death, myocardial infarction, hospitalization for unstable angina, stroke, transient ischemic attack, peripheral arterial ischemia, revascularization, or death from undetermined cause.	Secondary outcomes of composite of a major adverse cardiovascular event or death from any cause, individual components of the primary outcome, death from any cause, and LDL and non-HDL cholesterol, among others. The incidence of major adverse cardiovascular events or death from any cause was 9.18 per 1,000 person-years in the pitavastatin group compared to 11.63 per 1,000 person-years in the placebo group (HR, 0.79). There were deaths from noncardiovascular causes in 82 in the pitavastatin group compared to 81 in the placebo group, and nonfatal heart-failure events in 13 of the pitavastatin group compared to 12 in the placebo group. The LDL-C levels decreased from a median of 107 to 74 mg/dL in the pitavastatin group and from 106 to 105 mg/dL in the placebo group.

[a]SMART, Strategies for Management of Antiretroviral Therapy.

TABLE 2 Randomized controlled trials evaluating inflammation targeted for cardiovascular disease in the general population

Trial	Number of participants	Intervention/observation	Primary outcome and effect size	Secondary endpoints
CANTOS (2019) (193, 194)	10,061 patients with a history of MI	50, 150, or 300 mg of canakinumab or placebo subcutaneously every 3 months	Participants in the canakinumab treatment group who achieved IL-6 levels below 1.65 ng/L had a 32% reduction in major adverse cardiovascular events (MACE), a 30% reduction in MACE plus hospitalizations for unstable angina requiring urgent revascularization, a 52% reduction in cardiovascular mortality, and a 48% reduction in all-cause mortality compared to the placebo group.	Participants in the canakinumab group who did not achieve IL-6 levels below 1.65 ng/L did not have any significant benefits for these endpoints.
LODOCO2 (195)	5,522 patients between the ages of 35–82 years with evidence of coronary disease	0.5 mg of colchicine once daily or placebo	Primary endpoint composite of cardiovascular death, spontaneous MI, ischemic stroke, or ischemia-driven coronary revascularization. The primary endpoint occurred in 6.8% of the colchicine group and 9.6% of the placebo group.	A key secondary endpoint occurred in 4.2% of the colchicine group and 5.7% of the placebo group.
CIRT (197)	4,786 patients with previous MI or multivessel coronary disease who also had type 2 diabetes or metabolic syndrome	15 mg of methotrexate once weekly with increase to 20 mg at 4 months or matching placebo. All participants received 1 mg of oral folic acid daily	Primary endpoint of first occurrence of a major adverse cardiovascular event defined as a composite of nonfatal MI, nonfatal stroke, or cardiovascular death. Hospitalization for unstable angina that led to urgent revascularization was added to the primary endpoint. This final primary endpoint occurred in 201 patients in the methotrexate group and 207 in the placebo group [hazard ratio (HR), 0.96]. The original primary endpoint occurred in 170 patients in the methotrexate group and 167 in the placebo group (HR, 1.01).	Secondary endpoints of death from any cause, a composite of major adverse cardiovascular events plus coronary revascularization, hospitalization for congestive heart failure. There were no significant differences between the groups.
COLCOT (2019) (196)	4,745 patients with prior MI within 30 days of trial	0.5 mg once daily colchicine or placebo	Primary endpoint of composite of death from cardiovascular causes, resuscitated cardiac arrest, myocardial infarction, stroke, or urgent hospitalization for angina leading to coronary revascularization. Primary endpoint occurred in 5.5% of colchicine group compared to 7.1% of placebo group. Hazard ratios of 0.84 for death from cardiovascular causes, 0.83 for resuscitated cardiac arrest, 0.91 for myocardial infarction, 0.26 for stroke, and 0.50 for urgent hospitalization for angina needing coronary revascularization.	Diarrhea reported in 9.7% of colchicine group and 8.9% of placebo group. Pneumonia reported in 0.9% of colchicine group and 0.4% of placebo group.

landmark trials elucidated the benefits of long-term antiretroviral (ARV) use, as well as the importance of early and continuous ART. The Strategies for Management of Antiretroviral Therapy trial demonstrated the significant benefit of continuous ART over episodic use (185), even with the side effects of early antiretrovirals; in addition to improving HIV/AIDS-related outcomes, continuous ART actually reduced risk for myocardial infarction. Subsequently, the START (initiation of antiretroviral therapy in early asymptomatic HIV infection) demonstrated a clear clinical benefit of immediate and continuous ART initiation (29), though without a significant reduction in cardiovascular events with immediate ART. Thus, although one might extrapolate a reduction in overall cardiovascular risk with immediate ART based on the potential to reduce viremia and early CD4 decline, the clinical trial data from START do not resoundingly indicate cardiovascular-specific benefit of immediate ART.

