

## AHA SCIENTIFIC STATEMENT

# Characteristics, Prevention, and Management of Cardiovascular Disease in People Living With HIV

## A Scientific Statement From the American Heart Association

**ABSTRACT:** As early and effective antiretroviral therapy has become more widespread, HIV has transitioned from a progressive, fatal disease to a chronic, manageable disease marked by elevated risk of chronic comorbid diseases, including cardiovascular diseases (CVDs). Rates of myocardial infarction, heart failure, stroke, and other CVD manifestations, including pulmonary hypertension and sudden cardiac death, are significantly higher for people living with HIV than for uninfected control subjects, even in the setting of HIV viral suppression with effective antiretroviral therapy. These elevated risks generally persist after demographic and clinical risk factors are accounted for and may be partly attributed to chronic inflammation and immune dysregulation. Data on long-term CVD outcomes in HIV are limited by the relatively recent epidemiological transition of HIV to a chronic disease. Therefore, our understanding of CVD pathogenesis, prevention, and treatment in HIV relies on large observational studies, randomized controlled trials of HIV therapies that are underpowered to detect CVD end points, and small interventional studies examining surrogate CVD end points. The purpose of this document is to provide a thorough review of the existing evidence on HIV-associated CVD, in particular atherosclerotic CVD (including myocardial infarction and stroke) and heart failure, as well as pragmatic recommendations on how to approach CVD prevention and treatment in HIV in the absence of large-scale randomized controlled trial data. This statement is intended for clinicians caring for people with HIV, individuals living with HIV, and clinical and translational researchers interested in HIV-associated CVD.

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**W**ith contemporary antiretroviral therapy (ART), people living with HIV (PLWH) are living longer<sup>1</sup> and experiencing a rising burden of cardiovascular diseases (CVDs).<sup>2,3</sup> Relative risks of various CVD manifestations are generally 1.5- to 2-fold greater for PLWH compared with uninfected individuals.<sup>4</sup> Although the relative risk has decreased with effective ART, there is a large and rising absolute burden of CVD among PLWH (conceptual model in Figure 1).<sup>2-4</sup> In a meta-analysis of 793 635 individuals with a total of 3.5 million person-years of follow-up, the global burden of HIV-associated CVD tripled over the past 2 decades and accounted for 2.6 million disability-adjusted life-years per year, with the greatest impact in Sub-Saharan Africa and the Asia-Pacific regions (Figure 2).<sup>4</sup> PLWH have an excess risk of myocardial infarction (MI),<sup>5,6</sup> ischemic stroke,<sup>7,8</sup> heart failure (HF),<sup>9,10</sup> pulmonary hypertension,<sup>11,12</sup> and venous thrombosis.<sup>13,14</sup> Underlying mechanisms likely include an interplay among traditional risk factors, HIV-specific factors (eg, chronic immune activation/inflammation),<sup>15,16</sup> ART-related dyslipidemia and other metabolic comorbidities,<sup>17,18</sup> behavioral factors (eg, smoking),<sup>5,19</sup> and disparities in access to or receipt of care.<sup>20-22</sup>

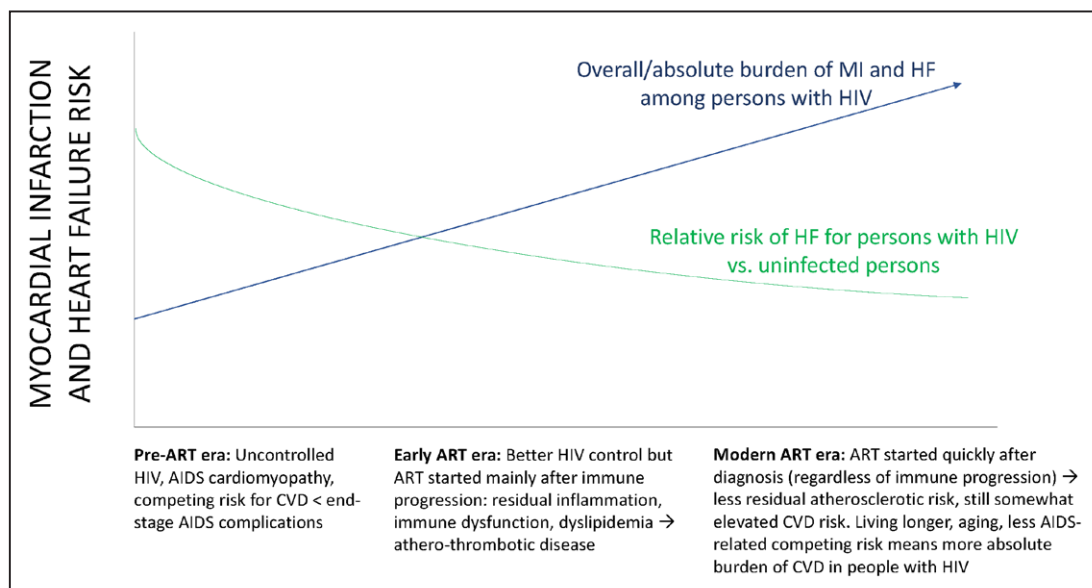
## HIV-ASSOCIATED ATHEROSCLEROTIC CVD: MI AND STROKE

Over the past decade, a variety of studies from around the world have reported an excess risk of MI among PLWH compared with uninfected people. The risk ranges from a 50% relative risk increase to a doubling of risk.<sup>5,23-25</sup> Regardless of study, HIV-related viremia and immune dysfunction are associated with higher MI

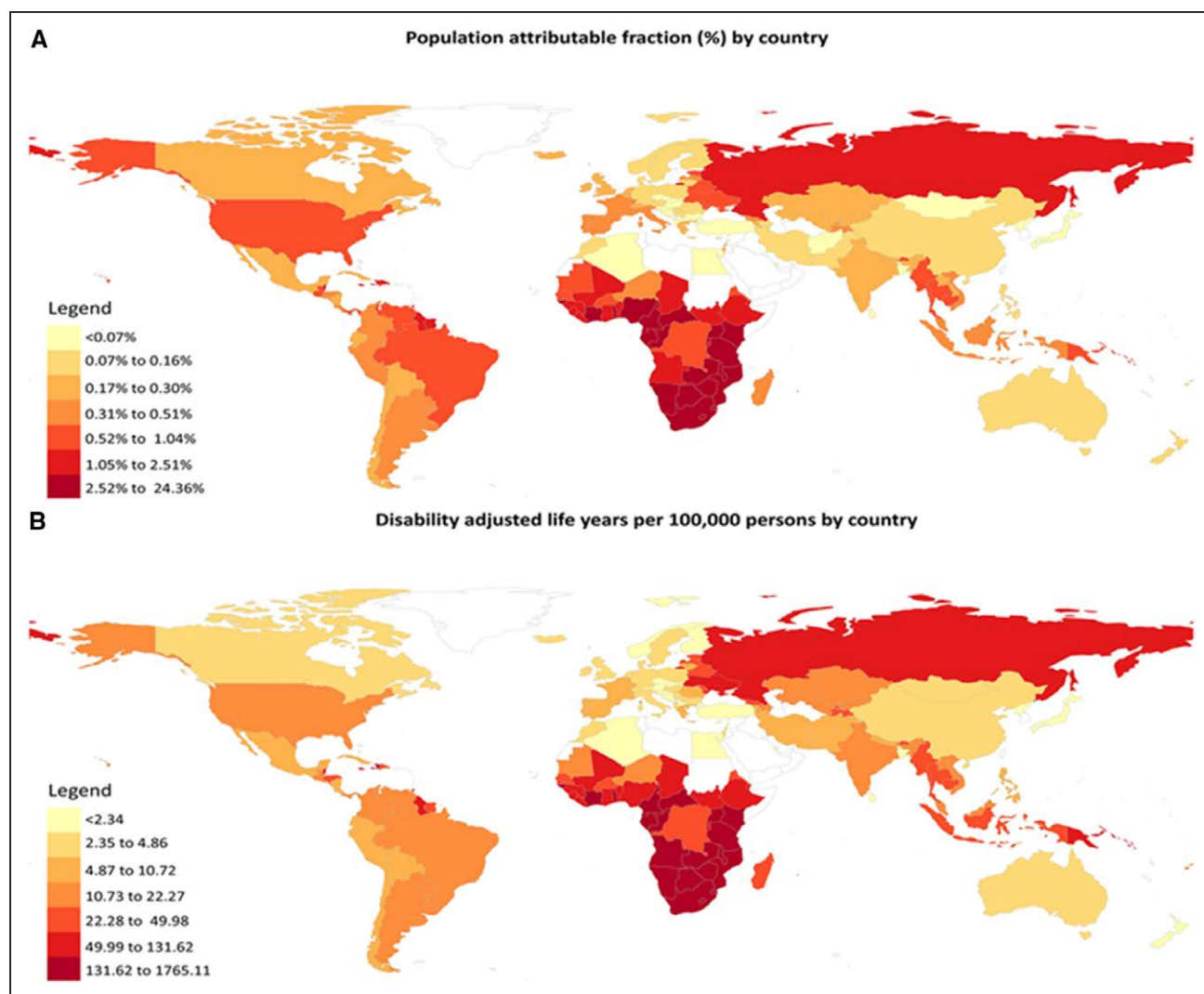
risks.<sup>5,25-27</sup> Several studies have found that lower CD4 count is associated with higher MI risks<sup>5,25-27</sup>; similarly, a lower CD4/CD8 ratio is associated with more coronary atherosclerosis.<sup>28</sup> Moreover, PLWH who achieve sustained HIV viral suppression<sup>5</sup> or have few, if any, cardiovascular risk factors<sup>23</sup> have higher MI risks than people without HIV infection. This excess MI risk may be greater among women living with HIV/AIDS.<sup>24,29</sup> PLWH also have significantly elevated risks for stroke. In HIV-endemic populations in Sub-Saharan Africa, HIV is the leading risk factor for stroke in young cohorts, with a population-attributable fraction of almost 50%.<sup>30</sup> Women with HIV may be at particularly elevated risk compared with uninfected women.<sup>31</sup> Both immunosuppression and HIV viremia appear to be risk factors: Both lower CD4 count and higher levels of HIV viremia are associated with greater stroke risk.<sup>7,30,32-34</sup> Coinfection with HIV and hepatitis C (versus HIV infection alone) may increase stroke risk further.<sup>35</sup>

