Invited Review

Prevention and Treatment of Cardiovascular Disease in HIV: Practical Insights in an Evolving Field

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Abstract: *People with HIV (PWH) are at higher risk for cardiovascular disease (CVD) than people without HIV. As antiretroviral therapy (ART) and the natural history of HIV have evolved, so have the pathogenesis and manifestations of HIV-associated CVD. Epidemiologic data from several cohorts demonstrate that PWH have an approximately 50% higher risk than people without HIV for CVD, including, but not limited to, myocardial infarction and heart failure. This elevated CVD risk is not universal among PWH; for instance, the risk is higher among individuals with a history of sustained unsuppressed viremia, diminished CD4+ cell count recovery, or hepatitis C virus coinfection. Specific antiretroviral drugs may also associate differently with CVD risk. Regarding management, the recent REPRIEVE (Randomized Trial to Prevent Vascular Events in HIV) study results demonstrated a 35% relative risk reduction in atherosclerotic CVD for PWH at low to moderate predicted risk taking pitavastatin; this is a larger reduction than for comparable moderate-intensity statins in the general population. Whether these higher-than-expected reductions in CVD risk among PWH also extend to higher-intensity statins and into secondary prevention settings for people with existing CVD merits further study. Nonlipid approaches to CVD risk reduction in PWH—ranging from antithrombotic therapy to inflammation-modulating therapy—remain under active investigation. Results of these studies will provide essential information to further guide CVD management in PWH.*

Keywords: atherosclerosis, antiretroviral therapy, ART, cardiovascular disease, CVD, heart failure, HIV, inflammation, myocardial infarction, statin

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Epidemiology of HIV-Associated Cardiovascular Disease (CVD): Evolving Phenotypes and Risks

Myocardial Infarction

Several epidemiologic studies over the past decade in distinct cohorts demonstrated that people with HIV (PWH) have significantly higher multivariable-adjusted risk for myocardial infarction (MI) than people without HIV.[1,2] Among PWH, those with detectable viremia have higher risks for MI than those without detectable viremia, with an underlying biologic gradient noted. PWH with an HIV RNA level below 500 copies/mL had a 1.39-fold higher risk for MI than PWH without detectable viremia; for PWH with an HIV RNA level above 500 copies/mL, this risk was 1.75-fold higher. Lower current or nadir CD4+ cell counts—markers of immunologic progression and incomplete recovery related to HIV, often in concert with histories of sustained viremia—have likewise been consistently associated with elevated MI risk among PWH.[1] In a more recent study, a large cohort of patients with HIV matched with people without HIV was followed up from 2005 to 2020. This study demonstrated that PWH had a 1.6-fold higher risk for MI than people without HIV, and that the cumulative incidence of MI increased from the period of 2005 to 2009 to the period of 2010 to 2017.[3]

Heart Failure, Arrhythmia, and Sudden Cardiac Death

HIV is likewise associated with a 1.5- to 2-fold elevated risk for heart failure, a complex clinical syndrome arising from heterogeneous pathophysiologic mechanisms (Figure 1).[4,5] Data are less consistent for HIV and atrial fibrillation. Analyses of data from MACS (Multicenter AIDS Cohort Study) and from within the Northwestern Medicine system observed no association between HIV and atrial fibrillation, whereas a study performed in a University of California San Francisco cohort observed an increased HIV-related risk for atrial fibrillation.[6-8]

