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EDITORIAL COMMENT

Myocardial Dysfunction With Contemporary Management of HIV

Prevalence, Pathophysiology, and Opportunities for Prevention*

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With the success of antiretroviral therapy (ART), long-term survival of patients living with HIV (PLHIV) worldwide has improved dramatically, and the population of PLHIV is aging. It was estimated in 2015 that a patient living with HIV survived to a median of 50 years of age (Online Ref. 1). In Massachusetts, 59% of PLHIV are now 50 years of age or older (Online Ref. 2). With patients' advancing age has come the recognition of HIV as a chronic disease with factors that promote remaining inflammation, including HIV-mediated immune activation, co-infection with other pathogens, and HIV-mediated breakdown of the intestinal mucosa with microbial translocation (Online Ref. 3). Mortality is still higher in PLHIV than in the general population, and excess mortality in PLHIV occurs now in large part due to noninfectious illnesses with major adverse cardiovascular events (MACE), including related myocardial infarction, and rates of stroke and death are estimated to be 2-fold higher in HIV patients than in those without HIV (Online Ref. 4). Coronary arterial disease is recognized as an inflammatory disorder, a finding directly applicable to PLHIV (Online Refs. 5,6). Conventional MACE risk algorithms used in the general population have not been found to accurately estimate cardiovascular risk in PLHIV (Online Ref. 7). To address this issue, the U.S. National Institutes of Health funded the 7,500-person REPRIEVE (Randomized Trial to Prevent Vascular Events in HIV [NCT02344290]) study to compare the efficacy of a statin strategy with that of placebo for primary prevention in PLHIV determined to be at low to moderate 10-year risk for MACE. A secondary endpoint will be incident heart failure hospitalization.

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It has long been recognized that HIV infection, particularly in the presence of AIDS, is associated with a high incidence of cardiomyopathy. Multiple causes have been proposed, including direct infection of the myocardium by the HIV virus, opportunistic infections, an autoimmune response, nutritional deficiencies, and specific ART that includes an early generation therapy using zidovudine (Online Refs. 8,9). In the current era of ART, the prevalence of left ventricular (LV) systolic dysfunction has declined (Online Refs. 8,9), and there is a greater recognition of the presence of diastolic dysfunction (Online Ref. 10). A recent, large U.S. Veterans Affairs study identified a higher incidence of both heart failure with reduced ejection fraction (HFrEF) and HF with preserved EF (HFpEF) in HIV-infected veterans than in veterans not infected with HIV after adjustment for multiple characteristics including conventional risk factors, findings that were still present, particularly for HFrEF, when evaluating just those patients with viral suppression or normalized CD4 counts (Online Ref. 11). When considering HF prevention strategies in PLHIV, assessment of different mechanisms of cardiac dysfunction needs to be considered, given the

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multiple unique factors in PLHIV, including regional differences in nutritional status or co-infections, availability and type of ART, degree of immune dysfunction, and aging of the HIV population, as reflected in more recent studies comparing older study populations.

To this end, the meta-analysis by Erquo et al. (1) addresses the challenging task of providing well-characterized prevalence rates that account for the many variables that may have opposing directionality with respect to cardiac dysfunction (i.e., aging of PLHIV and greater use of ART). Interesting findings from their meta-analysis includes the prevalence of asymptomatic LV systolic dysfunction in those studies of ART use >80% that is similar in prevalence to that estimated in general population cohorts (4.86; 95% confidence intervals [CIs]: 1.88 to 7.84 vs. 4.69; 95% CI: 2.29 to 7.09, respectively) (1,2). However, it is notable that PLHIV in these studies of high ART adherence were typically 2 to 3 decades younger than those included in the general population cohorts (2), suggesting biological differences despite similarities in overall rates of systolic dysfunction. Moreover, greater differences were found between rates of diastolic dysfunction with an increased relative risk of 3.0 for any grade of diastolic dysfunction in PLHIV compared to those in healthy controls. Notably, the analysis by Erquo et al. (1) demonstrates a prevalence rate of diastolic dysfunction that is higher than rates found in recent publications within the past several years, reinforcing the observation that more availability of ART and other management strategies directed at PLHIV may not be sufficient to ensure normal cardiac function, compared to those used in comparable, aged controls.