## HIV-ASSOCIATED HF

Given the excess risk of coronary heart disease, it is not surprising that PLWH also have elevated HF risks, with current estimates ranging from a 1.5- to 2-fold greater risk for HF among PLWH compared with uninfected individuals after adjustment for relevant confounders.<sup>9,10,36,37</sup> However, this excess risk is not entirely attributable to MI; after adjustment for prior MI, PLWH still have a >1.5-fold higher hazard for HF than uninfected individuals.<sup>10</sup> This risk extends to both HF with preserved ejection fraction (HFpEF) and HF with reduced ejection fraction (EF). Similar to MI risks, unsuppressed HIV viral load and lower CD4 count are associated with higher



**Figure 1.** Conceptual model of the changing epidemiology of myocardial infarction (MI) and heart failure (HF) risk in HIV. ART indicates antiretroviral therapy; and CVD, cardiovascular disease.



**Figure 2. Global burden of atherosclerotic cardiovascular disease in people living with HIV.**

**A**, Population-attributable fraction by country and **(B)** disability-adjusted life-years per 100 000 people by country. Reprinted from Shah et al.<sup>4</sup> Copyright © 2018, American Heart Association, Inc.

HF risks for PLWH.<sup>10,38</sup> The epidemiology and characteristics of HF in HIV are discussed in greater detail in the HF Pathogenesis and Presentation in HIV section of this document.

## OTHER MANIFESTATIONS OF CVD

In contrast to the evidence linking HIV infection to MI, HF, and stroke, there are fewer studies of atrial fibrillation, sudden cardiac death, and peripheral artery disease. However, 1 study reported that PLWH have a 4-fold greater rate of sudden cardiac death compared with expected rates in the general population.<sup>39</sup> Low CD4 counts (<200 cells/mm<sup>3</sup>) are associated with elevated incidence<sup>40</sup> and prevalence<sup>41</sup> of atrial fibrillation among PLWH, but it is unclear whether PLWH without detectable HIV viremia or immune compromise have elevated atrial fibrillation risks. Similarly, several studies

have reported that PLWH have an excess risk of peripheral artery disease compared with uninfected individuals.<sup>42,43</sup> HIV-related pulmonary arterial hypertension has been well described since the 1990s and is considered to be in group 1 of the World Health Organization classification of pulmonary hypertension.<sup>44–49</sup> The prevalence of HIV-associated pulmonary arterial hypertension is considerably higher than pulmonary arterial hypertension in the general population,<sup>50</sup> and ART has not changed this epidemiology.<sup>51</sup> Elevated pulmonary artery systolic pressure has also been reported in HIV.<sup>11,52</sup> As a result of limited data, treatment goals are similar to those of other pulmonary arterial hypertension subgroups.<sup>53</sup> Finally, given the confluence of sleep disorders, particularly obstructive sleep apnea, with CVD,<sup>54</sup> it is also worth noting that HIV is associated with sleep impairment in general<sup>55–57</sup> and that obstructive sleep apnea may be underdiagnosed among PLWH.<sup>58,59</sup>

## **PATHOPHYSIOLOGY AND PRESENTATION OF ATHEROSCLEROTIC CVD AND HF IN HIV**

After 2 decades of progress in studying the elevated risks for CVD among PLWH, the underlying mechanisms and biology of this process still remain incompletely defined. Furthermore, delineating risk that is attributable to HIV disease itself versus ART versus traditional risk factors is challenging because many of these factors are interrelated. The pathophysiology of HIV-associated CVD is multifactorial and includes the interplay among traditional risk factors, exposure to ART and virological suppression, and chronic inflammation/immune activation that persists in the setting of treated HIV in the face of an aging HIV population. An older person with a history of HIV for decades likely has a distinct risk profile for CVD compared with a newly diagnosed individual who has started on newer ART immediately. PLWH have high rates of traditional risk factors, including dyslipidemia, metabolic disease, smoking, hypertension, and substance use, as described in the sections below. Aside from traditional risk factors, HIV-specific issues are implicated in CVD and include ART, chronic inflammation, and immune activation in the setting of treated and suppressed HIV disease. Imaging techniques have provided valuable insight into CVD onset and progression in HIV.

### **Atherosclerosis Pathophysiology in HIV: Chronic Inflammation and Immune Activation**

Numerous studies have demonstrated that chronic inflammation and immune activation are abnormal in the setting of treated HIV infection<sup>60–64</sup> and, in turn, are strongly predictive of mortality, non-AIDS events,<sup>65</sup> and CVD.<sup>66–69</sup> Higher levels of several inflammatory markers, including IL (interleukin)-6 and soluble tumor necrosis factor receptors  $\alpha$ -1 and  $\alpha$ -2, have been associated with coronary atherosclerosis in HIV.<sup>70,71</sup> Arterial inflammation as assessed by fluorodeoxyglucose positron emission tomography/computed tomography (CT) is higher in the setting of HIV<sup>72–74</sup> and relates to circulating inflammatory markers. Likewise, elevated levels of monocyte activation markers, including soluble CD163 and soluble CD14, are associated with coronary atherosclerosis and carotid plaque progression.<sup>75–77</sup> However, it is worth noting that a recent systematic review did not identify a clear association between inflammatory markers and surrogate CVD outcomes in HIV.<sup>78</sup> Whether this is the result of insufficient follow-up data in the studies reviewed (the vast majority of which were cross-sectional) or a lack of a strong association is not clear.

Although treatment with ART reduces levels of circulating inflammation markers, many markers of inflammation remain elevated with viral suppression in PLWH relative to uninfected individuals.<sup>79</sup> Furthermore, several studies have included PLWH who are able to maintain an undetectable HIV RNA level despite not being on ART (elite controllers) and demonstrated heightened levels of subclinical vascular disease<sup>79,80</sup> and clinical events in this population relative to uninfected control subjects.<sup>81</sup> Inflammation is also elevated with hepatitis C coinfection and, if left untreated, may contribute to the development of atherosclerosis.<sup>82</sup> Lymph node activity is even more pronounced in individuals with treated HIV compared with uninfected people and is closely linked to HIV disease characteristics, suggesting that distinct patterns of immune activation exist<sup>73</sup> and that interventions to reduce HIV reservoirs may not predictably affect arterial inflammation. Despite the fact that the SMART study (Strategies for Management of Antiretroviral Therapy) demonstrated the key role of chronic inflammation in HIV-associated CVD >10 years ago,<sup>83</sup> effective interventions designed to lower inflammation in treated HIV have been elusive.

Large studies with hard clinical end points of common cardioprotective therapies such as statins and aspirin have not been completed in HIV. Small therapeutic studies of statins and aspirin targeting inflammation/coagulation (eg, hsCRP [high-sensitivity C-reactive protein], IL-6, and D-dimer) among PLWH or HIV-specific therapies have not reported consistent results.<sup>84–86</sup> Alterations in gut permeability and subsequent microbial translocation result in downstream chronic inflammation and immune activation. Therapeutic interventions that have targeted the gut, including rifaximin,<sup>87</sup> sevelamer,<sup>88</sup> and mesalamine,<sup>89</sup> have not consistently reduced circulating inflammatory markers or markers of immune activation. In the general population, a monoclonal antibody to IL-1 $\beta$  had no impact on low-density lipoprotein (LDL) cholesterol (LDL-C) but significantly reduced inflammatory markers cardiovascular events<sup>90</sup> and, in an analysis of nonprimary end points, also reduced lung cancer mortality.<sup>91</sup> Individuals whose hsCRP was reduced by <2 mg/L had a 25% reduction in major CVD events, a 31% reduction in CVD mortality, and a 31% reduction in all-cause mortality.<sup>92</sup> In a small study of treated PLWH, IL-1 $\beta$  inhibition significantly reduced IL-6, hsCRP, and arterial and bone marrow inflammation.<sup>93</sup> In contrast, among ART-treated PLWH, low-dose methotrexate did not affect inflammatory markers but reduced levels of CD8<sup>+</sup> T cells and T-cell activation.<sup>94</sup>

### **Atherosclerosis Pathophysiology in HIV: Metabolic Contributors**

HIV infection is associated with metabolic complications, including dyslipidemia, insulin resistance, and



body composition changes, which can contribute to CVD. Initially, dyslipidemia in HIV was characterized by increased triglyceride levels, thought to be related to immunodeficiency in the pre-ART era.<sup>95</sup> Later, specific ART medications, including several protease inhibitors (PIs) and efavirenz, a non-nucleoside reverse transcriptase inhibitor (NRTI), were associated with dyslipidemia (particularly elevated triglyceride levels).<sup>96–99</sup> However, current first-line ART regimens have minimal lipid effects.<sup>100</sup> Over time, additional research has suggested that inflammation and other factors may contribute to an atherogenic dyslipidemia, with low high-density lipoprotein cholesterol and increased oxidized LDL-C in association with increased innate immune activation.<sup>101</sup> In contrast, overall levels of LDL-C are often not elevated in PLWH; levels can be low with initial infection and related inflammation and then return to normal levels with improved health on ART.<sup>102</sup> Dyslipidemia in HIV may contribute to elevated atherosclerotic CVD (ASCVD) risk and has been shown to contribute independently to ASCVD among PLWH.<sup>103</sup> The specific contributions of dyslipidemia to ASCVD events in HIV are an important area for future investigation.

