Understanding Heart Failure Risk in a Diverse Cohort With Human Immunodeficiency Virus Infection

After 4 decades of study and numerous therapeutic advancements, human immunodeficiency virus (HIV) infection can today be considered and managed as a chronic disease, and in some parts of the world, the life expectancy of persons living with HIV (PWHs) is comparable to that of persons living without such infection. Since it was discovered in the early 1980s, HIV has been known to affect the heart. As PWHs are living longer, their burden of cardiovascular disease (CVD) and their clinical relevance have grown, raising important questions about the pathophysiologic process through which the HIV affects the heart despite optimal treatment with antiretroviral therapy (ART).

Infection with HIV has been associated with varied forms of CVD. Most attention has been directed toward atherosclerotic cardiovascular disease (ASCVD) in PWHs, attributable to a combination of the increased rates of traditional risk factors among PWHs, the untoward adverse effects of ART, and the effects of smoldering, long-term inflammation as a consequence of chronic infection. Pericardial and myocardial diseases, including myocarditis, have also been identified as manifestations of HIV infection, although some of these forms of CVD have decreased in prevalence with the advent of ART. A largely underrecognized type of CVD associated with HIV infection is heart failure (HF). Whereas many of the processes driving the heightened risk of HF in PWHs are likely to overlap with those conferring greater ASCVD risk, also implicated is evidence of myocardial fibrosis, steatosis, and increased left ventricular mass.

Considerable epidemiologic evidence describing the characteristics of PWHs and HF has emerged during the past 2 decades. In 2019, Erqou et al published a meta-analysis of 54 studies worldwide comprising 125,382 PWHs with a pooled incidence and prevalence of HF of 0.9 per 100 person-years and 6.5%, respectively. In North America, several major cohort studies have been published. Most recently, Feinstein et al described an 83% male cohort of 4640 PWHs and 4250 matched controls in which those with HIV infection were more than twice as likely to have HF after controlling for traditional risk factors (hazard ratio [HR], 2.10; CI, 1.38 to 3.21). Previously, the Veterans Aging Cohort Study, a 97% male cohort of 98,015 participants, reported that PWHs had 61% higher risk of HF with reduced ejection fraction (HFrEF), and this risk was particularly prominent in veterans younger than 40 years (HR, 3.59; CI, 1.95 to 6.58).

In this issue of Mayo Clinic Proceedings, Go et al present the HIV HEART Study, a retrospective cohort study of 38,868 PWHs and 386,586 age-, sex-, and race-matched persons without HIV infection observed for a median of 3.8 years. The study sample was young (mean age, 41±11 years), ethnically diverse (21.1% Black, 20.5% Hispanic, 3.9% Asian/Pacific Islander), and 12.3% female. The incidence of HF from 2000 through 2016, defined using a robustly validated approach, was 0.23 in PWHs compared with just 0.15 in those without HIV infection (P<.001). Importantly, Go et al also adjusted for ASCVD in their analysis by controlling for interim acute coronary syndrome events in addition to demographic characteristics, lifestyle factors, cardiovascular and medical history, and cardioprotective and other medications. The authors found that 3 demographic groups (women, Asian/Pacific Islanders, patients 40 years or younger) were associated with a 2.5-fold greater adjusted
The HIV HEART Study has 2 major strengths, its size and generalizability. This cohort study represents the largest analysis of HF trends in PWHs in recent times, including roughly 7000 more PWHs than in the Veterans Aging Cohort Study. Moreover, the contemporary US population living with HIV infection is 26% Hispanic, 19% female, and 2% Asian/Pacific Islander, close to the demographic profile of the cohort of Go et al (20.5% Hispanic, 12.3% female, 3.9% Asian/Pacific Islander). By contrast, the aforementioned study by Feinstein et al was composed of just 1.3% Hispanic and 0.04% Pacific Islander participants, and the Veterans Aging Cohort Study enrolled only 3% women. The representativeness of the HIV HEART Study lends generalizability to its findings, many of which confirm evidence from previous studies. Indeed, the adjusted HR for the incidence of HF in PWHs (HR, 1.63; CI, 1.47 to 1.81) is comparable to that of the Veterans Aging Cohort Study (HR, 1.58; CI, 1.37 to 1.82) and modestly lower than in the cohort of Feinstein et al (HR, 2.10; CI, 1.38 to 3.21). The subgroup analysis was also in agreement with the broader literature. Although Go et al present a cohort that is younger than in the Veterans Aging Cohort Study (41 vs 48 years), in both samples, PWHs younger than 40 years were at a roughly 2.5-fold greater risk of HF (HR, 2.45 [CI, 1.92 to 3.03] and *HR, 2.41 [CI, 1.60 to 3.63], respectively; *HR was even higher [HR, 3.59] when limited to HFrEF). This observation is supported by other recent retrospective observational studies as well. A sex-related disparity has also been observed in the HF incidence in this population, with female PWHs being at a 1.5-fold greater risk of HF compared with matched male PWHs, as was the case in the HIV HEART Study. Last, in contrast to the study by Feinstein et al, the HIV HEART Study was adequately powered to allow commentary on risk among PWHs stratified by HF subtype. Whereas PWHs demonstrated an elevated rate of HFrEF similar to that found in the Veterans Aging Cohort Study, the adjusted rate of HFrEF was higher in the HIV HEART Study (HR, 1.76 [CI, 1.44 to 2.16] vs 1.21 [CI 1.03 to 1.41]), although it must be noted that in the past, HFrEF may have been under-diagnosed and its clinical relevance underestimated. This may pose limitations in analyzing old registries.