In the current era, there are seven classes of antiretroviral drugs approved by the Food and Drug Administration: NRTIs, NNRTIs, PIs, INSTIs (integrase strand transfer

inhibitors), fusion inhibitors, CCR5 antagonists, and post-attachment inhibitors. People with HIV are commonly on three drugs from two different classes, although two-drug regimens are becoming increasingly common. The 2022 recommendations from the International Antiviral Society, USA Panel for preferred drug regimens pair one INSTI with one or more NRTIs (35). The formulations of antiretroviral drugs have changed from their first iterations to modern usages. Older variations of NRTIs, such as azidothymidine, were associated with higher mitochondrial toxicity leading to myopathies and neuropathies (212, 213) As mentioned previously, TDF and TAF have varying effects on lipid profiles (107). While more studies are needed to conclude their effect on CVD risk, it is possible that TDF-based regimens have positive effects on lipid profiles and, therefore, lessen CVD risk compared to TAF-based regimens. Despite the cardiometabolic conditions associated with INSTIs, a study based on the Swiss HIV Cohort Study just concluded that there is no difference in short-term or long-term risk for CVD in treatment-naïve PWH who start an INSTI-based ART compared to those who start another ART (184).

Overall, drug-/class-specific data are too inconsistent to inform a blanket recommendation for a particular drug or class as preferable to others. Protease inhibitors have been associated with modest increases in MI risk (214), but these findings do not appear to be a universal class effect: among protease inhibitors, ritonavir-boosted darunavir is associated with increased CVD risk, whereas ritonavir-boosted atazanavir is not (215). Meanwhile, abacavir has been associated with elevated MI risk in some (214, 216–221) but not all studies (222–225). Therefore, while ART is clearly preferable to no ART for control of HIV as well as blunting-related immunologic changes driving persistent inflammation among PWH, there is currently no single, clearly superior "CVD-friendly" ART regimen to recommend above others. In the presence of boosters, it is important for clinicians to likewise understand potential effects on other medications, as boosters such as cobicistat and ritonavir can substantially increase levels of other drugs metabolized by the

TABLE 3 Statin dosing-related considerations for people with HIV on ART

Statin	Intensity	Metabolism (226–229)	ARV-specific data
Atorvastatin	High (40 or 80 mg daily dose) Lower doses considered moderate (226, 230–232)	CYP3A4 Pgp OATP1B1	Interactions with PIs and NNRTIs which may require statin dose adjustments. Interacts with boosters including cobicistat given CYP3A4 metabolism; in these cases, atorvastatin downward dose adjustment recommended (105, 233–239).
Pitavastatin	Moderate (2–4 mg) (226)	Minimally metabolized (240)	No significant or severe noted interactions with antiretrovirals (105, 227, 233, 238, 241).
Lovastatin	Moderate (40 mg) (226, 242, 243)	CYP3A4 Pgp	Interactions with PIs and NNRTIs which may contraindicate use. Rarely used in modern era due to superior efficacy/safety profiles of other statins (105, 233, 244).
Rosuvastatin	High (20–40 mg) (226, 245, 246) Lower doses considered moderate	CYP2C9 OATP1B1 OATP1B3	Interactions with some PIs which may require downward dose adjustment (105, 233, 238, 241, 245).
Simvastatin	Moderate (20–40 mg) (226, 231, 247, 248)	CYP3A4 Pgp OATP1B1	Heavily metabolized by CYP3A4 system; strong interactions with PIs and NNRTIs which may contraindicate use. Rarely used in modern era due to superior safety profiles of alternative moderate-intensity statins (pravastatin, pitavastatin, and atorvastatin or rosuvastatin at moderate intensity) (105, 233–235, 239, 244).
Pravastatin	Moderate (40–80 mg) (226, 249)	OATP1B1 OATP1B3	Interactions with PIs and NNRTIs which may require modest downward pravastatin dose adjustments (105, 233–235, 237, 250, 251).
Fluvastatin	Moderate (80 mg) (226, 252)	CYP2C9 OATP1B3	Interactions with PIs which may require modest downward fluvastatin dose adjustments (105, 233, 253, 254)

cytochrome P450 system, including statins (105). An overview of statin-related considerations for PWH on ART is provided in Table 3.

OTHER CARDIOVASCULAR MANIFESTATIONS OF HIV: AN INCOMPLETE PICTURE

As discussed above, atherosclerosis has a largely stereotyped pathogenesis and presentation, which, despite some heterogeneity (255), result from a finite and largely predictable combination of triggers. Meanwhile, other CVDs for which PWH are at heightened risk—in particular, HF and fatal arrhythmia/sudden cardiac death—represent often later-stage sequelae of diverse CVD pathologies. Accordingly, mechanisms of HIV-associated HF, for instance, are challenging to define in a singular manner, as are HIV-specific preventive and therapeutic approaches. These challenges mirror those observed in the general population, where heterogeneity of HF mechanisms and manifestations has spurred more specific phenotype- and etiology-focused interventions (256, 257).