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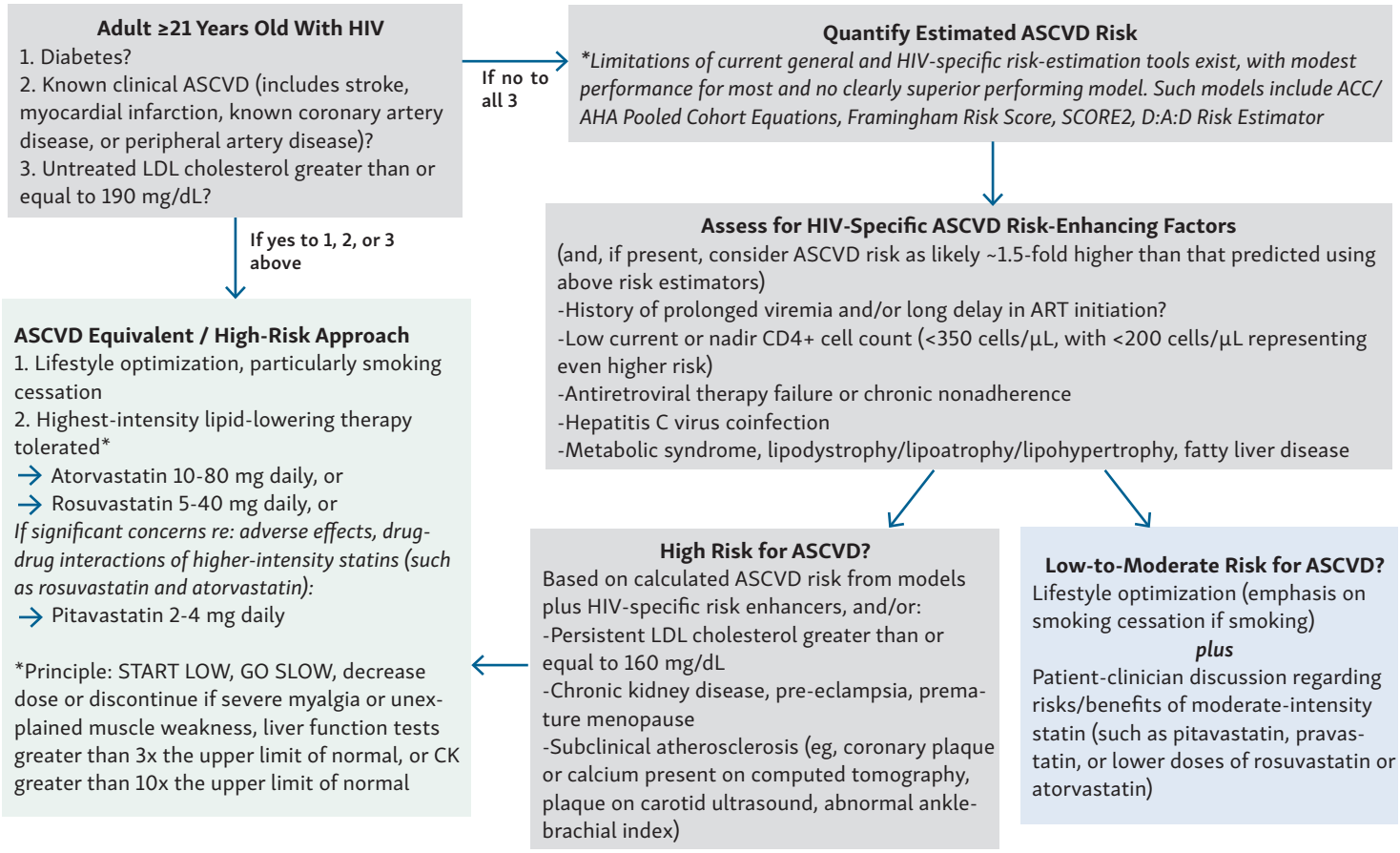

Figure 1. Approach to ASCVD Risk Assessment and Prevention for People with HIV. Adapted from Feinstein MJ, et al.[4] *Abbreviations: ACC/AHA = American College of Cardiology/American Heart Association; ART = antiretroviral therapy; ASCVD = atherosclerotic cardiovascular disease; CK = creatine kinase; LDL = low-density lipoprotein.*

Data on sudden cardiac death suggest a considerable HIV-associated increase in risk. In an autopsy study by the San Francisco medical examiner, PWH had nearly twice the incidence of sudden cardiac death as people without HIV.[9] Of those deaths among PWH, the mean CD4+ count was 475 cells/μL, and 79% were on antiretroviral therapy (ART), indicating that even in the setting of reasonable HIV control, underlying HIV-associated clinical factors or myocardial pathologies may confer particularly elevated sudden cardiac death risk.

