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STATE-OF-THE-ART REVIEW

Human Immunodeficiency Virus and Heart Failure in Low- and Middle-Income Countries

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ABSTRACT

Successful combination therapy for human immunodeficiency virus (HIV) has transformed this disease from a short-lived infection with high mortality to a chronic disease associated with increasing life expectancy. This is true for high- as well as low- and middle-income countries. As a result of this increased life expectancy, people living with HIV are now at risk of developing other chronic diseases associated with aging. Heart failure has been common among people living with HIV in the eras of pre- and post- availability of antiretroviral therapy; however, our current understanding of the pathogenesis and approaches to management have not been systematically addressed. HIV may cause heart failure through direct (e.g., viral replication, mitochondrial dysfunction, cardiac autoimmunity, autonomic dysfunction) and indirect (e.g., opportunistic infections, antiretroviral therapy, alcohol abuse, micronutrient deficiency, tobacco use) pathways. In low- and middle-income countries, 2 large observational studies have recently reported clinical characteristics and outcomes in these patients. HIV-associated heart failure remains a common cardiac diagnosis in people living with heart failure, yet a unifying set of diagnostic criteria is lacking. Treatment patterns for heart failure fall short of society guidelines. Although there may be promise in cardiac glycosides for treating heart failure in people living with HIV, clinical studies are needed to validate in vitro findings. Owing to the burden of HIV in low- and middle-income countries and the concurrent rise of traditional cardiovascular risk factors, strategic and concerted efforts in this area are likely to impact the care of people living with HIV around the globe. (J Am Coll Cardiol HF 2015;3:579–90)

People living with human immunodeficiency virus (PLHIV) around the globe and taking antiretroviral therapy (ART) now achieve a near-normal life expectancy (1,2). As a consequence, PLHIV increasingly experience the chronic diseases of aging. Of particular concern is the risk of coronary artery disease, myocardial infarction, and heart failure (HF) among PLHIV, as observed in North American, European, and Australian HIV cohorts (3–9). Sub-Saharan Africa (SSA), which accounts for 12% of the global population, is disproportionately affected by HIV, with 69% of all adults and 90% of all children living with HIV residing here (10). Cardiovascular manifestations of HIV infection in SSA have

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ABBREVIATIONS AND ACRONYMS

ADHF = acute decompensated heart failure

AIDS = acquired immunodeficiency syndrome

ART = antiretroviral therapy

AZT = zidovudine

DNA = deoxyribonucleic acid

EF = ejection fraction

HF = heart failure

LMICs = low- and middle-income countries

LVSD = left ventricular systolic dysfunction

PLHIV = people living with human immunodeficiency virus

RNA = ribonucleic acid

SSA = sub-Saharan Africa

Tat = transactivator of transcription

been reported for more than 25 years, but most of the reports are prior to 2004 when ART became widely available (11).

Prior to the advent of ART, studies supported a relationship between HIV and left ventricular (LV) dysfunction. Numerous terms were used to describe the syndrome, including HIV-associated cardiomyopathy, HIV-associated HF, and HIV-associated LV dysfunction. As initially described, HIV-associated HF was related to severe immune system compromise, had no specific therapy, and had a median survival of 101 days after diagnosis (12–15). Concurrent shifts in epidemiological patterns of HIV treatment and cardiovascular diseases produced a complex and evolving relationship between HF and HIV that merits a contemporary review. Most reports related to HF are focused on high-income countries (16) and are misaligned with the global predominance of HIV in low- and middle-income countries (LMICs) (**Figure 1**) (11,17–21). In this review, we summarize the epidemiology, approach to diagnosis, therapy, and prognosis of HIV-associated HF in LMICs in the ART era. Our review of the publications was accomplished by searching PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials for studies published through 2014. We used the following terms as keywords and subject headings: human immunodeficiency virus, heart failure, cardiomyopathy, echocardiography, antiretroviral therapy, low- and middle-income countries, developing countries, and each of the countries in the World Bank low- and middle-income groups. We included studies that report HF characteristic of HIV-infected individuals in LMICs receiving ART. Studies were excluded if the abstract was not available in English. Data extraction (e.g., year of study, location, study description, and findings) was performed and confirmed by 2 investigators (F.A., G.S.B.). In the present discussion we use the terms "HIV-associated HF" or "HF in PLHIV" to describe the syndrome of HF, including diastolic dysfunction, and use the term "HIV-associated left ventricular systolic dysfunction" (LVSD) only when discussing asymptomatic ventricular dysfunction or to describe heart muscle disease. Owing to the heterogeneity of definitions of HF in HIV, we defined HF according to the criteria proposed in each study. This represents the state of published reports. We ultimately propose a framework to invigorate research that will inform best-care practices for patients with HIV-associated HF in LMICs and the rest of the world.

CAUSES OF HIV-ASSOCIATED HF

There is no unifying definition of HIV-associated HF, and it is often a diagnosis of exclusion (22–25). This is due to the knowledge gaps regarding the causes of HF in PLHIV; however, there are a number of prevailing hypotheses (**Figure 2**) (21,26–29). Reports from high-, low-, and middle-income countries have shed light on the probable causes.

HIV VIRAL REPLICATION. One hypothesis implicates direct myocardial viral toxicity. HIV ribonucleic acid (RNA) concentrations ≥500 copies/ml are associated with a nearly 2.5-fold increased risk of developing HF compared with HIV-uninfected individuals (6). Targeted myocardial transgenic expression of HIV transactivator of transcription (Tat) protein activates endothelial cells, causing left ventricular systolic dysfunction (LVSD), increased LV mass, and expression of natriuretic peptides in mice that may lead to hemodynamic compromise (30). How and whether HIV directly damages cardiac myocytes, which do not possess CD4 receptors, have been hotly debated (31–33). In vitro studies of human and rat cardiac myocytes show that HIV can enter cardiac myocytes through pathways independent of CCR5 or CXCR4 receptors (32,34).

MITOCHONDRIAL INJURY. HIV may impair cardiac function through mitochondrial pathways. HIV infection initiates a mitochondrion-mediated cascade, releasing proteases that lead to cardiac myocyte damage and apoptosis (35). Tat protein also disrupts mitochondrial membrane permeability (36). The complete pathway between HIV infection and LVSD remains unclear. To date, a clear genetic predisposition does not appear to play a major role, as 1 specific mitochondrial deoxyribonucleic acid (DNA) polymorphism, mtDNA T16189C, is not more common in patients with HIV and HF than in HIV-infected controls without HF in South Africa (37).

OPPORTUNISTIC INFECTIONS. In SSA, there have been 2 studies examining myocardial biopsy specimens among patients with HIV-associated LVSD. In a 1998 postmortem study of 16 patients with HIV/acquired immune deficiency syndrome (AIDS), myocarditis was attributed to HIV (50%) and infection by *Toxoplasma gondii* (19%), *Cryptococcus neoformans* (19%), and *Mycobacterium avium intracellulare* (13%) (38). An antemortem study of patients compared analyses of endomyocardial biopsy specimens among HIV-associated HF patients (n = 14), HIV-uninfected