Insulin resistance and diabetes mellitus are also seen with increasing frequency in HIV.<sup>104</sup> Prevalence estimates range up to 26% and 47% in Sub-Saharan Africa for diabetes mellitus and prediabetes mellitus, respectively.<sup>99</sup> Mechanisms may relate to effects of specific ART on glucose translocation,<sup>105</sup> inflammation, and lipodystrophy. Diabetes mellitus has been linked to ASCVD in HIV such that PLWH with diabetes mellitus have a 2.4-fold increased risk of coronary heart disease events.<sup>106</sup>

Body composition changes are common in HIV. Patients presenting in the initial era of ART often demonstrated relative loss of subcutaneous fat and gain in abdominal visceral fat.<sup>107</sup> The changes in fat distribution were often heterogeneous and frequently were associated with insulin resistance and deposition of ectopic adipose in the liver and muscle. Multiple factors contributed to these changes, including effects of ART. Use of specific thymidine NRTIs is associated with subcutaneous fat loss and deposition of ectopic adipose tissue in the liver and muscle, as well as arterial inflammation.<sup>108</sup> Early PI therapy was associated with increased abdominal fat gain.

In the modern ART era, this phenotype has changed, and recent work has focused on dysfunctional subcutaneous fat, related in part to the effect of HIV on peroxisome proliferator-activated receptor- $\gamma$  and Dicer, as well as other mechanisms.<sup>109,110</sup> With increasingly effective ART, gains in both subcutaneous and visceral fat are often seen with the initiation of ART, regardless of regimen,<sup>111</sup> and rates of generalized obesity are increasing among PLWH.<sup>112</sup> Changes in body composition, including excess visceral adipose tissue, have been linked to overall mortality.<sup>113</sup> These changes have been associ-

ated with increased coronary plaque, including both noncalcified and calcified plaque.<sup>114,115</sup>

## Atherosclerosis Pathophysiology in HIV: ARTs

ART is a critical component of ASCVD prevention because treatment interruption and uncontrolled HIV viremia are associated with elevated risk of MI.<sup>5,83</sup> There were too few ASCVD events in the START trial (Strategic Timing of AntiRetroviral Treatment) to definitively answer whether immediate ART for all PLWH reduces ASCVD risk,<sup>116</sup> and changes in ASCVD risk factors levels were not clearly positive or negative.<sup>117</sup> Thus, the impact of early ART on ASCVD is uncertain.

Certain antiretroviral drugs and drug classes have been associated with elevated risk of ASCVD events, most notably among people with higher levels of traditional risk factors. PIs were first associated with MI in the landmark D:A:D study (Data Collection on Adverse Events of Anti-HIV Drugs),<sup>118</sup> in which each year of cumulative PI use was associated with a 10% greater risk of MI, even after adjustment for cholesterol changes caused by PIs. Analyses from the D:A:D cohort of atazanavir and darunavir, 2 current-generation PIs in widespread clinical use, suggest that ritonavir-boosted or unboosted atazanavir is not associated with increased risk, whereas cumulative exposure to ritonavir-boosted darunavir is associated with progressively increasing risk for CVD.<sup>119,120</sup> Rates of carotid intima-media thickness (IMT) progression were also noted to be slower with boosted atazanavir compared with darunavir and ritonavir in a randomized trial, with some of the proposed benefit thought to be the result of the bilirubin-increasing effect of atazanavir.<sup>121</sup> In contrast, the association of higher bilirubin with lower mortality in a Veterans Affairs study was not mediated by atazanavir use,<sup>122</sup> and another mechanistic clinical trial showed mixed effects of atazanavir on surrogate CVD risk markers (reduced oxidative stress but increased von Willebrand factor and no effect on endothelial function).<sup>123</sup> It appears that the association of PIs with ASCVD events is a class effect, with atazanavir being the exception.

NRTIs have also evolved over time, with newer generations of these drugs having fewer metabolic side effects and presumed less mitochondrial toxicity<sup>124</sup>; however, abacavir is a widely used NRTI that has been associated with increased risk of MI in observational studies. The association of current or recent abacavir use with MI was first described in the D:A:D cohort in 2008,<sup>125</sup> with subsequent D:A:D analyses demonstrating that the hazard ratio did not change substantially although abacavir use among individuals at high CVD risk decreased over time.<sup>126</sup> Similar associations of abacavir with CVD risk have been shown in the Kaiser Permanente California health system<sup>127</sup> and NA-

ACCORD (North American AIDS Cohort Collaboration on Research and Design).<sup>128</sup> Possible mechanisms of risk include endothelial dysfunction,<sup>129</sup> vascular inflammation, and platelet hyperreactivity.<sup>130</sup> Despite guideline recommendations to avoid abacavir or to use it with caution in patients at high CVD risk,<sup>131</sup> the issue remains controversial because of meta-analyses (US Food and Drug Administration and industry funded) that demonstrated no significant effect of abacavir on MI among generally low-risk individuals in shorter-duration clinical trials.<sup>132,133</sup>

The population-level impact of ART toxicities on ASCVD risk among PLWH may be relatively low<sup>134</sup> and may be further attenuated by the use of antiplatelet agents and statins among high-risk individuals.<sup>135</sup> The decision of what ART to start and whether to switch because of comorbidities or side effects is complex and depends on many factors, including cardiovascular risk assessment, HLA-B\*57:01 testing (for hypersensitivity to abacavir), HIV resistance testing, medication compliance, pregnancy/child-bearing age, and other comorbidities such as bone and renal disease.

### Atherosclerosis Pathophysiology in HIV: Hypertension, Smoking, and Other Factors

Other traditional risk factors, including hypertension and cigarette smoking, play an important role in the pathogenesis of ASCVD in PLWH. A meta-analysis of 63 554 participants from studies published from 2011 to 2016 estimated hypertension prevalence to be 35% for PLWH on ART and 13% for ART-naïve PLWH.<sup>136</sup> Although untreated HIV is typically associated with lower blood pressure, resulting perhaps from uncontrolled inflammation and periseptic states of vascular permeability,<sup>136–138</sup> studies are inconsistent on whether individuals with treated HIV have a higher prevalence of hypertension compared with uninfected individuals.<sup>139–141</sup> Mechanisms of hypertension in PLWH may include chronic inflammation and activation of the renin-angiotensin-aldosterone system.<sup>141,142</sup> Overt hypertension, prehypertension, and borderline hypertension (systolic blood pressure, 120–140 mm Hg) were associated with greater risk for acute MI in VACS (Veterans Aging Cohort Study), but there was no evidence that this association was stronger among PLWH compared with uninfected people.<sup>140</sup>

On a population-level scale, smoking may be the most important modifiable CVD risk factor among PLWH. Smoking is highly prevalent among PLWH (42% were current smokers and 20% were former smokers in a nationally representative US sample<sup>143</sup>) and is strongly associated with coronary artery plaque and MI.<sup>144,145</sup> In 1 study, the population-attributable fraction for MI associated with ever smoking was 72%

for PLWH compared with 24% for general population control subjects.<sup>144</sup> These data underscore the critical public health importance of including smoking cessation as a cornerstone of any efforts related to CVD prevention in HIV.

Heavy alcohol use, although not generally considered a traditional atherosclerotic risk factor, may contribute disproportionately to CVD among PLWH.<sup>19</sup> In addition to (and often in conjunction with) substance use disorders, mood and anxiety disorders are quite common among PLWH<sup>146–148</sup> and may contribute to elevated CVD risk (including MI<sup>149</sup> and HF<sup>36</sup>). PLWH also have low levels of physical and cardiorespiratory fitness, which are associated with vascular dysfunction, inflammation, and risk for CVD, as well as all-cause mortality, in patients with HIV (and in the general population).<sup>150–153</sup>

### Atherosclerosis Pathophysiology in HIV: Insights From Imaging

PLWH have more subclinical atherosclerosis relative to those who are uninfected as measured with a variety of imaging modalities. Carotid ultrasound studies have demonstrated that PLWH have more carotid plaque and higher IMT compared with uninfected individuals in cross-sectional and longitudinal studies.<sup>66,154,155</sup> The pattern of atherosclerosis progression in the carotid artery has been demonstrated to be particularly marked in the bifurcation region.<sup>66</sup> Whereas some studies of carotid IMT have not found an association with HIV,<sup>156</sup> the majority of studies demonstrate significantly higher IMT for PLWH than uninfected control subjects.<sup>157</sup>

Imaging with noncontrast CT allows measurement of coronary artery calcium (CAC), which has been shown to progress more rapidly in PLWH compared with HIV-negative individuals.<sup>158</sup> Coronary CT angiography provides visualization of both calcified and noncalcified components of atherosclerotic plaque. HIV is associated with a greater prevalence and extent of noncalcified plaque<sup>159–161</sup> and with coronary artery remodeling.<sup>162,163</sup> Both of these atherosclerotic features predispose to plaque rupture and may represent a phenotype of elevated risk associated with HIV infection. Treatment with statin therapy reduced noncalcified plaque volume and high-risk plaque features relative to placebo in a small pilot study.<sup>84</sup> The effects of statin therapy on coronary atherosclerosis in PLWH are being comprehensively evaluated in a substudy of the ongoing REPRIEVE trial (Randomized Trial to Prevent Vascular Events in HIV; URL: ClinicalTrials.gov. Unique identifier: NCT02344290).