Heart failure in HIV: evolution of a final common pathway

Heart failure is a complex clinical syndrome with varying manifestations, resulting from underlying myocardial tissue abnormalities coupled with extracardiac contributors such as neurohormonal activation, pulmonary and renal disease, and morbid obesity (258). Given this diversity of contributors and manifestations, the nature of HIV-associated HF has unsurprisingly evolved as the natural history of HIV has changed (158). In the pre-ART era, PWH commonly experienced overt severe systolic dysfunction, resulting, in many cases, in HF with reduced ejection fraction (HFrEF) (259)—a manifestation particularly common among PWH with high viremia, overt immunodeficiency, and AIDS (259–262). In the modern ART era, rates of severe systolic dysfunction have declined, but systolic dysfunction remains common among PWH as does, increasingly, diastolic dysfunction (a common underlying contributor to HF with preserved ejection fraction, HFpEF) (5, 259, 263). These underlying abnormalities in myocardial function predispose to HF, for which PWH have 1.5- to 2-fold higher risk than HIV-uninfected individuals in the modern ART era, even after adjustment for clinical and other confounders (12, 13). In both of these studies investigating HF risk, conducted in distinct cohorts and with distinct HF ascertainment methods, PWH with higher viral load and lower CD4 counts were at especially elevated risk—mirroring the elevated risk of MI and stroke observed among PWH with viremia and/or low CD4.

Although the scope and presentation (e.g., HFrEF versus HFpEF) are increasingly defined among PWH, several major questions remain. Little data from the modern ART exist on specific etiologies of HF (e.g., post-MI damage versus valvular origin versus stimulant-induced HF, among other potential causes) among PWH. This represents a major gap, given the vast diversity of potential HF etiologies (264). As a result of this gap, biologic insights into HIV-associated HF have depended largely on small imaging studies investigating intermediate subclinical manifestations on cardiac magnetic resonance imaging (CMRI) of myocardial disease, such as fibrosis and mechanical dysfunction. These studies suggest that PWH have more myocardial inflammation/edema, fibrosis, steatosis, and mechanical dysfunction than HIV-uninfected controls (265–267). The myocardial substrate may also be especially vulnerable to ischemia and damage following ischemia/MI among PWH (268, 269); one study observed twice the extent of myocardial fibrosis following MI for PWH versus controls with similar coronary artery disease extent and MI culprit lesions (269), with the result being more myocardial area at risk and resulting dysfunction during ischemic events. Nevertheless, despite these interesting data, the optimal role for cardiac imaging—whether with echocardiography, CMRI, and/or computed tomography—in PWH without existing cardiac symptoms is unclear. At a minimum, it is important that clinicians maintain a high index of suspicion for coronary ischemia and/or myocardial dysfunction in their PWH presenting with potential cardiopulmonary symptoms (in particular, chest pain or shortness of

breath), with subsequent symptom-directed imaging studies informing early diagnosis and treatment.

Despite these emerging data, limited HF etiology-specific knowledge among PWH limits HIV-specific insights into HF prevention and treatment. For HIV care providers, understanding that PWH have heightened HF risk—particularly in the setting of current or historical sustained viremia and/or CD4 decline—is an essential first step that should raise the index of suspicion for HF in PWH experiencing potential HF symptoms such as dyspnea or lower extremity edema. In 2013, The HIV Organ Policy Equity Act allowed for HIV-infected patients to receive organ transplants from HIV-infected donors in order to further research (270). While most data come from kidney and liver transplants, there are studies to show the 5-year survival rate for PWH receiving heart transplants is similar to that of the HIV-uninfected population (270). Similar studies have shown the effectiveness of ventricular assist devices (VAD) in PWH suffering from advanced HF, even in the setting of higher rates of preimplant comorbidities than the HIV-uninfected population (271). Access to both heart transplants and VAD is currently limited for PWH due to persisting views that HIV infection is a contraindication for these interventions (272, 273). In the coming years, as more HF etiology-specific knowledge emerges, more targeted insights for HF prevention and therapy among PWH may likewise emerge.

