Editorial

Inflammation and Fibrosis in HIV
Getting to the Heart of the Matter
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The treatment and disease course of HIV infection have changed dramatically since the discovery of HIV in 1983. AIDS, once the axiomatic cause of early death in HIV-infected individuals, has now become an uncommon complication among individuals treated with antiretroviral therapy (ART). However, with the success of ART comes new challenges for the HIV-infected, namely a substantial burden of cardiovascular disease (CVD). HIV infection is associated with high rates of CVD complications, including acute myocardial infarction,1 sudden cardiac death,2 and heart failure.3

See Articles by Luetkens et al and Ntusi et al

The mechanisms leading to CVD in HIV remain incompletely understood. HIV-infected individuals often have a greater burden of traditional cardiac risk factors, though such traditional risk factors alone do not nearly account for the observed increased risk. A wealth of research suggests that, paradoxically, chronic upregulation of inflammatory activity, which is present even among antiretrovirally treated and suppressed individuals, may play an important role in predicting mortality, CVD as well as other non-AIDS conditions.4–6 Although the hallmark of untreated HIV infection is an immunodeficient state, treated, virally suppressed HIV disease is associated with immune activation.7,8 Numerous potential causes are thought to contribute to this immune activation, including toxicity from ART, low-level viral replication, and disease-mediated shifts in inflammatory cell subsets, among other mechanisms. Delineation of the precise mechanisms underlying immune activation in HIV, as the driver of cardiovascular complications, is the focus of an increasing number of studies.

In line with the immunopathological hypothesis of CVD complications in HIV, several studies have clearly established the predictive value of inflammatory and coagulation biomarkers for CV events and mortality in HIV.9–11 Recent imaging studies have added to our understanding of the relationship between immune activation and atherosclerotic inflammation in HIV. In studies that used fluorine-18-fluorodeoxyglucose PET/contrast-enhanced computed tomography, individuals with HIV have been shown to have higher levels of atherosclerotic inflammation compared with noninfected controls.12,13 One such study showed that the atherosclerotic inflammation correlates with markers of monocyte activation. Subsequent studies showed an association between arterial inflammation and structural measures of coronary atherosclerosis, including the presence of high-risk morphological features.12 Furthermore, among HIV-infected individuals, immune activation and chronic inflammation persist and are thought to lead to collagen deposition and fibrosis of lymphoid tissue13; as fibrosis has been reported in other organs such as the liver14 as well as the myocardium. Myocardial fibrosis, which has been shown to be a consequence of several chronic inflammatory conditions as well as traditional cardiovascular risk factors,15 is characterized by an accumulation of collagen and has been identified as a contributor to diastolic dysfunction, heart failure, and sudden cardiac death.16 Indeed, ART-treated HIV as associated with a greatly increased incidence of myocardial fibrosis17 as well as both systolic and diastolic left ventricular (LV) dysfunction.18 However, the relationship between myocardial inflammation and fibrosis in HIV has been less well studied.

Cardiac magnetic resonance (CMR) can be used to measure many of the features needed to develop an improved understanding of myocardial fibrosis and inflammation in HIV. LV function and fibrosis are well characterized by CMR. Although CMR cannot directly measure myocardial inflammation, it can be used to build a case for its presence through circumstantial evidence. CMR can image several of the hallmark components of inflammation: hyperemia (early gadolinium enhancement), edema (T2-weighted imaging), and scar/necrosis (late gadolinium enhancement). Previous studies suggest that the diagnostic accuracy of acute myocarditis is improved when 2 of the 3 criteria are present, also known as the Lake Louise criteria.19 Accordingly, the 2 studies published in this issue of Circulation: Cardiovascular Imaging, which used CMR to study HIV-infected individuals, may help shed additional light on the relationship between HIV, inflammation, fibrosis, and CVD.

