HIV and Cardiovascular Disease: We Need a Mechanism, and We Need a Plan

Matthew S. Freiberg, MD, MSc; Kaku So-Armah, PhD

With the advent of antiretroviral therapy (ART) and increased survival, HIV-infected people are now at risk for diseases of aging including cardiovascular disease (CVD). In the ART era, multiple large cohort studies have found that HIV infection is associated with an increased risk of acute myocardial infarction (AMI), ischemic stroke, and heart failure.[1–3] Although total mortality has been decreasing for a decade among HIV-infected people, CVD mortality has significantly increased over that same time period.[4] The underlying mechanism driving excess CVD risk is not clear but likely involves a combination of factors including the virus itself, the side effects of ART, and the burden of traditional risk factors for coronary heart disease (eg, smoking) and nontraditional risk factors (eg, hepatitis C, substance use or abuse). In addition, some evidence suggests that HIV-infected people are less likely than uninfected persons to receive treatment for some CVD risk factors[5] and for procedures related to acute coronary syndrome.[6] Taken together, these data suggest that health care disparities may also contribute to the increased CVD morbidity and mortality among HIV-infected people.

In the early part of the ART era, observational studies reported that ART is an important risk factor for CVD in HIV-infected people.[7] In fact, the concern about excess risk of CVD associated with ART was one of the findings that led to the Strategies for Management of Antiretroviral Therapy (SMART), a randomized controlled trial that examined CD4+ cell count–guided interruption of ART (ie, less ART) versus continuous ART (ie, less HIV virus) and the risk of opportunistic infections, death, and other adverse events including CVD.[8] SMART clearly demonstrated that episodic ART did not reduce the risk of opportunistic infections, death, or adverse events, including CVD, that were associated with ART. Moreover, the results suggested that unsuppressed HIV virus plays a larger role in the risk of CVD events than ART.

Coronary heart disease is largely a function of progressive atherosclerosis, which involves inappropriate lipid metabolism and activation of the innate and adaptive immune systems in the arterial wall.[9] HIV-infected people can experience T cell depletion related to the HIV virus and dyslipidemia caused by ART and have increased levels of inflammation, monocyte activation, and altered coagulation compared with uninfected people.[10] It follows that HIV infection and ART treatment may independently increase the risk of coronary heart disease by progressive atherosclerosis. Unfortunately, initial reports examining the cross-sectional association between HIV infection and subclinical atherosclerosis have been inconsistent. A 2009 meta-analysis found that HIV status was associated with increased carotid intima–media thickness (cIMT) but not carotid plaque or coronary artery calcium.[11] These inconsistent results may have been a consequence of the significant heterogeneity in methods and differential prevalence of CVD risk factors by HIV status across studies.

Similarly, longitudinal studies examining HIV infection and subclinical atherosclerosis among children and adults have reported inconsistent results. Among children without a significant burden or duration of risk factors for coronary heart disease, those who were ART-naïve had increased cIMT, whereas those who were ART-exposed had similar cIMT compared with children without HIV infection.[12] A 144-week longitudinal study described higher cIMT at baseline among HIV-infected children but similar levels compared with uninfected children by study end.[13] Among adults, the Multicenter AIDS Cohort Study and the Women's Interagency HIV Study reported that HIV infection was associated with higher incidence but not progression of coronary artery calcium.[14] Hsue et al also reported higher rates of cIMT progression in HIV-infected versus uninfected people, with greater differences observed in the carotid bifurcation

region, an area predisposed to atherosclerotic lesions.[15] In contrast, a 96-week prospective cohort study involving ART-naïve and matched HIV-uninfected people demonstrated that cIMT increased significantly overall but similarly between groups.[16]

More recently, investigators have turned to computed tomography angiography and positron emission tomography to examine the association between HIV infection and noncalcified plaque and arterial inflammation, respectively. In this issue of the journal, Lai et al used computed tomography angiography and reported that HIV-infected people on ≥36 months of ART had a higher prevalence of subclinical atherosclerosis than uninfected people, but they did not report an association per se between HIV infection and subclinical atherosclerosis.[17] In this cohort, cocaine use was significantly associated with subclinical disease. In contrast, a study by Post et al reported that HIV infection was associated with higher incidence of coronary artery calcium and a higher prevalence and extent of noncalcified plaque.[18] Using positron emission tomography, levels of arterial inflammation (a marker of future vascular risk) were higher in HIV-infected participants compared with uninfected Framingham score–matched controls and similar to uninfected controls with known atherosclerosis.[19] The comparison in this study to Framingham score–matched controls suggests that HIV infection or HIV-related factors have an effect on arterial inflammation. The other comparison suggests that the magnitude of this HIV effect is at least on par with that related to clinical atherosclerosis.

Although the results examining the association between HIV infection and subclinical atherosclerosis are not consistent, there is little doubt that established CVD risk factors among HIV-infected people play an important role in the development of future CVD events. Importantly, even without major CVD risk factors, HIV infection is still associated with nearly twice the risk of AMI compared with uninfected people[20]; however, without CVD risk factors, the absolute rates of AMI among HIV-infected people are low. In contrast, increasing CVD risk factor burden can increase the risk of AMI by 7- to 10-fold among HIV-infected people.[20] HIV-infected people with a high burden of CVD risk factors also continue to have higher rates of AMI than uninfected people.[20]

Preventing risk factors and reducing morbidity associated with CVD in the HIV population is a priority; however, some evidence suggests that the receipt of treatment for CVD risk factors and acute coronary syndromes among HIV-infected people may not be adequate and less than that of HIV-uninfected people. Among HIV-infected people who qualified for aspirin therapy under US Preventive Services Task Force guidelines, only 17% received this therapy.[21] Among those who met National Cholesterol Education Program Adult Treatment Panel III guidelines for the receipt of lipid-lowering therapy, HIV-infected people—particularly those coinfected with hepatitis C —were significantly less likely to receive this therapy compared with uninfected people.[5] Lastly, among those with an AMI, use of typical AMI procedures including thrombolytic agents, coronary arteriography, left cardiac catheterization, and coronary artery bypass grafting was significantly less common among HIV-infected compared with uninfected people.[6]

In summary, HIV infection and ART are risk factors for atherosclerotic CVD events. The mechanisms underlying this risk are not clear and are likely multifactorial. The evidence to date suggests that atherosclerosis—whether caused by the HIV virus, its treatment, risk factors for coronary heart disease, or substance use and abuse—likely contributes to the excess risk of CVD among HIV-infected people. The role, if any, of health care disparities involving CVD treatment for adverse CVD outcomes in this population remains to be determined. Presently, the National Institutes of Health is funding major initiatives designed (1) to help elucidate the underlying mechanisms driving the excess risk of CVD among HIV-infected compared with uninfected people and (2) to improve CVD outcomes among HIV-infected people. A major initiative is the Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE), a randomized clinical trial designed to test whether statin administration can reduce the risk for major CVD events among HIV-infected people. Results from REPRIEVE will help inform clinical providers about the best clinical approach to prevent CVD in this high-risk population. Other studies are targeting chronic inflammation such as a study of low-dose methotrexate in HIV infection (AIDS Clinical Trials Group 5314), which is a proof-of-concept study designed to evaluate the safety and impact of lowering inflammation in treated HIV. While we are awaiting the results of this science, health care providers should, at a minimum, focus on providing guideline-driven care to HIV-infected people to reduce the impact of HIV infection and CVD risk factors on future CVD events.

Disclosures

None.

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