

Heart Failure With Reduced Ejection Fraction in Human Immunodeficiency Virus Infection

The More Things Stay the Same

Gerald S. Bloomfield, MD, MPH; G. Michael Felker, MD, MHS

Heart failure is a recognized complication of human immunodeficiency virus (HIV) infection dating back to the first case report in 1986.¹ Over the subsequent years, the prevailing view of heart failure (HF) in HIV infection has evolved significantly. It is commonly suggested and at least 1 review has shown that in the era of antiretroviral therapy (ART), systolic dysfunction has become less common than diastolic dysfunction in people living with HIV (PLWH).² Heart failure with reduced ejection fraction (HFrEF) and HIV-associated cardiomyopathies are thought to be pertinent mostly to PLWH in the era before widespread access to ART or in developing countries.³ In this issue of *JAMA Cardiology*, robust data from a large epidemiological study provide key insights into the contemporary epidemiology of HF in PLWH.⁴

Building on their previous work,⁵ the authors analyzed the electronic medical records of 98 015 HIV-infected and uninfected US veterans. All participants were free of cardiovascular disease at baseline. Heart failure status and events (median 7 years of follow-up) were defined by *International Classification of Diseases, Ninth Revision* codes, and echocardiogram reports were used to categorize patients with HF into HFrEF, HF with preserved ejection fraction (HFpEF), borderline HF, and unknown type of HF. The authors calculated total incidence for all types of HF and generated hazard ratios (HRs) for the association between HIV and risk for HF, with and without adjustment for other covariates. Commendable method choices include the use of time-updated CD4+ cell count and HIV-1 RNA level, as well as subgroup analyses according to age category and race/ethnicity.

Of the 2636 HF events, 941 were in PLWH and HFrEF was the single most common type (40%). Human immunodeficiency virus infection conferred a 41% increased risk (95% CI, 29%-54%) for total HF, with a stronger risk for developing HFrEF (HR, 1.61; 95% CI, 1.40-1.86) than HFpEF (HR, 1.21; 95% CI, 1.03-1.41). Risk for HF was greater among PLWH despite having a lower burden of traditional HF risk factors, including hypertension, diabetes, high low-density lipoprotein cholesterol level, and obesity. In subgroup analyses adjusted for numerous clinical variables, the HF risk was driven mainly by HFrEF for white, black, and young (<40 years of age) veterans. Consistently low CD4+ cell counts significantly increased the risk for HFrEF (HR, 1.87; 95% CI, 1.36-2.57) and HFpEF (HR, 1.87; 95% CI, 1.28-2.73), but CD4+ cell count greater than 500 cells/mm³ at baseline also portended greater HF risk (HR, 1.25; 95% CI, 1.08-1.43). Consistently detectable viremia increased the risk for HFrEF (HR, 1.63; 95% CI, 1.28-2.08), but not HFpEF. In a robust set of sensitivity analyses, the risk for HF attributed to HIV per-

sisted after restricting the data set to those without hypertension, alcohol or cocaine abuse, and never smokers and adjusted for incident myocardial infarction.

This study advances our knowledge on the spectrum of HIV-associated cardiovascular disease in important ways.⁴ First, the results challenge the notion that HFrEF has become an uncommon type of HF among PLWH in the ART era in a high-income country setting. Studies are yet needed to validate and replicate these findings in the general population. Nonetheless, both young and old appear to be at risk and HFrEF is the major HF manifestation among those younger than 40 years old. These individuals, now into their fifth and sixth decades, represent a vulnerable group for which HFrEF has received scant attention. From a public health standpoint, more attention should be paid to heighten awareness of the comorbidity of HIV and HFrEF in the aging HIV-positive population and to design approaches to incorporate HF screening, risk estimation, and treatment. Considering that by 2020 more than 50% of all PLWH will be older than 50 years old,⁶ there is a critical need to design and implement effective HF prevention strategies in this population. Recent data from randomized trials focusing on HF prevention in the general population could provide a useful template for designing effective prevention strategies in PLWH.^{7,8}

Second, immune system function is an important determinant of HF in HIV. This study supports prior epidemiological research⁹ that shows that restoring immune system function, as measured by CD4+ cell count, decreases HF risk. Thus, while we await empirical evidence, it is reasonable to initiate therapies early in the disease course to mitigate HF and total cardiovascular disease risk as some have suggested.¹⁰ Consistently detectable viremia increased the risk for HFrEF, but not HFpEF in this cohort. The potential reasons for the apparent differential effects of HIV viremia and CD4+ cell count on chronic inflammation and immune activation leading to different HF types. More work is needed in this area to validate, replicate, and put these findings in their appropriate context.