The Role of Immune Dysregulation in HIV-Associated CVD

Innate and adaptive immune dysregulation resulting in persisting inflammation is a hallmark of HIV and is likewise implicated in the pathogenesis of an array of CVDs. In coronary artery disease, these inflammatory responses lead to plaque rupture, erosion, and eventual vasculopathies. In heart failure, they contribute to maladaptive responses to cell injury, microvascular dysfunction, and direct myocardial inflammatory infiltrates, each of which can contribute to systolic and diastolic dysfunction. This complex interplay between comorbidities, underlying immunologic abnormalities, and inflammatory bias can accelerate inflammation and ultimately result in CVD.[10-13] In homeostatic conditions, effectors of inflammation such as inflammatory monocytes and macrophages and inflammatory T-cell populations—initially activated in response to foreign antigens or neoantigens—are counterbalanced by immunoregulatory populations such as regulatory T cells and resident macrophages.[14] Over time, and in conditions of viral reactivation and persistence, "appropriate" inflammation transforms into a sustained inflammatory state, loss of self-tolerance, and amplified autoreactivity resulting in overt CVD; this is especially the case in HIV as a result of diminished regulatory immunity and vulnerability to additional pathogens due to microbial translocation and viral coinfection.[15] Persistent

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unresolving inflammation among PWH has also been associated with worse clinical outcomes. Indices of immune activation and elevated levels of inflammatory effectors, such as interleukin-6, soluble CD14, and chemokine C-X-C motif ligand 13, have been associated with decreased survival in PWH even with HIV control on ART.[16]

In addition to chronic inflammation, PWH have higher rates of traditional CVD risk factors, such as smoking, which is substantially more prevalent among PWH than among people without HIV. Dyslipidemia and metabolic dysfunction are also common in PWH as a result of complex factors ranging from viremia-associated inflammation to ART-associated lipid dysregulation.[17-20]

Heterogeneous Associations Between ART and CVD Risk

With the widespread adoption of ART, PWH have life expectancies similar to patients without HIV.[21] Given early concerns related to off-target ART effects, the SMART (Strategies for Management of Antiretroviral Therapy) study investigated HIV/AIDS-related endpoints, as well as non–AIDS-related endpoints, for PWH randomly assigned to either continuous or interrupted ART. Although continuous ART unsurprisingly reduced AIDS-related endpoints, it also conferred a lower risk for MI than interrupted ART.[22] This trial, coupled with subsequent trials such as START (Strategic Timing of Antiretroviral Treatment), helped confirm early and continuous ART as the standard of care for PWH.[23]

In this context, understanding the diverse cardiovascular effects of distinct antiretroviral drugs is of interest to aid in CVD risk stratification, prevention, and management among PWH. Protease inhibitors were originally associated with elevated MI risk,[24] although emerging data suggested against this being a class effect, but rather being related to more nuanced drug-specific effects. For instance, ritonavir-boosted darunavir is associated with elevated CVD risk among PWH, whereas ritonavir-boosted atazanavir may be associated with decreased CVD risk.[25,26]

The putative effects of nucleoside reverse transcriptase inhibitors (nRTIs) on CVD risk are likewise complex. Older nRTIs have been linked to mitochondrial damage leading to myopathy, neuropathy, and other subsequent toxic effects.[4,27] Regarding more contemporary nRTIs, tenofovir alafenamide (TAF) increased total cholesterol and low-density lipoprotein levels compared with tenofovir disoproxil fumarate (TDF), but no significant difference in overall CVD risk was observed between the 2 drugs.[28,29] In a separate analysis, switching from TDF to TAF led to marked weight gain, suggesting an independent effect of TAF on metabolic health. Yet, the net CVD effect largely remains uncertain.[30]

In longer-term follow-up cohort studies, abacavir increased risk for CVD overall, and some studies specifically showed increased MI risk compared with non-abacavir ART.[31,32] However, in shorter-term clinical trials, there was no observable effect on CVD risk.[33] This discrepancy may relate to the younger ages of patients in these clinical trials, precluding sufficiently high absolute event numbers to disentangle abacavir-associated CVD risk in younger, lower-risk cohorts.[21,31-33]