In the study by Luetkens et al,20 28 HIV-infected individuals with chronic HIV on antiretroviral medication with an HIV RNA <200 copies/mL underwent CMR and were compared with healthy controls.21 Authors found that HIV-infected individuals had lower ejection fraction and lower strain values. Of note, myocardial inflammation (native T1 relaxation times: 1128 ms versus 1086 ms, P=0.009; relative T2 signal intensity ratio: 1.6 versus 1.4, P=0.046, and early gadolinium enhancement ratio: 3.1 versus 2.1) and myocardial fibrosis were elevated among the HIV-infected individuals (82% versus 27%, P<0.001) when compared with controls. The patchy pattern
of myocardial fibrosis in HIV has been previously reported by several groups,17,21 who observe a pattern of fibrosis that is similar to that seen with other causes of myocarditis. Authors note that although the prevalence of fibrosis is higher in HIV, the difference in scar burden was low in both the studies, namely 2% to 3%. Although the study is small and descriptive in nature, it is the first to report myocardial inflammation using CMR tissue characterization in HIV. Although HIV has been described as a cause of myocarditis,22 detection of HIV in cardiac myocytes remains controversial.23 It is likely that the cardiac fibrosis and myocardial inflammation reported in the study by Luetkens et al23 resulted from chronic inflammation (as opposed to a direct effect of HIV on the heart).

The study by Ntusi et al24 provides additional evidence that treated HIV is associated with chronic myocardial inflammatory changes, including chronic subclinical myocardial edema and a high incidence of pericardial effusions. The investigators extend their previous study21 and report that compared with controls, HIV-infected individuals had lower (though still normal) LV ejection fraction, higher myocardial mass and lower peak diastolic strain rate, findings that are in-line with previous observations. Furthermore, the investigators make the novel observations that pericardial effusions and myocardial fibrosis are 3x to 4x more common in the setting of HIV. No differences were seen between ART-treated versus untreated individuals in CMR characteristics with the exception of higher LV ejection fraction (68% in ART treated versus 64% in ART naive, \( R^2 = 0.23, P = 0.03 \)). However, no associations were observed between imaging findings and: HIV medication, HIV RNA levels, CD4 nadir, or CD4 count.

The findings from both papers provide additional information to the field of HIV-associated CVD by applying CMR imaging parameters to describe subtle differences in myocardial tissue, which include myocardial edema, inflammation, fibrosis, and pericardial effusions. Authors suggest that chronic inflammation in the setting of treated HIV likely underlies the findings, which include structural and functional differences and high levels of fibrosis in the setting of treated HIV. Because patients from both studies were relatively young and asymptomatic, it is remarkable that subtle differences in myocardial inflammation and edema compared with uninfected individuals were found. Both studies also confirm the previous reports of high rates of myocardial fibrosis in HIV. Similar findings have been reported in other chronic inflammatory conditions, such as rheumatoid arthritis.25,26

Along with the CMR imaging findings come unanswered questions. First, authors note that the myocardial volumes, function and tissue characteristics overall are within the normal range among individuals with HIV, making the clinical impact of these findings unclear. Second, aside from high-sensitivity C-reactive protein no biomarkers or tissue samples that might shed some light on underlying mechanism of the CMR findings were performed. Similarly, aside from HIV infection in general, no definitive correlations between indices of HIV infection, chronic inflammation, or ART were uncovered in these studies. The 2 studies highlight the advantages of CMR in general over echocardiography with respect to reproducible measurements of ventricular volume and function, smaller sample size,28 and assessment of fibrosis, injury, and inflammation. Of note, markers of cardiac stress such as ST2 and cardiac inflammation, GDF-15 are associated with cardiac dysfunction and all-cause mortality in HIV.29

Taken together, these new reports extend previous observations and suggest that treated and suppressed HIV infection is associated with myocardial inflammation and fibrosis as well as LV dysfunction. These findings may represent important culprit responsible for the observed excess incidence of CV events seen in HIV infection—a hypothesis that will require larger studies, detailed biomarker analysis, and proof of concept clinical trials to definitively establish.

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References

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