Arterial inflammation can be measured with <sup>18</sup>F-fluorodeoxyglucose positron emission tomography imaging of the aorta relative to venous background. PLWH have greater aortic arterial inflammation than uninfected individuals with similar cardiovascular risk factors.<sup>72</sup> Arte-

rial inflammation is associated with soluble CD163, a marker of monocyte activation, with visceral fat, and with high-risk coronary atherosclerotic plaque.<sup>164</sup> Arterial inflammation is a process that appears to be independent of HIV disease activity as measured by inflammation seen in the lymph nodes.<sup>73</sup>

## Stroke Pathophysiology and Presentation in HIV

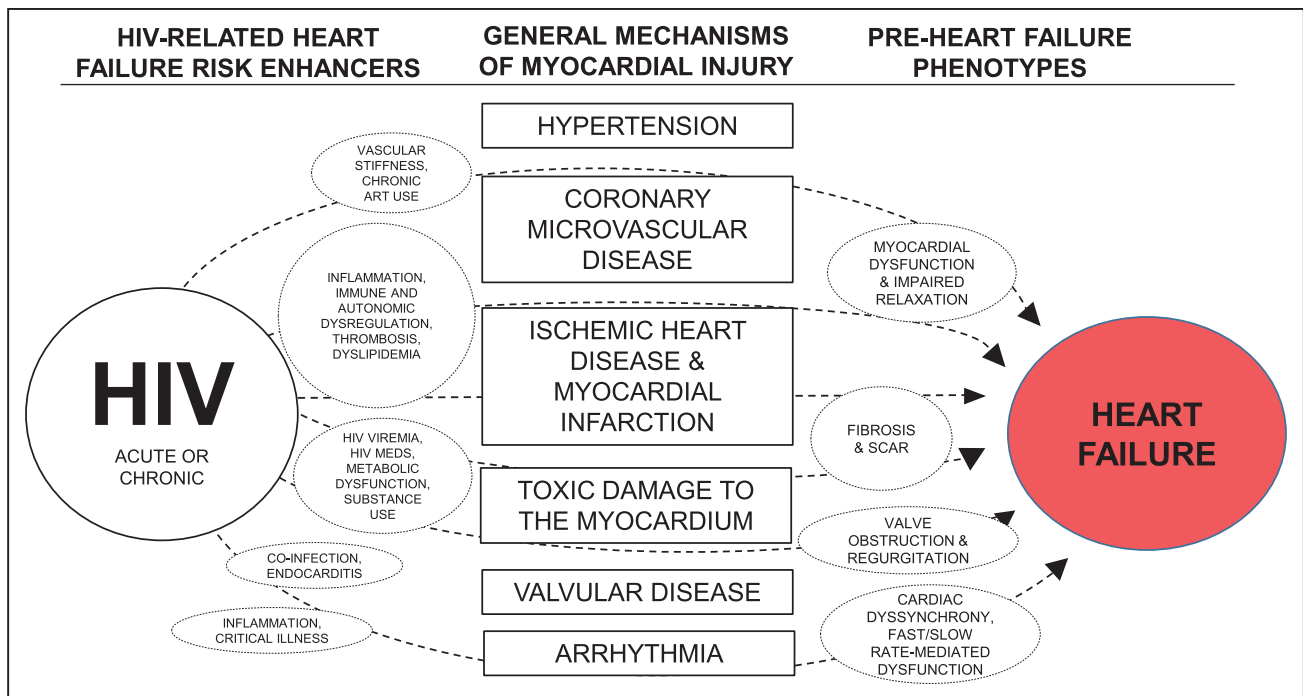
The phenotypes of extracranial (eg, carotid and vertebral) and intracranial (eg, middle cerebral and perforator) arteries are distinct and differ in their degree of media and adventitia thickness and presence or absence of dura mater. The additional barrier from the blood-brain interface, which is relevant to intracranial arteries, prevents systemic infection and freely circulating antibodies in the brain. However, HIV infection manipulates this barrier and enters an immune-naïve brain early during primary infection.<sup>165</sup> These characteristics influence how extracranial and intracranial arteries respond to vascular risk factors and inflammation. Common pathways of atherosclerosis and CVD events relate more closely to extracranial (eg, proximal carotid arteries and aorta) than intracranial arterial causes of ischemic stroke.<sup>166</sup>

The body of evidence on the pathogenesis of HIV infection and CVD pertains largely to extracranial disease.<sup>143,167,168</sup> However, more than one-third of ischemic stroke in HIV is the result of intracranial disease.<sup>169,170</sup> Advanced HIV infection is associated with secondary causes of ischemic stroke such as opportunistic infection (eg, varicella zoster) and coagulopathy.<sup>169,170</sup> Once an individual is on ART, HIV-associated vasculopathy, which encompasses several subtypes (eg, atherosclerosis, HIV-associated vasculitis, nonatherosclerotic vasculopathy, and small vessel disease), becomes more prevalent.<sup>169–171</sup> Knowledge about intracranial HIV-associated vasculopathy is sparse. However, emerging data suggest that vessel wall remodeling occurs through neuroinflammation and that this may be independent of atherosclerosis.<sup>172,173</sup> Furthermore, as the immune system recovers, thinning and erosion of intracranial arteries ensue.<sup>174</sup> The latter is in keeping with the first 6 months of ART in immunosuppressed patient being associated with a high risk of stroke.<sup>30</sup> Although neuroinflammation appears to be an important factor, it remains unclear whether this occurs in conjunction with or independently of atherosclerosis and warrants further investigation. Nevertheless, as pharmacological strategies evolve for CVD prevention in HIV (ranging from statins with demonstrated stroke prevention benefit<sup>175</sup> to newer anti-inflammatory drugs), consideration for those that cross the blood-brain barrier will be critical in addressing the burden of intracranial arterial disease in the future.

## HF Pathogenesis and Presentation in HIV

Myocardial dysfunction and HF have been known complications of HIV since the first reports of AIDS cardiomyopathy in the 1980s.<sup>176–178</sup> Cases of AIDS cardiomyopathy in the pre-ART era were common and marked by progressive viremia and immune dysfunction, opportunistic infection, and global ventricular dysfunction, with myocarditis commonly seen on pathology.<sup>178–180</sup> As HIV has evolved from a fatal disease marked by severe immune compromise and viremia to a chronic, manageable disease marked by inflammation and variable immune dysfunction, the pathophysiology and characteristics of myocardial dysfunction and HF in HIV have likewise evolved. Diastolic dysfunction and HF associated with coronary artery disease have become more common among PLWH.<sup>181</sup> A seminal contemporary study from VACS demonstrated that PLWH followed up since 2003 had significantly higher risks than uninfected individuals for HF overall.<sup>10</sup> After adjustment for possible confounders, PLWH had significantly higher risks for each HF phenotype analyzed: HF with reduced EF, HFpEF, and borderline HFpEF. Among PLWH, the most common incident HF cases were HF with reduced EF (40%), followed by HFpEF (30%), then borderline HFpEF (15%), and then HF with unknown EF (15%). As expected, worse HIV viremia and related immune dysfunction were associated with the highest risks for HF in this study and another that used physician-adjudicated HF end points.<sup>38</sup> Nevertheless, PLWH with viral control (HIV viral RNA <500 copies/mL) and minimal immune compromise (CD4 ≥500 cells/mm<sup>3</sup>) were still significantly more likely than uninfected individuals to have HF.<sup>10</sup> The greater HF risks among PLWH remained after restriction to nonhypertensive people without documented alcohol, tobacco, or cocaine abuse and after adjustment for MI. This suggests that the higher risk for HF in HIV is not solely attributable to substance abuse or MI, although residual confounding from drug use is possible given underreporting by patients. Studies in different cohorts and settings have likewise demonstrated elevated rates of HF in PLWH.<sup>29,182</sup> In regions of the world where HIV disease control rates are low, the pattern of HIV-associated HF still resembles the pre-ART epidemiology.<sup>183</sup> The prognosis of HF in HIV also may be worse, with a recent small study finding significantly higher rates of HF hospitalization and mortality among women with HIV compared with uninfected women.<sup>184</sup>

In light of the still-evolving epidemiology, data investigating mechanisms and phenotypes of HIV-associated HF in the modern ART era are limited. However, several cross-sectional studies have indicated that subclinical myocardial disease is particularly prevalent among



**Figure 3. Proposed mechanisms of myocardial dysfunction and heart failure in HIV.**  
ART indicates antiretroviral therapy.