Although integrase strand transfer inhibitors (InSTIs) have a well-established risk of weight gain, the net effect on CVD is uncertain, and data regarding long-term CVD risk are limited—particularly compared with other ART regimens.[34,35]

CVD Risk Stratification and Treatment: Understanding Net Clinical Benefit

Although PWH have elevated overall CVD risk compared with those without HIV, these HIV-associated risks differ depending on the presence or absence of underlying HIV-associated risk enhancers, such as sustained viremia and low CD4+ cell count. Accordingly, it is important to avoid adopting a "one size fits all" model for PWH and CVD risk, and instead to incorporate HIV-specific risk enhancers in risk stratification and optimal CVD prevention strategies for PWH. As discussed above, variability in immune progression and degree of recovery, viremic exposure, ART (historic and current), along with traditional risk factors ranging from smoking to dyslipidemia are all associated with distinct CVD risk profiles among PWH.

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A limited but growing body of literature exists to inform approaches to CVD prevention and treatment in

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PWH. In general, hydroxy-methyl-glutaryl coenzyme A reductase inhibitors (ie, statins) reduce atherosclerotic CVD (ASCVD) risk by 20% to 25%, but whether this risk reduction differs in PWH remained largely unknown until recently. The recently published results of the REPRIEVE (Randomized Trial to Prevent Vascular Events in HIV) study of more than 7000 PWH with low to moderate risk for ASCVD demonstrated that the risk-reducing effects of statins in PWH may be even higher than in the general population.[36] In REPRIEVE, PWH randomly assigned to pitavastatin 4 mg daily compared with those assigned a placebo experienced a 35% relative reduction in risk for major adverse cardiovascular events (hazard ratio, 0.65; 95% CI, 0.48-0.90), with some increase in adverse events including muscle symptoms (2.3% of PWH on pitavastatin vs 1.4% on placebo) and diabetes mellitus (5.3% vs 4.0%, respectively).

Net Clinical Benefit and Risk-Informed Clinical Decision-Making

A crucial concept informing the benefits and risks of statin therapy in PWH, as in the general population, is net clinical benefit. Simply put, net clinical benefit reflects the absolute benefit minus absolute risk of a particular therapy or intervention.[37] Therefore, assuming somewhat similar relative risk reductions across clinical strata from statins,[38,39] higher absolute risk means higher potential benefit of therapy. Thus, if there is a uniform ~35% relative risk reduction from statins, a patient with a 50% CVD risk over 10 years would have a 17.5% absolute reduction in CVD risk by initiating a statin. Meanwhile, a patient with a 5% CVD risk over 10 years would experience a 1.75% absolute reduction in CVD risk by initiating a statin. Taking this into account, the benefit of therapy when weighed against potential harms is clearly favorable for the individual at high ASCVD risk, but less obviously favorable for the person with low ASCVD risk. Data from the REPRIEVE study suggest a somewhat higher than expected ASCVD risk reduction with a moderate-intensity statin in PWH, raising the possibility that the benefit/risk tradeoff of statins in PWH is more favorable than in the general population, supporting a somewhat lower threshold for statin initiation.

These considerations highlight the need to consider individual ASCVD risk when discussing ASCVD prevention approaches in PWH. Certainly, PWH with existing clinical ASCVD should be treated aggressively with lipid-lowering therapy as is done in the general population, particularly given higher HIV-associated ASCVD risks and emerging data suggesting PWH may derive greater than expected benefit from statin therapy. For those without preexisting ASCVD, a reasonable approach is to derive a CVD risk estimate—whether using the Framingham Risk Score, the ASCVD Pooled Cohort Equations, the Systematic Coronary Risk Evaluation Score 2 (SCORE2), or another tool—with the understanding that many such models tend to underpredict risk for PWH,[40-42] and that HIV-specific models do not yet dramatically improve discrimination or calibration.[43]

Following such an assessment of ASCVD risk, considering unique patient-level factors (eg, history of sustained viremia, low nadir CD4+ cell count, and coinfection with hepatitis C virus) is essential to inform clinical decision-making. In other words, if a person with HIV has a predicted 10% 10-year ASCVD risk based on the Pooled Cohort Equations but also a nadir CD4+ count below 200 cells/μL and evidence of incomplete immune recovery, this individual likely has a somewhat higher ASCVD risk than inferred by the risk prediction tool alone. In such cases, extrapolation of epidemiologic data, an inexact science but one that leverages what is currently available,[44] would suggest this 10% 10-year ASCVD risk may be closer to 15%.

