The Broad Spectrum of HIV-Related Cardiovascular Disease*

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In recent years, there has been an explosion of knowledge regarding human immunodeficiency virus (HIV)-related cardiovascular disease (CVD). Contemporary studies have shown that in HIV-infected patients, rates of acute myocardial infarction are up to twice as high as in noninfected patients (1–4). Recent reports have also found that chronic inflammation and immune activation play a more dominant role in HIV-related CVD compared with CVD in the general population (5,6). Although the majority of recent studies on HIV-related CVD have focused on atherosclerosis, a growing body of published reports describes an array of contemporary cardiovascular complications associated with HIV, including sudden cardiac death, pulmonary hypertension (PH), and heart failure (7–11). In this issue of JACC: Heart Failure, Secemsky et al. (12) further contribute to our understanding of the broad spectrum of HIV-related CVD by showing that HIV-infected patients have significantly higher rates of diastolic dysfunction and PH. The authors also show for the first time a strong association between the cardiac biomarkers ST2 and growth differentiation factor (GDF)-15 and cardiac dysfunction and mortality in an HIV-infected cohort.

The higher rates of diastolic dysfunction in this relatively young group of HIV-infected patients may be due to a number of factors, including an increased rate of underlying occult coronary artery disease and possibly higher rates of cardiac fibrosis (12). Recent imaging studies have reported a high prevalence of myocardial fibrosis in asymptomatic HIV-infected patients (13). Cardiac fibrosis may also be increased in HIV-infected patients due to heightened inflammation, accelerated aging, and intensified oxidative stress from antiretroviral therapy (14–16). The strong association between higher levels of ST2 and diastolic dysfunction in this study also suggests the possibility of increased cardiac fibrosis, as ST2 is a mediator of this pathological process (17). In addition, the study findings highlight the possible therapeutic promise of interventions that attenuate cardiac fibrosis, such as aldosterone receptor antagonists and angiotensin receptor antagonists-neprilysin inhibitors, in patients with HIV, and highlight the need for future clinical trials testing these interventions in the HIV population (18).

Another important finding from the study by Secemsky et al. (12) was the significantly higher rate of PH in the HIV-infected group. Although HIV is a known cause of pulmonary arterial hypertension, the association of high rates of diastolic dysfunction and moderately elevated pulmonary pressures in this study suggest that the PH in this cohort may be due to cardiac dysfunction. A better understanding of the type of PH associated with HIV in the contemporary era may have important implications for clinical management and therapy, and this study highlights the need for further research describing the current manifestations of HIV-associated PH. This study also underscores the importance of screening for both diastolic dysfunction and PH in even young, asymptomatic, HIV-infected patients and suggests that checking the levels of biomarkers, such as ST-2, GDF-15, and N-terminal pro-B-type natriuretic peptide.
natriuretic peptide, might be considered a first-line step in screening for cardiac dysfunction, followed by echocardiography if biomarker levels are elevated.

The most novel finding from this study (12) is the observation that increasing ST2 and GDF-15 levels significantly predicted mortality in HIV-infected patients. In the analysis, with each doubling of ST2, there was a 104% increased risk of mortality. Similarly, there was a strong linear association between increasing levels of GDF-15 and death. The use of these biomarkers in clinical practice may help providers more accurately risk-stratify patients with HIV and better individualize diagnostic testing and medical therapy. Thus, the findings from this study have the potential to influence clinical management.

These results (12) also have the potential to improve the design and conduct of future clinical trials focused on HIV-related CVD. Major scientific gaps in HIV-related CVD identified during a recent National Heart, Lung, and Blood Institute AIDS Working Group included a paucity of clinical trials testing evidence-based cardiovascular therapies in HIV-infected patients and randomized studies evaluating novel therapies targeting the unique pathophysiology of HIV-related CVD (19). The use of ST2 and GDF-15 to enrich study populations may streamline future HIV-related CVD clinical trials by permitting smaller sample sizes. Developing strategies to efficiently design HIV-related CVD studies would be critical to expeditiously test a wide array of new cardiovascular therapies. In addition, because HIV-related CVD trials often focus on prevention, identifying high-risk, asymptomatic patients would be critical to reduce potentially large sample sizes and long follow-up periods. The use of ST2 and GDF-15 might also allow investigators to better identify high-risk study candidates who would potentially benefit the most from promising new interventions.

Perhaps most importantly, by highlighting the broad spectrum of HIV-related CVD, the study by Secemsky et al. (12) underscores why it is crucial for cardiovascular clinicians to become fully engaged in the care of patients with HIV. Expert cardiovascular care is needed to address not only HIV-related coronary artery disease but also heart failure, PH, and arrhythmias. In addition, the expertise, knowledge, and full engagement of cardiovascular investigators, as well as their collaboration and teamwork with HIV investigators and researchers from other disciplines, are critical to addressing the many recognized scientific gaps in HIV-related CVD and to identify future critical questions to further advance the field. The current study sets the stage for future research that could further describe the wide range of HIV-related CVD and for future trials in the HIV population to further test proven therapies as well as novel interventions. By providing important insights regarding the role of inflammation, fibrosis, and other pathophysiological processes, HIV-related CVD research has the potential to improve not only the lives of patients with HIV but also in all patients with CVD.

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