

EDITORIAL COMMENT

Cardiovascular Outcomes in Persons With HIV and Heart Failure

Medication Class or Suboptimal Viral Suppression?*



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Human immunodeficiency virus (HIV) infection is a global epidemic that currently affects 1.1 million people in the United States and 37 million people worldwide (1). The widespread use of combination antiretroviral therapy (cART) in persons with HIV (PHIV) has dramatically reduced deaths from opportunistic infections and improved survival (2). However, PHIV demonstrate higher rates of multiple chronic illnesses such as ischemic heart disease (3), as well as pulmonary hypertension and heart failure (HF) (4). HIV cardiomyopathy may result from direct viral toxicity, autoimmune response, myocarditis secondary to toxoplasmosis or cryptococcosis, HIV medications, nutritional deficiencies, and coronary artery disease (5). Most studies of cardiovascular risk have found higher risks of atherosclerotic cardiovascular disease in virally suppressed PHIV (3). Specifically, PHIV have higher rates of myocardial infarction (3), stroke, and sudden cardiac death (6). Although PHIV have a 50% higher relative risk of myocardial infarction after adjustment for traditional risk factors (3), when compared with controls, a recent study from Kaiser Northern and Southern California reported a decline in myocardial infarction risk that was attributed to a decline in use of protease inhibitor (PI) combination ART (cART) regimens and more attention to traditional risk factor management (7).

In this issue of the *Journal*, Alvi et al. (8) investigate cardiovascular mortality (primary endpoint) and 30-day HF readmission rate (secondary outcome) among PHIV (8). This retrospective single-center study included 394 ART-treated participants who

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were hospitalized for HF beginning in 2011. Cardiovascular events were stratified by treatment with PI and non-PI (NPI) cART regimens. After a mean follow-up of 2 years, the use of PI versus NPI was associated with higher cardiovascular mortality (35% vs. 17%; $p < 0.001$) and 30-day HF readmission (68% vs. 34%; $p < 0.001$). In multivariate regression analyses, the hazard ratio (HR) for cardiovascular mortality was 1.797 (95% confidence interval [CI]: 1.257 to 2.567; $p = 0.001$) in the PI group. The higher mortality risk was similar in the subset of 179 HF patients with reduced left ventricular ejection fraction (HR: 1.755; 95% CI: 1.063 to 2.741) and 172 patients with preserved left ventricular ejection fraction (HR: 2.013; 95% CI: 1.107 to 3.234). In addition to PI use, predictors of cardiovascular mortality included coronary artery disease (HR: 2.113; 95% CI: 1.512 to 2.971), higher pulmonary artery systolic pressure (HR: 1.083; 95% CI: 1.053 to 1.179), uncontrolled viremia (HR for HIV viral load: 1.332; 95% CI: 1.121 to 1.635), and immunosuppression (HR for CD4 count: 0.968; 95% CI: 0.955 to 0.957).

Although these results are intriguing, there are several important limitations to this study, including the following: 1) it consists of a retrospective analysis from a single site; 2) the absence of HIV cardiomyopathy diagnostic criteria (contrast magnetic resonance imaging findings of fibrosis, early gadolinium enhancement, myocardial edema) (9); 3) the lack of pathological specimens (endomyocardial biopsy) at the time of HF diagnosis; 4) serial change in clinical

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presentation; 5) low rates of viral suppression; 6) absence of data on adherence to cART and cardiovascular therapies (diet, exercise, medications); and 7) absence of serial measures of HF medications and biomarkers. Despite these limitations, this retrospective analysis provides novel insights into cardiovascular mortality in PHIV and the potential for certain cART regimens to contribute to acute HF decompensation.

Although mechanism cannot be deduced from observational studies, particularly in the absence of data obtained from myocardial imaging and pathological findings at the time of HF diagnosis, Alvi et al. (8) propose that ritonavir-boosted PI regimens cause an increase in myocardial fibrosis (10,11). However, on the basis of the presented data, we suggest that immune dysregulation and inflammation are also plausible mechanisms for the higher mortality seen in PHIV. In the study by Alvi et al. (8), uncontrolled viremia and immunosuppression were more common than would be expected for modern-day cohort studies in PHIV, and both would likely have biased clinicians to the increased use of PI over NPI-based ART regimens because at that time PI-based regimens were believed to be more potent and more robust than alternatives in the context of poor adherence. Furthermore, both uncontrolled viremia and immunosuppression were independently associated with higher HF mortality in multivariate analysis, a finding suggesting that they may have acted as important study confounders.

Chronic inflammation and disordered immune regulation, even among ART-treated and virologic-suppressed individuals, increases cardiovascular disease risk (12), and poorly controlled viremia drives much higher levels of inflammation. Proinflammatory cytokines (tumor necrosis factor [TNF]- α , interleukin [IL]-1, and IL-6) and cardiac autoantibodies are increased in patients with HIV cardiomyopathy (13). TNF- α and other inflammatory cytokines also increase myocardial expression of inducible nitric oxide synthase expression and cause myocyte apoptosis (14).

The causes of immune activation in poorly controlled HIV infection are multifactorial, including proliferation of HIV-specific and bystander T cells, reactivity of innate immune cells to HIV-encoded toll-like receptor (TLR) ligands, loss of immunoregulatory cells (15), and potentially HIV-associated coinfections. In addition, alterations in gut flora generate lipopolysaccharide and 16S ribosomal DNA (16S rDNA) that binds soluble CD14 and the myeloid differentiation-2 (MD-2) TLR4 complex. Ligation of TLR4 complex activates nuclear factor kappa B and production of the proinflammatory cytokines IL-1B, TNF- α , type 1 interferon, and IL-6 (16,17). Activation of M1-polarized macrophages, as defined by the expression of soluble cluster of differentiation 163 (sCD163), sCD14, and galectin-3 binding protein (Gal-3BP), was significantly associated with carotid artery disease in the Women's Interagency HIV Study (18), and tissue macrophage polarization itself is driven by TLR2 and TLR4 ligands, NOD-like (nucleotide-binding oligomerization domain) receptor activation of NLRP3 (NOD-like receptor family, pyrin domain containing 3) inflammasome, and T-helper cytokines (19,20).

This study by Alvi et al. (8) is intriguing and will prompt further investigations into HIV-associated HF. If possible, future studies should include PHIV with incident HF, the use of myocardial biopsy and specific biomarkers that allow for more precise diagnosis of the pathological and clinical features associated with HF, and serial measures of clinical and HF-specific biomarkers. In addition, data on medication adherence and viral suppression should be carefully collected because not only is medication adherence an important predictor of health outcomes among PHIV, but also differences by drug class may serve as important confounders for cardiovascular endpoints.

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