PLWH. On cardiac magnetic resonance imaging and CT, PLWH have more myocardial fibrosis and steatosis than uninfected control subjects; these subclinical abnormalities are closely associated with myocardial injury and mechanical dysfunction among PLWH.<sup>185–187</sup> PLWH with a history of advanced immune suppression are at higher risk of left ventricular hypertrophy and diastolic dysfunction than PLWH with preserved immune function.<sup>188</sup> Likewise, PLWH have a substantially higher prevalence of diastolic dysfunction and higher left ventricular mass index than uninfected people on echocardiography, independently of demographics and cardiovascular risk factors.<sup>189</sup>

The pathophysiology underlying subclinical myocardial dysfunction and overt HF in HIV is less clearly defined. A substantial portion of PLWH in low- and middle-income countries (and some in high-income countries) are not on ART, have uncontrolled HIV, and remain at risk for severe myocardial inflammation, fibrosis, and systolic dysfunction characteristic of AIDS cardiomyopathy.<sup>178,179,190</sup> For PLWH on ART with viral control, several mechanisms may predispose them to myocardial dysfunction and HF (Figure 3). Given the predilection of PLWH for atherosclerosis, thrombosis, and MI, myocardial fibrosis and scar resulting from MI may explain some of the higher HF risks in HIV. This may be particularly true if the myocardium of PLWH is highly vulnerable to ischemia<sup>191</sup> and MI, resulting in larger areas of scar and dysfunction after MI for PLWH, as a study of PLWH and uninfected people who underwent coronary angiography and

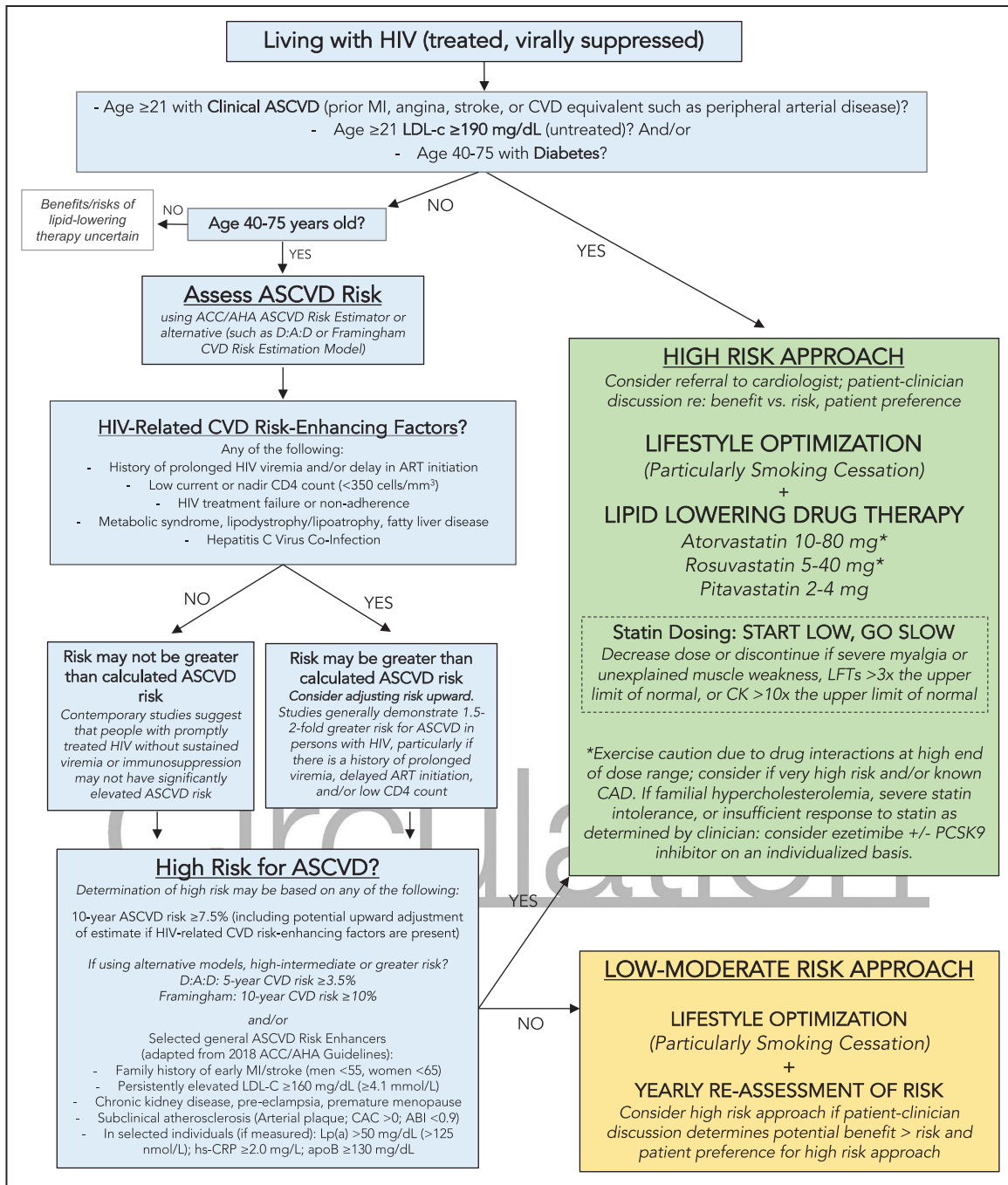
subsequent cardiac magnetic resonance imaging suggested.<sup>192</sup> Furthermore, microvascular dysfunction is a contributor to diastolic dysfunction and HFpEF<sup>193</sup> and may play a role given the association of HIV-related inflammation and immune dysfunction with microvascular disease.<sup>194</sup>

Nonvascular mechanisms are also implicated in HIV-associated myocardial dysfunction and HF. Substance use is a common cause of cardiomyopathy and HF in general and is common in HIV (particularly alcohol, methamphetamine, and cocaine). However, this is unlikely to be the primary driver of HF in HIV, particularly in light of the aforementioned VACS analysis demonstrating greater HF risks in HIV after the analyses were restricted to people without substance use.<sup>10</sup> Cardiac arrhythmias contribute to myocardial dysfunction and may be particularly common in HIV. PLWH appear to have a several-fold greater risk of sudden death than uninfected people, although the extent to which malignant arrhythmias drive these sudden deaths is not known.<sup>39</sup> Although worse HIV disease severity is associated with atrial arrhythmias among PLWH,<sup>40,41</sup> atrial arrhythmias were no more common among PLWH than in uninfected individuals after adjustment for demographics and CVD risk factors in a recent analysis.<sup>41</sup>

Whether specific antiretrovirals predispose to or protect from HF remains controversial. The mitochondrial toxicity of some older-generation NRTIs (zalcitabine, didanosine, stavudine, and zidovudine) led to concerns related to cardiomyopathy development,<sup>124,195</sup> whereas







**Figure 4. Pragmatic approach to atherosclerotic cardiovascular disease (ASCVD) risk assessment and prevention in treated HIV infection.**

This figure applies to people with treated HIV. For people with uncontrolled HIV, the first priority is appropriate HIV therapy to achieve viral suppression per the HIV provider. Thresholds based on findings of elevated CVD risk at current or nadir CD4 count <200, <350, and <500 cells/mm<sup>3</sup> in Silverberg et al,<sup>25</sup> Lichtenstein et al,<sup>26</sup> and Triant et al.<sup>27</sup> Hazard ratios and incidence rate ratios of 1.4 to 2.1 for myocardial infarction (MI) for people living with HIV (PLWH) vs uninfected people demonstrated in Freiberg et al,<sup>9</sup> Triant et al,<sup>24</sup> and Silverberg et al.<sup>25</sup> Hazard ratio of stroke for PLWH vs uninfected people was 1.40 in Chow et al.<sup>8</sup> 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.

concerns are more mixed for contemporary NRTIs: Abacavir has inconsistently been associated with elevated MI (but not necessarily HF) risk,<sup>196,197</sup> whereas tenofovir disoproxil fumarate was associated with a lower HF risk among veterans with HIV.<sup>198</sup> Data are lacking on the

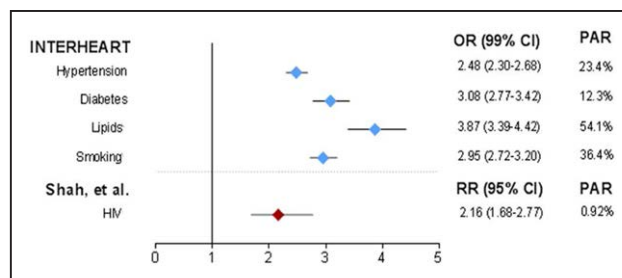
associations of other specific antiretrovirals with HF. In any case, the cardiovascular and general health benefits of taking ART clearly outweigh the risks according to large, seminal studies of ART strategy favoring early and continuous ART.<sup>83,116</sup>

## CVD RISK ASSESSMENT IN HIV\*

CVD risk assessment in HIV is challenging given the relatively recent evolution of HIV as a chronic disease and the resulting dearth of long-term data on CVD incidence in the modern ART era.<sup>199</sup> In general, the purpose of predicting disease risk is to inform the risk-benefit calculus of different preventive interventions. Theoretically, the higher the person's risk is for a particular disease, whether over the next 5 or 10 years or the course of a lifetime, the greater the absolute risk reduction (benefit) from therapy is, and the higher tolerance is for some amount of risk from the intervention. The 2013 and 2018 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines on CVD risk assessment<sup>200</sup> and lipid-lowering therapy<sup>201,202</sup> applied this principle, defining groups of adults in whom the benefit of statin therapy generally outweighs the risks resulting from elevated absolute risks for ASCVD:  $\geq 21$  years of age with clinical ASCVD (known coronary artery disease or stroke) and/or significantly elevated LDL-C ( $\geq 190$  mg/dl) and 40 to 75 years old with diabetes mellitus and/or  $\geq 7.5\%$  10-year ASCVD risk according to the ACC/AHA ASCVD Risk Calculator.<sup>203</sup> The European Society of Cardiology applied a similar central principle in its 2016 guideline on CVD prevention, although with a different risk prediction model.<sup>204</sup> Although differences certainly exist among CVD risk prediction equations, they are broadly similar in that they predict a person's risk of CVD on the basis of risk factor levels known to be associated with CVD.<sup>205–208</sup>

Traditional ASCVD risk factors such as age, diabetes mellitus, current smoking, hypertension, and dyslipidemia are associated with elevated ASCVD risk among PLWH just as they are in the general population.<sup>5,24,34</sup> Similar to traditional ASCVD risk factors, HIV infection is associated with elevated ASCVD risk (Figure 5),<sup>209</sup> particularly for PLWH with low current or nadir CD4 count (especially  $< 200$  cells/mm<sup>3</sup>)<sup>5,25,26,210</sup> or a history of sustained untreated HIV.<sup>5,210</sup> No general population risk assessment models have focused on PLWH. The D:A:D study used a large, primarily white European<sup>211</sup> cohort to derive a CVD risk prediction model among PLWH.<sup>212,213</sup> The D:A:D model incorporates traditional ASCVD risk factors in addition to certain HIV-specific factors associated with CVD (CD4 count, cumulative exposure to PIs and NRTIs, and current abacavir use). Several studies have evaluated CVD risk estimation models derived from the general population or the

\*Note: The sections on CVD risk assessment and prevention in HIV are accompanied by Figure 4, which provides a pragmatic approach to ASCVD risk assessment and prevention in treated HIV infection based on available evidence. The lack of data related to HF risk assessment in HIV and adjudicated HF events in HIV precludes informed discussions of HF risk assessment here.