The study population represents a racially/ethnically diverse cohort (48% African American and 7% Hispanic).⁴ Such diversity is essential to the field if we are to address populations with the greatest burden of HIV in the United States and globally. Given the overlap in geographic, racial/ethnic, and sex disparities in HIV and HF in the United States (ie, overlap between Heart Attack Belt, HIV Belt, and HIV-positive African Americans in the US South), nationally and regionally representative studies will continue to be important to provide actionable epidemiology. In addition to the obvious limitations of using administrative data for such an analysis, the other major limitation is that there are virtually no women (approxi-



Related article page 536

mately 3%). Other cohorts in the United States have helped to fill in this gap.^{11,12}

The elephant in the room, which this study was not designed to address, is the mechanism by which HIV infection and its treatment impact HF risk. The HF risk identified in this study appears to be independent of hypertension and myocardial infarction, which are the 2 leading determinants of HF risk in the general population. The extent to which this risk is driven by direct effects on the myocardium vs more systemic effects (such as inflammation or vascular injury) are uncer-

tain. Can preclinical abnormalities be detected in PLWH using imaging (eg, myocardial strain imaging and diastolic dysfunction) or circulating biomarkers that predict incident HF? Which ART regimens are most “cardiac friendly”? Is the HFREF seen in the group younger than 40 years old reversible with appropriate HF and HIV therapy? Last, treatment patterns for HF among PLWH remain poor.¹³ Effective approaches to improve HF medication use patterns for this group have also not been demonstrated. On these issues, there is great need and opportunity for further knowledge generation.

ARTICLE INFORMATION

Author Affiliations: Duke Clinical Research Institute, Duke University, Durham, North Carolina.

Corresponding Author: Gerald S. Bloomfield, MD, MPH, Duke Clinical Research Institute, Duke University, 2400 Pratt St, Durham, NC 27705 (gerald.bloomfield@duke.edu).

Published Online: April 5, 2017.
doi:10.1001/jamacardio.2017.0282

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

REFERENCES

- Cohen IS, Anderson DW, Virmani R, et al. Congestive cardiomyopathy in association with the acquired immunodeficiency syndrome. *N Engl J Med*. 1986;315(10):628-630.
- Cerrato E, D'Ascenzo F, Biondi-Zoccai G, et al. Cardiac dysfunction in pauci symptomatic human immunodeficiency virus patients: a meta-analysis in the highly active antiretroviral therapy era. *Eur Heart J*. 2013;34(19):1432-1436.
- Bloomfield GS, Alenezi F, Barasa FA, Lumsden R, Mayosi BM, Velazquez EJ. Human immunodeficiency virus and heart failure in low- and middle-income countries. *JACC Heart Fail*. 2015;3(8):579-590.
- Freiberg MS, Chang C-CH, Skanderson M, et al. Association between HIV infection and the risk of heart failure with reduced ejection fraction and preserved ejection fraction in the antiretroviral therapy era: results from the Veterans Aging Cohort Study [published online April 5, 2017]. *JAMA Cardiol*. doi:10.1001/jamacardio.2017.0264
- Butt AA, Chang C-C, Kuller L, et al. Risk of heart failure with human immunodeficiency virus in the absence of prior diagnosis of coronary heart disease. *Arch Intern Med*. 2011;171(8):737-743.
- Brooks JT, Buchacz K, Gebo KA, Mermin J. HIV infection and older Americans: the public health perspective. *Am J Public Health*. 2012;102(8):1516-1526.
- Huelsmann M, Neuhold S, Resl M, et al. PONTIAC (NT-proBNP selected prevention of cardiac events in a population of diabetic patients without a history of cardiac disease): a prospective randomized controlled trial. *J Am Coll Cardiol*. 2013;62(15):1365-1372.
- Ledwidge M, Gallagher J, Conlon C, et al. Natriuretic peptide-based screening and collaborative care for heart failure: the STOP-HF randomized trial. *JAMA*. 2013;310(1):66-74.
- Pugliese A, Isnardi D, Saini A, Scarabelli T, Raddino R, Torre D. Impact of highly active antiretroviral therapy in HIV-positive patients with cardiac involvement. *J Infect*. 2000;40(3):282-284.
- Longenecker CT, Triant VA. Initiation of antiretroviral therapy at high CD4 cell counts: does it reduce the risk of cardiovascular disease? *Curr Opin HIV AIDS*. 2014;9(1):54-62.
- Feinstein MJ, Bahiru E, Achenbach C, et al. Patterns of cardiovascular mortality for HIV-infected adults in the United States: 1999 to 2013. *Am J Cardiol*. 2016;117(2):214-220.
- Janjua SA, Triant VA, Addison D, et al. HIV infection and heart failure outcomes in women. *J Am Coll Cardiol*. 2017;69(1):107-108.
- Al-Kindi SG, ElAmm C, Ginwalla M, et al. Heart failure in patients with human immunodeficiency virus infection: epidemiology and management disparities. *Int J Cardiol*. 2016;218:43-46.