Suboptimal viral control in PWHs has been associated with HF risk. In the cohort of Go et al, 20.5% (7973) of the 38,868 PWHs were known to have a baseline HIV RNA viral load less than 500 copies/mL, whereas viral load data were missing for 50% of the PWHs, and only 17.1% of PWHs were receiving baseline ART. It was not clarified whether those PWHs with such high proportions of missing data for viral load and CD4 count (43.2%) and untreated status (not receiving ART) could have been due to patients’ refusing therapy, delays in ART initiation, patients’ receiving care for their HIV infection outside of the network covered by the registries used, or other factors.

By contrast, in the cohort of Feinstein et al, 53.5% of PWHs had a viral load of less than 500 copies/mL, and almost twice as many PWHs were receiving baseline ART (33.7%), suggesting better care. What is more, 73.4% of participants in the Veterans Aging Cohort Study received baseline ART. Importantly, several studies show that higher viral loads are associated with HF risk in PWHs, although even those with a suppressed viral load are still at an increased risk of HF compared with controls without HIV infection. Whereas the HIV HEART Study controlled for ART in their analysis, there seemed to be no adjustments made for CD4 count or viral load, both of which are important future considerations given the association between viral control and HF risk, in addition to the considerable inter-cohort variation in RNA viral loads and ART adherence. In addition to these limitations, the HIV HEART Study included significant differences in baseline characteristics and comorbidities between people with and people without HIV infection (body mass
index, liver disease, proteinuria, depression, use of recreational drugs and alcohol), although these confounders were adjusted for in regression models.

Go et al did not comment on mortality outcomes in patients with and without HF; this will be an important next step as it may elucidate differences in the pathophysiologic process of HF between PWHs and non–HIV-infected persons. Looking forward, one may also consider examining how the CD4 nadir affects the HF risk profile in PWHs as this variable has been found to be a potent predictor of HIV-associated neurocognitive impairment and implicated in endothelial cell dysfunction.\(^\text{12,13}\) It may also be worth investigating a potential relationship between the risk of HF and time since HIV infection and viral load over time rather than at a specific time point, if possible accounting for ART.\(^\text{14}\)

Much attention has been directed toward the association between HIV infection and CVD, yet the specific field of HF in PWHs remains underexplored. Go et al elegantly add to the current body of knowledge by presenting the largest and most representative epidemiologic study to date characterizing the interplay between age, sex, and race/ethnicity with respect to HF in PWHs.

Christian Faaborg-Andersen, BS
Emory University School of Medicine
Atlanta, GA

Adrian daSilva-deAbreu, MD, MSc, PhD(c)
Heart and Vascular Center
Yale-New Haven Hospital
Section of Cardiovascular Medicine
Yale University School of Medicine
New Haven, CT

Hector O. Ventura, MD
John Ochsner Heart and Vascular Institute
Ochsner Medical Center
New Orleans, LA

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Correspondence: Hector O. Ventura John Ochsner Heart and Vascular Center 1514 Jefferson Highway New Orleans, LA 70121-2483 (hventura@ochsner.org).

ORCID
Christian Faaborg-Andersen: https://orcid.org/0000-0002-9134-4671; Adrian daSilva-deAbreu: https://orcid.org/0000-0002-6739-5946; Hector O. Ventura: https://orcid.org/0000-0002-9869-9600

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