**Figure 5. Cardiovascular risk of HIV compared with traditional risk factors.**

OR indicates odds ratio; PAR, population-attributable risk; and RR, relative risk. Reprinted from Hsue and Waters.<sup>209</sup> Copyright © 2018, American Heart Association, Inc.

D:A:D model among PLWH using HIV cohorts in the United States (multicenter<sup>214–216</sup> and single center<sup>217</sup>), Europe,<sup>218,219</sup> and Sub-Saharan Africa.<sup>220</sup> Although the individual conclusions on model performance in these studies varied slightly depending in large part on the validation cohort used, the CVD risk prediction models performed similarly overall, with apparent underestimation of CVD risk among PLWH.<sup>214,216,217</sup> Therefore, a clear best risk estimation model for HIV has not been identified.

The presence and extent of subclinical atherosclerosis can be used to refine CVD risk, especially in those considered to be at intermediate risk.<sup>19</sup> CAC, measured from noncontrast CT scans, is a potent predictor of coronary heart disease events and has been studied extensively in the general population.<sup>20</sup> However, assessment of CAC alone may not reflect underlying coronary artery disease among PLWH because they have more noncalcified plaque than uninfected individuals, and this can be detected only with coronary CT angiography.<sup>161</sup> CT angiography is not recommended for screening in asymptomatic individuals. The ability of CAC to discriminate risk for coronary heart disease events in PLWH has not been determined; however, those with CAC (particularly if extensive) can be presumed to be at elevated risk. Carotid IMT is also a predictor of future MI and stroke in the general population<sup>221</sup> and has been associated with mortality in HIV.<sup>222,223</sup>

In the absence of robust data on the adjunctive value of subclinical imaging and biomarker levels for ASCVD risk stratification among PLWH, it is reasonable to consider selected ASCVD risk enhancers identified in the 2018 ACC/AHA cholesterol clinical practice guidelines as likely ASCVD risk enhancers in HIV (Figure 4).<sup>202</sup> These include early family history of MI or stroke (men, age  $< 55$  years; women, age  $< 65$  years), persistently elevated LDL-C  $\geq 160$  mg/dL ( $\geq 4.1$  mmol/L), chronic kidney disease, preeclampsia or premature menopause, subclinical atherosclerosis on imaging (including CAC), and high levels of selected biomarkers associated with elevated ASCVD risk independently of traditional risk factors (Lp(a) [lipoprotein(a)], hsCRP, and apoB [apolipoprotein B]).

poprotein B]).<sup>202</sup> Unlike the 2018 ACC/AHA guidelines, we did not include elevated triglycerides as a significant ASCVD risk enhancer in HIV because studies in large HIV cohorts demonstrated that triglyceride levels, which are often labile and sensitive to ART changes in HIV, either were not predictive of CVD end points independently of other traditional CVD risk factors or were associated with marginally elevated ASCVD risk.<sup>224–226</sup> At present, there are insufficient data to recommend routine measurement of subclinical atherosclerosis on imaging or inflammatory biomarkers because the additive value of these measurements for CVD risk stratification in HIV is unclear. Nevertheless, if already measured, atherosclerosis on imaging and elevated levels of Lp(a), hsCRP, or apoB suggest higher ASCVD risk and may warrant more aggressive strategies for ASCVD prevention (Figure 4).

## PREVENTION AND TREATMENT OF HIV-ASSOCIATED ASCVD AND HF

### Lifestyle Optimization

As in the general population,<sup>200–202</sup> adherence to a healthy lifestyle is an essential first step for primary and secondary prevention of CVD among PLWH. Smoking cessation is of paramount importance given the high prevalence of smoking among PLWH<sup>143</sup> and the clear role of smoking in atherosclerosis and MI.<sup>144,145</sup> (An extensive library of resources for patients and providers to approach smoking cessation can be found online.<sup>227,228</sup>) Limiting alcohol consumption is likewise important given the potential disproportionate contribution of alcohol to CVD in HIV.<sup>19</sup> Although it is clear that heavy alcohol consumption has adverse effects on CVD and other disease end points,<sup>229</sup> there is debate about whether a “healthy” level of alcohol consumption exists; some large analyses suggested a cardioprotective effect of light to moderate alcohol consumption (<100 g/wk [ $<7$  drinks/wk]),<sup>230,231</sup> whereas others found no benefit and perhaps elevated HF and stroke risks for light to moderate alcohol consumption.<sup>232,233</sup> Regular physical activity is also an essential aspect of lifestyle optimization in HIV given the associations of physical inactivity with poor health and adherence in HIV and, conversely, the improvement in inflammation and cardiometabolic health with increasing physical activity in HIV.<sup>226,234,235</sup> (HIV-specific resources for exercise and physical activity can be found online.<sup>236,237</sup>) A randomized trial of sedentary PLWH at high risk for CVD demonstrated feasibility of a lifestyle-focused behavioral intervention to reduce sweetened beverage consumption and weight, although there was no significant effect of the intervention on physical activity levels.<sup>238</sup> Absent HIV-specific data on optimal diets to prevent CVD, adherence to ACC/AHA dietary guidelines is recommended. This dietary approach emphasizes vegetables, fruits, legumes,

healthy protein sources (fish/seafood, nuts, low-fat poultry, and low-fat dairy), whole grains, and nontropical vegetable oils while limiting intake of sweets, sugar-sweetened and artificially sweetened beverages (associated with coronary plaque burden in HIV<sup>239</sup>), and red meats.<sup>202</sup>

### Pharmaco-Prevention of Coronary Artery Disease in HIV

Primary prevention to reduce the risk of ASCVD is an important goal for PLWH. Statins significantly reduce CVD events in patients without HIV with increased inflammation and low levels of LDL-C.<sup>240</sup> As discussed, PLWH often present with normal LDL but increased systemic and arterial inflammation<sup>72</sup> and persistent immune activation despite successful ART.<sup>241</sup> Traditional CVD risk factors, particularly smoking, are also more common and should be targeted in HIV.<sup>242</sup>

Statin use in HIV is complicated by potential drug interactions, although newer statin and ART therapies appear to have more benign drug-drug interaction profiles.<sup>243</sup> Potent cytochrome P450 (CYP) inhibitors such as ritonavir and cobicistat interact with specific statins with significant CYP metabolism.<sup>244</sup> Simvastatin and lovastatin are extensively metabolized by the CYP system and can have levels increased >500% when coadministered with CYP inhibitors; accordingly, they should be avoided in HIV.<sup>244–246</sup> Pravastatin and pitavastatin are least likely to interact with ART because of minimal CYP metabolism, whereas atorvastatin and rosuvastatin, the 2 highest-intensity statins, with LDL-C lowering of >50% at the highest commonly prescribed doses, have modest interactions with ART.<sup>244,245</sup> A comprehensive guide to HIV medications and drug-drug interactions may be found online.<sup>247</sup>

In terms of clinical adverse events, observational cohorts have shown that most statins (simvastatin and lovastatin excluded) can be safely prescribed for PLWH with lipid-lowering effects similar to those for people without HIV.<sup>248,249</sup> A caveat to this may be people >75 years of age, for whom there are conflicting data on net statin benefits in the general population.<sup>250–252</sup> As in the general population, vitamin D deficiency also is associated with statin intolerance in HIV.<sup>253</sup> In a randomized study among hypercholesterolemic PLWH, pitavastatin lowered LDL more than pravastatin, and neither was associated with increases in glucose, an important consideration for PLWH.<sup>254</sup> In this study, pitavastatin also lowered soluble CD14, oxidized LDL, and Lp-PLA2 (lipoprotein-associated phospholipase 2), important markers of innate immune function and arterial inflammation, but did not significantly lower IL-6 or hsCRP.<sup>255</sup> A randomized controlled trial of rosuvastatin 10 mg versus placebo among PLWH demonstrated a reduction in some markers of inflammation, monocyte

activation markers, and vascular inflammation with ro-suvastatin.<sup>256,257</sup> There was a significant increase relative to placebo in insulin resistance but no significant difference in fasting glucose, hemoglobin A<sub>1c</sub>, or the incidence of diabetes mellitus.<sup>258</sup> However, other studies have not shown effects on specific inflammatory indexes, including IL-6, hsCRP, and D-dimer.<sup>84,85</sup> Efficacy data for the primary prevention of ASCVD are not yet available, and statins may be underused in HIV.<sup>215,259,260</sup>

To address this knowledge gap, the National Institutes of Health launched REPRIEVE, a randomized, placebo-controlled, 7,500-person global trial to test a primary prevention strategy in HIV.<sup>261,262</sup> REPRIEVE includes patients at low to moderate risk and assesses whether treatment with pitavastatin will prevent adjudicated major adverse cardiovascular events. REPRIEVE will also assess the degree to which changes in lipids, immune activation, and inflammation contribute to this effect. Furthermore, little is known about the differential effects of statins in women with HIV, but immune activation is higher among women.<sup>159</sup> This knowledge gap is being investigated in REPRIEVE, which has enrolled a high percentage of female PLWH.

