HIV and Atherosclerosis: Moving From Associations to Mechanisms and Interventions

In the decade since the first reports of an increased risk for atherosclerosis among patients being treated for HIV infection, multidisciplinary research teams around the globe have made substantial progress in understanding this important problem. Several studies have described an increase of approximately 50% in the relative risk for myocardial infarction, including recent work with well-matched control populations (1, 2). In addition, studies using noninvasive measures of subclinical atherosclerosis have provided an opportunity to closely examine associations between traditional risk factors for atherosclerosis and HIV-specific risk factors. The findings from the large cross-sectional study reported by Post and colleagues (3) in this issue confirm and extend findings from earlier, smaller studies and lay the groundwork for future research priorities in this critical area of investigation.

Harnessing the power of the MACS (Multicenter AIDS Cohort Study), a well-established HIV cohort study with a demographically matched control group, Post and colleagues examined the prevalence, extent, and characteristics of coronary artery plaque. They used cardiac computed tomography (CT) to measure coronary artery calcium (CAC) and coronary CT angiography to assess plaque extent and characteristics. The participants were men at an average age of 50 years. As seen in other studies, these men had high prevalence of traditional risk factors for cardiovascular disease, with a high prevalence of smokers among those infected with HIV. Strengths of Post and colleagues' study include the consistent and detailed manner in which data on potential confounders were collected from the HIV-infected and control participants and the extent of the measures of the coronary segments. Consistent with earlier work in the MACS (4), coronary calcification as measured by CT did not seem markedly increased among patients in the HIV group compared with those in the control group after adjustment for traditional risk factors for cardiovascular disease, although it is notable that the prevalence of CAC in this study (53.1% of men who had noncontrast CT scans and an Agatston score >0) was higher in both the HIV and control groups compared with earlier studies done in younger patients.

The most notable observation in Post and colleagues' study was the greater prevalence and extent of noncalcified plaque in the HIV-infected group compared with the control group, which is a difference that persisted after adjustment for traditional atherosclerosis risk factors. In addition, in the HIV-infected group, lower nadir $CD4^+$ T-cell count and longer duration of HIV treatment were associated with the presence and extent of noncalcified plaque. The latter observation may be due, in part, to a positive and novel finding of an interaction between age and noncalcified plaque. Because aging typically is associated with increases in CAC and calcified plaque, an increase in noncalcified plaque with increasing age among HIV-infected persons provides a potentially important pathophysiologic insight into the biology of atherosclerosis in HIV-infected persons. At least 3 independent groups reported higher rates of noncalcified coronary plaque, as measured by CT angiography, in HIV-infected persons, including women (5–7). Prior studies have consistently identified strong associations between higher levels of innate immune activation (as measured by soluble markers, such as sCD163) and cellular measures (such as $CD16^+$ monocytes) and noncalcified plaque. The association between lower nadir $CD4^+$ T-cell count and noncalcified plaque may reflect a longer duration of HIV infection and antiretroviral therapy and a greater degree of immune impairment. As noted by Post and colleagues, noncalcified plaque may represent a more vulnerable plaque and may contribute to the higher rates of myocardial infarction seen in patients with HIV.

Increased levels of innate immune activation among patients being treated for HIV infection are well-described (8); however, the drivers of this finding are not completely understood. Ongoing low-level HIV replication, microbial translocation, and inflammatory lipids are among the possible mediators. Important next steps for this research field include clarification of the relationships of CAC, noncalcified plaque, and their longitudinal changes with risk for cardiovascular disease events; confirmation of the association among noncalcified plaque, immune activation, and progression of atherosclerosis in longitudinal studies; and interventional trials designed to probe whether reducing innate immune activation in the setting of treated HIV infection delays progression of atherosclerosis. Several efforts, including studies using 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, low-dose methotrexate, and other anti-inflammatory agents are now in progress (for example, ClinicalTrials.gov trials NCT00965185, NCT01813357, and NCT01949116). Whether the increased prevalence of noncalcified plaque reflects an alteration in the process of arterial calcification during treatment of HIV infection and the relation of noncalcified plaque to myocardial infarction risk are other avenues for further investigation. A small autopsy study describing the histopathology of atherosclerosis in HIV identified dystrophic patterns of calcification in patients with AIDS (9) and highlights an area that deserves further evaluation.

As the global population of people living with HIV ages, we must continue to focus on prevention of long-term comorbid conditions. While we wait for results of longitudinal studies aimed at clarifying the mechanisms of

disease and identifying effective strategies for prevention, it is critical that we not lose sight of the importance of addressing well-established risk factors for cardiovascular disease in the HIV-infected population. Efforts to address smoking cessation, blood pressure control, and screening and treatment of lipid and glucose disorders need to remain at the forefront of our endeavors to ensure that the gains in the treatment of HIV infection translate into the most favorable long-term outcomes possible.

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