HIV-associated arrhythmias: inconsistent data—except for excess sudden cardiac death

As with HF, cardiac rhythm disturbances (arrhythmias) can result from a diversity of intrinsic myocardial (e.g., tissue fibrosis) and extracardiac (e.g., adrenergic over-activation) stimuli. Arrhythmias likewise vary in their anatomic sites of origin, with implications for clinical severity. Generally speaking, supraventricular arrhythmias—ranging from atrial fibrillation or flutter to atrial tachycardia, among others—have a more benign clinical profile than sustained ventricular arrhythmias such as ventricular tachycardia or fibrillation, the latter of which is usually fatal. Data vary on whether PWH have higher risk for atrial fibrillation compared with controls and may depend on cohort and atrial fibrillation ascertainment methods (274–276). Regarding ventricular arrhythmias, PWH do not appear to have elevated risk for isolated (usually benign) ventricular ectopy or nonsustained ventricular tachycardia (277, 278). However, the risk for sudden cardiac death—often resulting from fatal arrhythmias such as sustained ventricular tachycardia degenerating into ventricular fibrillation (279)—is higher among PWH than HIV-uninfected individuals and may be driven by more fibrosis among PWH (11, 14, 280). Whether and how these findings should alter thresholds for arrhythmia screening and preventive therapy (in the case of sudden cardiac death, via implantable cardioverter-defibrillator for very high-risk individuals based on HF and/or arrhythmic history) remains to be seen (281). In the meantime, a reasonable approach is for HIV care providers to maintain a high index of suspicion in the presence of concerning symptoms (particularly syncope or presyncope without prodrome) and a low threshold for electrocardiographic screening and/or referral to a cardiologist. Furthermore, although the role for broad screening of asymptomatic PWH with electrocardiograms is uncertain, a low threshold for screening is supported by (i) the relatively common presence of abnormal baseline electrocardiogram findings in PWH (282, 283) and (ii) the potential value of screening for QT prolongation in the setting of polypharmacy.

HIV and pulmonary arterial hypertension

PAH is one of the earliest described HIV-associated CVD manifestations and remains relevant in the modern era, with several-fold higher prevalence of PAH remaining among PWH compared with HIV-uninfected individuals (15, 16, 284–286). HIV-related PAH has a significantly higher prevalence than PAH in the general population and has been well described since the 1990s. The effect of ART on HIV-related PAH remains controversial (284, 287), and the common underlying mechanism is hypothesized to be a combination

of vascular injury, pulmonary arteriole remodeling, and increased inflammation (284, 287).

CONCLUSIONS, LIMITATIONS, AND FUTURE DIRECTIONS

People with HIV have higher risks for cardiovascular diseases than people without HIV, and these heightened risks apply to varied manifestations including myocardial infarction, stroke, heart failure, and sudden death. Putative HIV-specific mechanisms for these manifestations differ and are incompletely defined, particularly for heart failure and sudden cardiac death. Furthermore, an important limitation of current data on HIV-associated cardiovascular diseases is that the vast majority come from high-income settings, particularly in North America and Europe. This knowledge gap may have important implications for understanding and curbing cardiovascular pathologies in the global HIV population. For instance, the long-term immunologic effects of perinatal HIV infection—much more common in regions with higher HIV endemicity than North America and Europe—on athero-thrombotic and myocardial disease likely differ dramatically from the cardiovascular effects of HIV acquired at middle age or later. More research is needed to inform on such questions and generate more precise knowledge on how diverse immune phenotypes may differentially drive HIV-associated cardiovascular risk (150).

Despite these knowledge gaps, a common theme is that prolonged viremia and low CD4 count—current or historical—are consistently associated with higher risk for cardiovascular diseases among people with HIV. From a management perspective, an emphasis on immediate and continuous ART to control viremia and assist with CD4 recovery is therefore essential not only for HIV control but for reduction in cardiovascular risk. Recent data also suggest people with HIV receive particular athero-protective benefit from lipid-lowering therapy with statins, which may justify a lower clinical threshold to consider these therapies among PWH when perceived benefit exceeds risk. Considerably, more work is needed to define etiologies and underlying mechanisms of HIV-associated heart failure and sudden cardiac death, with the ultimate goal that these data will inform screening, prevention, and, perhaps, therapy.

Importantly, given the evolving natural history of HIV and available therapies for PWH, even these data will represent an incomplete picture. With increasing availability of long-acting therapies such as lenacapavir (288) and other novel approaches to treating HIV, natural histories of HIV viremia, immune progression, and related systemic and tissue-specific inflammation may evolve, with potential implications for CVD pathogenesis and burden. Of course, factors such as age and duration of infection also vary widely by geographic region; for instance, half of PWH in the United States or more are over age 50, whereas this proportion is considerably lower in sub-Saharan Africa, though expected to increase several-fold in the coming years (289). These considerations ensure that HIV-related CVD pathogenesis and burden will likely evolve in somewhat setting-specific manners in the decades ahead. Careful clinical and mechanistic research as well as surveillance studies will remain essential in the coming decades as HIV-associated cardiovascular diseases continue to evolve.

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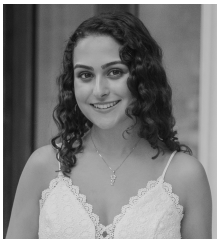

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