In addition to statin therapy, other strategies to potentially reduce CVD risk in HIV include antithrombotic agents, which may be underused in HIV<sup>263</sup> but have not yet been assessed in prospective studies powered to evaluate CVD events. Given the prothrombotic milieu common in HIV,<sup>61,264–266</sup> inconsistent findings related to aspirin effects on inflammation and endothelial dysfunction in HIV,<sup>86,267</sup> and the tradeoff seen between reduced vascular events and increased bleeding with aspirin for primary ASCVD prevention in non-HIV populations,<sup>268</sup> further studies are needed to elucidate the role of antithrombotic therapy for ASCVD prevention in HIV. Diabetes mellitus and hypertension should be managed as recommended for the general population because there are insufficient data to recommend a divergent approach in HIV.

A practical expert consensus approach to ASCVD risk assessment and primary prevention in HIV that is based on available (albeit incomplete) evidence is provided in Figure 4.

### Acute Coronary Syndromes and Secondary Prevention of Coronary Artery Disease

PLWH who experience an acute coronary syndrome such as ST-segment–elevation and non–ST-segment–elevation MI tend to have lower overall coronary plaque burden,<sup>269</sup> more single-vessel disease,<sup>270</sup> lower TIMI (Thrombolysis in Myocardial Infarction) risk,<sup>270</sup> and a higher likelihood of proximal lesions than uninfected individual.<sup>271</sup> A meta-analysis<sup>272</sup> of 6 studies<sup>273–278</sup> con-

ducted between 2003 and 2015 suggests that after percutaneous coronary intervention, PLWH have similar mortality, cardiac death, recurrent MI, target vessel revascularization, target lesion revascularization, major adverse cardiac events, and stroke (pooled hazard ratios, 1.13–1.47; all  $P>0.15$ ) compared with uninfected control subjects over 1 to 3 years of follow-up. Despite this and further evidence that drug-eluting stents (compared with bare metal stents) are associated with better outcomes among PLWH,<sup>278,279</sup> PLWH were less likely to undergo percutaneous coronary intervention and less likely to receive drug-eluting stents after acute MI compared with uninfected control subjects in a propensity-matched analyses of the US Nationwide Inpatient Sample.<sup>279</sup> Furthermore, women with HIV appear to be less likely than men with HIV to receive invasive cardiac procedures.<sup>280</sup> In the nonacute setting, however, 1 single-center study showed that PLWH were more likely to receive percutaneous coronary intervention after an abnormal stress test.<sup>191</sup> As with other aspects of CVD among PLWH, inflammation and immune activation appear to be important drivers of restenosis risk after stent placement.<sup>270,281</sup> For those with more advanced disease or complex anatomy, coronary artery bypass graft surgery appears to be safe and effective for PLWH without advanced immunosuppression, with similar inpatient mortality and only modestly higher rates of postoperative blood transfusions (adjusted odds ratio, 1.19 [95% CI, 1.01–1.40]).<sup>282,283</sup> However, rates of longer-term major adverse cardiac events after coronary artery bypass graft surgery may be higher for PLWH compared with uninfected individuals.<sup>283</sup>

Although aggressive secondary ASCVD prevention measures are indicated for PLWH, uptake has not been consistent. Compared with uninfected individuals, PLWH are less frequently prescribed high-intensity statin after acute coronary syndrome (15% versus 45%), and LDL reduction 6 months after the acute coronary syndrome event is lower.<sup>284</sup> Similarly, 57% of PLWH with prior CVD events did not meet guideline-recommended blood pressure targets in a Dutch study.<sup>285</sup> With regard to aspirin use, a similar difference in secondary prevention exists, with only 52% of PLWH with coronary disease on aspirin compared with 65% of uninfected people in a large urban health system.<sup>263</sup>

### Nonstatin Strategies to Prevent ASCVD and to Reduce Inflammation in HIV: Investigational Approaches

Both initiation of ART<sup>60</sup> and early initiation of ART<sup>286</sup> lower inflammation in HIV, but levels remain high compared with levels in uninfected people. Similarly, switch-



ing ART regimens (namely a PI-based to an integrase inhibitor-based strategy) or intensifying ART does not appear to significantly reduce inflammatory markers.<sup>287–290</sup> These findings suggest that alternative and adjunctive approaches may be needed to reduce excess ASCVD risk in HIV.

In recent years, several studies of lipid-lowering therapies added to a background of statin therapy have demonstrated that aggressive LDL-C lowering in populations at high ASCVD risk reduces cardiovascular events.<sup>291,292</sup> The benefit of aggressive LDL-C lowering is demonstrated by data from 14 large statin studies in the non-HIV population (Cholesterol Treatment Trialists' Collaborators) in which each 38.6-mg/dL reduction in LDL-C translated to a reduction in cardiovascular events by 22%.<sup>293</sup> PCSK9 (proprotein convertase subtilisin-kexin type 9) binds and degrades LDL receptors, leading to an increase in LDL-C.<sup>294</sup> PCSK9 inhibitors are monoclonal antibodies with minimal significant drug-drug interactions identified thus far that reduce LDL-C by ≈60% even in the setting of high-intensity statin therapy.<sup>292</sup> Two PCSK9 inhibitors are approved by the US Food and Drug Administration for individuals with heterozygous familial cholesterolemia or clinical ASCVD on maximally tolerated statins who require additional LDL-C lowering. Among uninfected people with ASCVD, PCSK9 inhibitor therapy in addition to statin therapy reduced clinical events by 15% ( $P < 0.001$ ).<sup>292</sup> A longer study demonstrated that PCSK9 inhibitor therapy reduced rates of major adverse cardiovascular events significantly overall and reduced mortality among individuals with an LDL-C  $\geq 100$  mg/dL.<sup>295</sup> PCSK9 levels are higher in PLWH than in uninfected person, particularly in the setting of hepatitis C virus coinfection, and are increased in parallel with inflammatory markers such as IL-6.<sup>296</sup> This relationship may be more pronounced among individuals who are ART naïve.<sup>297</sup> A clinical trial investigating the impact of PCSK9 inhibitor therapy on lipids, inflammatory markers, and subclinical ASCVD (including noncalcified plaque and arterial inflammation) in HIV is currently being conducted (EPIC-HIV study [Effect of PCSK9 Inhibition on Cardiovascular Risk in Treated HIV Infection]; URL: ClinicalTrials.gov. Unique identifier: NCT 03207945). Future studies are needed to evaluate the impact of PCSK9 inhibition on clinical events in HIV.

As discussed, chronic inflammation and immune activation remain elevated in effectively treated HIV infection<sup>60</sup> and are strongly predictive of non-AIDS events, including CVD and mortality.<sup>67,68</sup> In particular, IL-6 and D-dimer are strongly associated with mortality in HIV.<sup>64</sup> In the non-HIV population with known CVD and hsCRP  $\geq 2$  mg/L, treatment with a monoclonal antibody targeting IL-1 $\beta$  (canakinumab) significantly reduced IL-6 and hsCRP and led to a significantly lower rate of recurrent cardiovascular events

but also increased the rate of fatal infections in CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcomes Study).<sup>90</sup> Treatment with canakinumab was also associated with a significant reduction in incident lung cancer and lung cancer mortality, although this was not the primary study end point.<sup>91</sup> Individuals who achieved an on-treatment hsCRP  $< 2$  mg/L had relative reductions in both cardiovascular mortality and all-cause mortality by 31% compared with placebo<sup>92</sup>; a similar finding was demonstrated for individuals with on-treatment IL-6  $< 1.65$  ng/L.<sup>298</sup> Conversely, in the CIRT trial (Cardiovascular Inflammation Reduction Trial) of uninfected individuals with stable atherosclerosis, low-dose methotrexate did not reduce inflammatory biomarkers or CVD events.<sup>299</sup> In this study, methotrexate was associated with elevations in liver transaminases and reductions in leukocyte counts. In light of the positive results from CANTOS (with the notable exception of increased fatal infections) and the null findings from CIRT, further study is needed to define the role of targeted therapies to reduce inflammation and CVD risk in HIV.