Although clearly imperfect, such general risk assessments can inform patient-clinician discussions regarding how likely an individual patient is to benefit from, rather than be harmed by, a therapeutic intervention such as statin treatment. Alternatively, adjunctive CVD risk-reducing interventions such as smoking cessation and pursuing a heart-healthy diet have a high potential for impact without similar adverse effect profiles.

New Horizons in CVD Prevention and Therapy for PWH

In addition to lipid-lowering therapy, antiplatelet therapy is an essential component of secondary prevention of ASCVD events, such as MI, though the role of antiplatelet therapy in primary prevention is less clear.[45] Small mechanistic studies suggest that the most common antiplatelet therapy, aspirin, may have somewhat reduced therapeutic effects in PWH. In a randomized clinical trial comparing daily aspirin with placebo in PWH on ART, researchers found that aspirin did not impact markers of immune activation or endothelial dysfunction.[46] In another trial studying clopidogrel and aspirin, clopidogrel reduced platelet activation and platelet-induced endothelial inflammation, but aspirin did not.[47] More clinical data are needed to inform the risks and benefits of antiplatelet therapy for primary

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prevention in PWH. These results suggest clopidogrel may be a more desirable alternative for the secondary prevention of ASCVD in PWH; however, considerably more clinical data are needed to assess this.

Apart from lipid-lowering and antithrombotic therapy for ASCVD risk reduction, there is also considerable interest in modulation of inflammation to reduce risk for ASCVD among PWH. Complicating matters is the complex immunology of chronic HIV, whereby some

Small mechanistic studies suggest that the most common antiplatelet therapy, aspirin, may have somewhat reduced therapeutic effects in people with HIV

interventions (eg, the inhibition of monocyte activation and the myeloid inflammation common in treated PWH[48]) offer theoretical promise, and rigorous larger-scale studies are needed to evaluate various potential off-target effects. Likewise, inflammation-targeted therapies such as canakinumab have demonstrated a reduction of inflammation in PWH,[49] although the net clinical effects of such therapies for PWH remain unclear. Colchicine was recently approved by the US Food and Drug Administration for ASCVD risk reduction in the general population, but the potential role in PWH remains to be seen, given colchicine's effects as a substrate for cytochrome P450 3A4 (CYP3A4) with potentially serious drug-drug interactions, particularly in PWH on ART.

Future approaches will also need to consider the prevention and treatment of heart failure and arrhythmia, and the prevention of sudden cardiac death. Few data from large-scale clinical trials exist—apart from observational studies of incidence—to inform optimal approaches in PWH. In the interim, diagnosis and treatment paralleling that in the general population is reasonable, with a particular focus on underlying risk factors (eg, hypertension, metabolic dysregulation, and substance and stimulant use) for these conditions. In addition, practitioners are encouraged to maintain a high index of suspicion for early evidence of forms of CVD in their patients with HIV to ensure appropriate and prompt diagnosis, treatment, and referral to specialty care as needed.

Conclusion

PWH are at elevated risk for atherosclerotic disease, thrombosis, and cardiac dysfunction. HIV sequelae such as chronic inflammation and immune activation persist despite effective ART and appear to play a pivotal role in the pathogenesis of diverse forms of CVD in PWH. Recent results from the REPRIEVE trial indicate a potentially greater-than-expected benefit of statins in PWH. Nevertheless, considerably more mechanistic and clinical research is needed to optimize the prevention and treatment of CVD in PWH.

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All relevant financial relationships with ineligible companies have been mitigated.

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