

# Inflammation, Immune Activation, and CVD Risk in Individuals With HIV Infection

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**A**NTIRETROVIRAL THERAPY (ART) PROLONGS LIFE, BUT individuals infected with human immunodeficiency virus (HIV) have a shorter life span than their uninfected counterparts and a greater than expected risk of cardiovascular disease (CVD).<sup>1,2</sup> Part of the increased CVD risk associated with HIV infection can be attributed to an increased burden of traditional risk factors such as cigarette smoking, as well as the effects of ART on lipids, insulin resistance, and body composition. However, increasing evidence suggests that chronic inflammation and immune activation may play key roles in HIV-associated CVD.

In individuals without HIV infection, markers of inflammation such as high-sensitivity C-reactive protein (CRP) and interleukin-6 predict CVD events and mortality. Similar although less robust findings have been described in individuals infected with HIV. In an observational study of 70 357 patients from Partners HealthCare, increased CRP levels and presence of HIV were independently associated with risk of acute myocardial infarction.<sup>3</sup> Compared with patients who had normal CRP levels and without HIV infection, the odds ratio for acute myocardial infarction was greater than 4-fold higher among patients with HIV and increased CRP levels.

In the Strategies for Management of Antiretroviral Therapy (SMART) study, interruption of ART was associated with greater mortality and CVD events compared with continuous ART, and higher levels of interleukin-6 and D-dimers were associated with all-cause mortality, suggesting that improvements in mortality in the setting of continuous ART may be mediated by a reduction in inflammation.<sup>4,5</sup> Furthermore, among treatment-naïve individuals infected with HIV, initiation of ART improved endothelial function within 4 weeks of treatment despite worsening lipids and the degree of improvement was associated with lower HIV RNA-1 levels.<sup>6</sup> Taken together, these findings suggest that immediately after initiation, ART reduces CVD risk by decreasing inflammation and viral replication, despite having adverse effects on traditional CVD risk factors. However, individuals receiving treatment who have suppression of HIV

replication have higher levels of inflammatory markers than uninfected individuals and persistent inflammation while taking ART appears to increase long-term CVD risk.

The factors that contribute to ongoing inflammation and immune activation in the setting of chronic, treated HIV infection are incompletely understood and likely are different than in individuals without HIV in whom inflammation is driven, in large part, by visceral adiposity and its associated metabolic abnormalities. Depletion of CD4 cells in gut mucosal lymphoid tissue occurs early in HIV infection and may contribute to ongoing microbial translocation. This process is not completely reversed with ART, even when HIV replication appears to be suppressed. Increased levels of lipopolysaccharide and soluble CD14 (sCD14) persist in some individuals with treated HIV infection, suggesting that intestinal microbial translocation may contribute to persistent immune activation. Furthermore, increased levels of sCD14 are associated with increased all-cause mortality and HIV disease progression, as well as more rapid progression of carotid atherosclerosis.<sup>7,8</sup> Other putative drivers of cellular activation and associated cytokine secretion include indirect effects of HIV gene products, direct infection of macrophages by HIV, and antigenic stimulation by latent viruses that are common in patients with HIV.<sup>9</sup> Immunological abnormalities that are affected directly by HIV infection such as current and nadir CD4 cell count have been independently associated with CVD risk, as have markers of immune activation and senescence.

In this issue of JAMA, Subramanian et al<sup>10</sup> describe for the first time imaging of arterial wall inflammation using <sup>18</sup>fluorine-2-deoxy-D-glucose positron emission tomography (<sup>18</sup>F-FDG-PET) in individuals with HIV. In a small cross-sectional study, the authors demonstrated that individuals with HIV but without known coronary artery disease have higher aortic uptake of FDG (expressed as the target-to-background ratio [TBR]) than risk factor-matched individuals without HIV, and have a level of aortic TBR similar to that of individuals without HIV with coronary artery disease. Patients with HIV infection had higher aortic TBR than controls even after adjusting for traditional CVD risk fac-

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tors, and in models stratified by presence or absence of coronary artery calcification, undetectable viral load, use of statins, and several other potentially confounding factors. The results of this study are novel, robust, and valid. That HIV infection is associated with arterial inflammation is not unexpected; both atherosclerosis and HIV infection are inflammatory diseases and previous studies have demonstrated associations between HIV infection and other subclinical vascular disease markers such as carotid intima-media thickness, brachial artery reactivity, and aortic pulse wave velocity. In this regard, the major scientific advance of this study may be the description of the association between aortic TBR and soluble CD163 (sCD163). Aortic arterial inflammation was found to be significantly correlated with sCD163 levels ( $P = .04$ ). Soluble CD163 is a marker of monocyte and macrophage activation that parallels levels of HIV-1 RNA before and after ART and is associated with indices of immune activation. Thus, the association between sCD163 and vascular inflammation described by Subramanian et al suggests that monocyte and macrophage activation may play a mechanistic role in HIV-associated CVD and that sCD163 may be a marker for CVD risk in the setting of HIV infection.

These findings contribute to an emerging evidence base for therapeutic strategies to reduce inflammation and immune activation (beyond ART) that may reduce CVD risk in patients with HIV. Hydroxychloroquine is an immunomodulatory and anti-inflammatory agent used for the treatment of autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis. Hydroxychloroquine interferes with T-cell activation and has both in vivo and in vitro anti-HIV properties. In this issue of *JAMA*, Paton et al<sup>11</sup> report results from a randomized trial that assessed the effects of hydroxychloroquine on immune activation and the rate of CD4 cell decline in 83 asymptomatic patients with HIV who were not receiving ART. The primary end point (percentage of CD8+ CD38+ DR+ T cells) did not differ between those patients treated and not treated with hydroxychloroquine. More concerning, individuals treated with hydroxychloroquine experienced greater declines in CD4 cell counts and also had evidence for increased HIV replication, which required more patients treated with hydroxychloroquine to initiate ART during the 48 weeks of the trial. Although the findings from this trial did not verify the concept that reducing immune activation could slow progression of HIV disease, the results do not exclude the possibility that hydroxychloroquine or other immunomodulators could reduce immune activation and inflammation in virologically suppressed patients receiving ART.

In this regard, it is important to consider disease states such as rheumatoid arthritis that, similar to HIV infection, are characterized by excess mortality and increased CVD risk in the setting of systemic inflammation. Methotrexate is a potent anti-inflammatory treatment that has been used safely in low doses in individuals with rheumatoid arthritis and

psoriasis. Among individuals without HIV, low-dose methotrexate reduces CRP and interleukin-6 levels, improves endothelial function, reduces progression of carotid atherosclerosis, and most importantly has been associated with reduced CVD risk and mortality.<sup>12</sup> The Cardiovascular Inflammation Reduction trial (NCT01594333) will enroll 7500 patients without HIV in a randomized clinical trial to evaluate the effects of low-dose methotrexate on the secondary prevention of CVD events and mortality among patients with prior CVD and persistent inflammation. In the setting of HIV, clinical trials that assess the safety of inexpensive and generally well-tolerated agents like low-dose methotrexate and their effects on CVD end points are needed to better understand the complex interrelationships between inflammation, immune activation, ART, and CVD risk. The articles by Subramanian et al<sup>10</sup> and by Paton et al<sup>11</sup> in this issue of *JAMA* set the stage for further interventions targeting inflammation and immune activation in patients with HIV.

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