### Stroke Prevention and Therapy in HIV

Although the risk for ischemic stroke is elevated in HIV,<sup>8</sup> data on pharmacotherapy for stroke prevention in HIV are sparse. Whereas systemic atherosclerosis is a likely driver of the elevated stroke risk in HIV, atrial fibrillation (which may be more common overall in HIV but not after adjustment for common CVD risk factors)<sup>41</sup> accounts for 30% of ischemic stroke among PLWH.<sup>169</sup> Using risk stratification tools, for example, the CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED scores, to estimate cardioembolic stroke and hemorrhagic complications of antithrombotic therapy, respectively, is an important step to rationalize primary and secondary intervention in general and perhaps in HIV.<sup>300</sup> However, the reliability of these scores in PLWH is unclear,<sup>300</sup> as are the safety of anticoagulants (particularly direct-acting oral anticoagulants) and their interactions with ART.<sup>168,301</sup>

There are no trials on the safety and efficacy of thrombolysis in HIV infection, but retrospective studies have shown that the risk of death with thrombolysis was similar for PLWH and uninfected individuals.<sup>302,303</sup> Endovascular treatment is now routine in acute stroke treatment<sup>304</sup>; 1 case series, with limited safety data, showed successful endovascular treatment in patients with HIV-associated vasculopathy.<sup>305</sup> HIV-associated vasculitis may manifest as acute stroke, driven by inflammation alone or secondary infection. This may occur soon after the patient starts ART, suggesting an immune reconstitution inflammatory syndrome.<sup>170</sup> Optimal workup, including cerebral angiogram and lumbar puncture, if safe, is essential in diagnosing this potentially treatable pathogenesis.<sup>171</sup> High-dose corticosteroids may be nec-

essary in patients with immune reconstitution inflammatory syndrome with impending brain herniation and helpful in less severe cases with symptomatic central nervous system inflammation.<sup>306</sup>

## HF Diagnosis and Treatment

The uncertainty about the mechanisms and course of HF in HIV precludes evidence-based recommendations on HIV-specific HF diagnosis and treatment. There are insufficient data to suggest approaches to HF workup and therapy differing from those used in the general population. However, given the elevated risks for HF in HIV, it would be reasonable for clinicians engaged in the care of PLWH to have a high index of suspicion for HF in the setting of possible HF symptoms, along with a low threshold to pursue noninvasive diagnostic testing (such as echocardiography) in the setting of such symptoms or cumulative exposures to high-risk features (eg, high cumulative viremia, low CD4 count, or substance abuse). Furthermore, given the importance of left ventricular EF as a predictor of sudden cardiac death for PLWH<sup>307</sup> (as in the general population), it is reasonable to follow general population indications for implantable cardioverter-defibrillator therapy in PLWH. For PLWH with end-stage HF requiring advanced therapies, HIV should not be considered a contraindication to transplantation or left ventricular assist device implantation given the longer life expectancy of PLWH, which is approaching that of uninfected people.<sup>308</sup>

## DISPARITIES IN CARE AND PLWH AS A VULNERABLE POPULATION

PLWH represent a vulnerable and often stigmatized population that faces structural and economic barriers to optimal healthcare services.<sup>309</sup> Understanding and addressing CVD in PLWH necessitates recognizing the systematic barriers that perpetuate disparities in care delivery. (A comprehensive review of HIV-associated CVD in resource-limited settings is beyond the scope of this statement; however, given the clear importance of this topic, we have included a brief discussion here.)

Many factors exacerbate vulnerability for PLWH, including education level, residential location, healthcare literacy, disenfranchisement from the healthcare system, cognitive impairment, injection drug use, internalized and anticipated stigma, gait and mobility impairment, frailty, depression, and social isolation. These factors can be intensified by disparities in care according to individual factors such as age, race, ethnicity, and sex, as well as factors associated with high HIV transmission rates such as homosexual contact between men, heterosexual contact among black women, and injection drug use.<sup>310</sup>

There are well-documented disparities in care for CVD among PLWH. PLWH have fewer clinic visits that meet guideline-directed medical therapy for aspirin therapy (5.1% versus 13.8%) and use of statins (23.6% versus 35.8%).<sup>21</sup> Data from a large cohort of PLWH in Europe demonstrated that women are less likely to receive lipid-lowering therapy, antihypertensive medications, angiotensin-converting enzyme inhibitors, and invasive cardiovascular procedures after MI.<sup>311</sup> Data from the Veteran's Health Administration Corporate Data Warehouse also demonstrate that blood pressure, diabetes mellitus, and lipid management are worse in black compared with white PLWH.<sup>312</sup> Black and Hispanic PLWH have among the highest estimated 10-year risk of ASCVD compared with other racial and ethnic groups.<sup>214,313</sup> Substance-related disorders also impair CVD care in PLWH; they are associated with less appropriate statin use (23% versus 40%) compared with those without substance-related disorders.<sup>314</sup> Such disparities in CVD prevention for PLWH portend greater risk for MI.<sup>315</sup> Furthermore, major depressive disorder is particularly common in HIV and associated with elevated risk for HF in HIV.<sup>36</sup>

Geographic factors also affect CVD prevention and management. MI, stroke, and stroke mortality rates are up to 4 times higher in the South compared with other regions in the United States.<sup>316-318</sup> HIV prevalence is highest in the South, with significant racial disparities in incidence and prevalence.<sup>319</sup> Black men and women have lower rates of HIV viral suppression, which predisposes to more inflammation and CVD. On a global landscape, 67% of all PLWH reside in Sub-Saharan Africa. A large systematic review and meta-analysis of longitudinal studies of CVD in HIV infection examined CVD rates among PLWH worldwide.<sup>4</sup> Between 1990 and 2015, the global population-attributable fraction of CVD caused by HIV tripled from 0.36% to 0.92%. There was marked regional variation, with most cardiovascular disability-adjusted life-years lost in the Sub-Saharan Africa (0.87 million) and Asia-Pacific (0.39 million) regions.

## Addressing Disparities: Opportunities for Positive Impact

Given the physiological, socioeconomic, and geographic factors that make PLWH particularly vulnerable to the onset and progression of CVD, there is considerable room for improvement in CVD prevention and treatment. The investment in HIV care and research over the years has resulted in a growing infrastructure and strategies that can be leveraged for optimal CVD prevention and management. The HIV treatment cascade and the global 90-90-90 initiatives aim to maximize diagnosis, treatment, and viral suppression.<sup>320</sup> Expanding the HIV treatment cascade for the prevention of non-AIDS co-

morbidities is a necessary extension of the treatment cascade paradigm.<sup>321</sup> Empowered PLWH are also driving the conversation about CVD prevention and management (see the [Data Supplement: HIV, Aging, and the Patient's Perspective](#)) through the use of publicly available resources such as the National AIDS Treatment Advocacy Project.<sup>322</sup>

Targeted attention and investment are needed. The quality of our care for HIV is further limited by shortcomings in the US healthcare reimbursement system. Healthcare providers are often unable to spend the time required to understand the problems facing the aging HIV population. PLWH who also have CVD often need longer visit times,<sup>323</sup> care coordination, and multidisciplinary team engagement. There are many opportunities for implementation research aimed at leveraging the HIV care infrastructure to deliver integrated cardiovascular preventive and therapeutic care for PLWH.<sup>324</sup> Such structures could include improving health insurance access to specialists, strengthening specialist referral pathways, nurse management, clinical pharmacist engagement,<sup>325</sup> team-based approaches,<sup>326</sup> electronic medical record–based approaches to targeting high-risk patients, colocated clinics, and other approaches that consider the specific vulnerabilities in this population.

Models of integration of primary care and HIV services have been demonstrated to be feasible and effective,<sup>327</sup> but little information is available on cost or effectiveness of specific approaches in the United States. A research agenda has been suggested for Sub-Saharan Africa that prioritizes developing evidence-based service delivery models, generating data through informatics platforms and research, and advancing research-informed policy, among other cross-cutting health system issues. The impact of interventions to reduce the burden of CVD in PLWH in the United States likewise needs to be evaluated and optimized. This will require continued funding support from the National Institutes of Health and public-private partnerships, including support from industry to study the effects of emerging therapies.

## CONCLUSIONS AND FUTURE DIRECTIONS

Although much progress has been made over the past decade in understanding HIV-associated CVD, considerable gaps exist, and much work remains to be done in the future. Even with effective HIV viral suppression, inflammation and immune dysregulation appear to in-

crease risks for MI, stroke, and HF. Several studies have analyzed the pathophysiology of atherosclerosis in HIV, but relatively few have been devoted to understanding thrombosis and HF. Therefore, further studies of the pathophysiology of thrombosis and HF in HIV are sorely needed. Similarly important is the lack of large-scale clinical trials on CVD prevention and treatment in HIV; these trials are necessary for informed decision-making and effective CVD prevention and treatment in the aging HIV population. In the meantime, a reasonable approach may be to consider PLWH at particularly elevated CVD risk and therefore more likely to benefit from CVD-preventive therapy if risk-enhancing factors that are related to HIV (eg, low current or nadir CD4 count or a history of prolonged viremia) or are more general (eg, family history of premature ASCVD, chronic kidney disease, or atherosclerosis on imaging) are present. Future studies should also address gaps in implementation to ensure that PLWH who are at risk for CVD or have existing CVD are identified and provided appropriate CVD care. If these steps are taken, perhaps we can reverse the trend of the growing burden of CVD in HIV.

## ARTICLE INFORMATION



The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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## Disclosures

## Writing Group Disclosures

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Matthew J. Feinstein	Northwestern University	AHA (research support)†; NIH (research support)†	None	None	None	None	None	None
Priscilla Y. Hsue	San Francisco General Hospital	NIH (grant support)†; Regeneron/Sanofi (study drug and placebo provided for trial)*; Novartis (study drug and placebo provided for trial)*	None	None	None	None	Gilead*; Merck*	None
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Gerald S. Bloomfield	Duke Clinical Research Institute, Duke Global Health Institute and Duke University Medical Center	NIH (research grant R01MD013493)*	None	None	None	None	None	None
Judith S. Currier	Center for AIDS Research and Education	NIH grant (steering committee of REPRIEVE trial)*; Theratechnologies (PI of clinical trial at UCLA, ended June 2018)*	None	None	None	None	None	None
Matthew S. Freiberg	Vanderbilt University	NIH (grants studying HIV and CVD)†	None	None	None	None	None	None
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\*Modest.

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## Reviewer Disclosures

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Edgar Overton	University of Alabama at Birmingham	None	None	None	None	None	Merck*; Viiv*	None
Virginia A. Triant	Massachusetts General Hospital–Harvard Medical School	NIH (co-PI of R01 on cardiovascular risk prediction in HIV)†	None	None	None	None	None	None
Allison R. Webel	Case Western Reserve University	Gilead Sciences (My university received a research grant for our work from Gilead)†	None	Association of Nurses in AIDS Care*	None	None	None	None

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\*Modest.

†Significant.

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