What mechanisms then may explain this high prevalence of systolic and diastolic dysfunction in contemporary cohorts of PLHIV being treated with ART? The first mechanism may be the common pathophysiology shared with accelerated atherosclerotic cardiovascular disease in the form of ongoing vascular inflammation. Using positron emission tomography imaging, aortic vascular inflammation remains unchanged despite initiation of successful ART and, thus, may contribute to vascular stiffening and diastolic dysfunction (3, Online Ref. 12). However, the impact of HIV-related vascular inflammation on vascular stiffness is controversial (Online Ref. 13). Second, cardiac magnetic resonance studies using late gadolinium enhancement have shown evidence of focal fibrosis and increased myocardial lipid content in PLHIV in the presence of a normal LVEF and adequate ART, compared to matched noninfected controls (Online Refs. 14,15). The present authors have shown that the soluble biomarker of subtle myocardial injury, high-sensitivity cardiac troponin T (hs-cTnT), was higher in PLHIV than in controls but was not associated with the presence of coronary plaque, suggesting myocardial injury is not the result of ischemic injury from epicardial plaque rupture (Online Ref. 16).

Other mechanisms may uniquely contribute to HFpEF in PLHIV. Recently the MESA (Multi-Ethnic Study of Atherosclerosis) trial identified a strong association between the extent of pro-inflammatory visceral adipose tissue (VAT) and incident HFpEF (4). This finding may be particularly germane to PLHIV, who frequently have fat redistribution with loss of subcutaneous fat (SAT) and/or VAT accumulation. The present authors have shown that increased VAT in PLHIV is associated with not only generalized inflammation markers such as high-sensitivity C-reactive protein but also with progressive myocardial injury, as measured using hs-cTnT (5). The present authors also previously showed in the MESA trial that higher hs-cTnT levels are associated with a higher prevalence of cardiac fibrosis, as measured by using cardiac magnetic resonance, in patterns not consistent with ischemic injury and with subsequent incident HF (Online Ref. 17). The mechanisms of the way in which increased VAT in PLHIV could result in progression to symptomatic HF are complex. The present authors showed that angiotensin II and aldosterone concentrations during a low-sodium diet are higher in PLHIV than in HIV-negative controls under similar conditions of sodium intake and are highly related to VAT in PLHIV but not in controls (Online Ref. 18). Furthermore, B-type natriuretic peptide levels remain suppressed in PLHIV compared to those in HIV-negative controls under conditions that stimulate renin-angiotensin-aldosterone system (RAAS) activation (Online Ref. 19). In a small pilot study comparing eplerenone with placebo in PLHIV, 6 months of eplerenone therapy resulted in a decrease in intramyocellular lipids and monocyte chemoattractant protein-1 with trends toward reduction in the generalized inflammatory biomarkers including C-reactive protein and interleukin-6 (Online Ref. 20). With the high prevalence of diastolic dysfunction in contemporary cohorts of PLHIV, the greater abundance of VAT, relative to that of SAT, and VAT's association with RAAS activation and cardiac injury make suppression or blockade of RAAS activity and augmentation of B-type natriuretic peptide a potentially attractive

target for preventing progression to incident HF in PLHIV. In summary, the meta-analysis by Erquo et al. (1) is an important step in defining the prevalence of pre-HF phenotypes in the contemporary management of an aging population of PLHIV, for whom symptomatic HF will become increasingly common. Similar to the prevention of atherosclerotic disease in PLHIV, development of prevention strategies for HF is an imperative for those infected with HIV to continue to enjoy hard-won victories to improve duration and quality of life.

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APPENDIX For an expanded list of references, please see the online version of this paper.