Heart failure in persons living with HIV infection

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Purpose of review
To discuss presentation, pathophysiology, complications, and treatment of heart failure in persons living with HIV (PLWHIV) in the antiretroviral therapy (ART) era.

Recent findings
Since the advent of effective ART and improved longevity, heart failure has become more chronic and insidious and is often characterized by preserved ejection fraction, diastolic dysfunction, and left ventricular (LV) hypertrophy. The mechanism underlying heart failure in the setting of HIV infection remains unknown. A high burden of coronary risk factors is often present in PLWHIV, and clinical manifestations of coronary disease appear at a younger age compared with uninfected persons. Heart failure is more common in the year following myocardial infarction in HIV-infected compared with uninfected patients. Epidemiological data suggest the incidence of atrial fibrillation in PLWHIV is increasing, likely due to advancing age and increasing rates of LV hypertrophy in this population. The treatment of heart failure in PLWHIV is extrapolated from treatment of uninfected patients, as clinical trials have not been done specifically in HIV.

Summary
Symptoms of heart failure or echocardiographic evidence of cardiomyopathy increase the risk of death in PLWHIV. Additional studies are needed to ascertain if HIV-specific issues such as newer ART, chronic inflammation/immune activation, illicit drug use, and early initiation of ART are implicated in heart failure pathogenesis.

Keywords
antiretroviral therapy, atrial fibrillation, heart failure, HIV infection, left ventricular hypertrophy

INTRODUCTION

Heart failure is common among persons living with HIV (PLWHIV) infection and portends a poor prognosis [1]. Heart failure in PLWHIV changed drastically with the advent of highly effective antiretroviral therapy (ART) and is now much different among persons receiving or not receiving ART, as summarized in Table 1. In the pre-ART era, HIV-associated cardiomyopathy was expressed as symptomatic, systolic dysfunction with left ventricular (LV) dilatation and was seen almost exclusively in patients with advanced HIV disease and AIDS. This type of heart failure is still common in geographic areas where ART is not widely available (which will be covered in another article in this series). The incidence of this type of HIV-associated cardiomyopathy has decreased dramatically from the pre-ART era, from 25.6 cases per 1000 person-years to 3.9 cases, according to one recent review [1].

In contrast, in the current era, the diagnosis of heart failure includes many more asymptomatic PLWHIV, and often refers only to systolic or diastolic dysfunction detected by echocardiography. In a recent cohort study of 98 015 uninfected and HIV-infected veterans, 2636 heart failure events occurred over 7.1 years of follow-up [2▪▪]. Heart failure with preserved ejection fraction (HFpEF) accounted for 34.6% of these, borderline HFpEF accounted for 15.5%, heart failure with reduced ejection fraction (HFrEF) for 37.1%, and heart failure of unknown type for 12.8%. Compared with uninfected veterans, HIV-infected veterans had an increased risk of HFpEF [hazard ratio 1.21; 95% confidence interval (CI) 1.03–1.41], borderline HFpEF (hazard ratio 1.37; 95% CI 1.09–1.72), and HFrEF (hazard ratio 1.61; 95% CI 1.40–1.86). Higher viral loads and lower CD4 counts were associated with heart failure in PLWHIV. These data provide a helpful current snapshot of heart failure

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KEY POINTS

- Heart failure in PLWHIV changed drastically with the advent of highly effective ART and is now much different among persons receiving or not receiving ART.
- In the pre-ART era, HIV-associated cardiomyopathy was expressed as symptomatic, systolic dysfunction with LV dilatation and was seen almost exclusively in patients with advanced HIV disease and AIDS; in contrast, in the current era, the diagnosis of heart failure includes many more asymptomatic PLWHIV and often refers only to systolic or diastolic dysfunction detected by echocardiography.
- Heart failure in PLWHIV who are receiving ART are older and carry a high cardiovascular risk factor burden, with high prevalence of hypertension, smoking, dyslipidemia, diabetes, and the metabolic syndrome.
- In PLWHIV, ART itself has both adversely increased the risk of heart failure as well as played an important role in the prevention of heart failure; still patients with cardiomyopathy and heart failure who have not received ART should receive this intervention.
- Treatment recommendations for heart failure in PLWHIV are based upon trials done in uninfected heart failure patients; however, additional studies are needed to ascertain if HIV-specific issues such as newer ART, chronic inflammation/immune activation, illicit drug use, and early initiation of ART are implicated in the development of CHF in HIV.

with HIV but the mechanism underlying these findings in HIV remain unknown.

PATHOPHYSIOLOGY OF HEART FAILURE IN PERSONS LIVING WITH HIV WITHOUT ANTIRETROVIRAL THERAPY

The pathophysiology of HIV-associated cardiomyopathy is multifactorial, with proposed causes including direct HIV infection of the myocardium with or without myocarditis, coinfection with other viruses such as Coxsackie virus B3 and cytomegalovirus, opportunistic infections, and nutritional disorders. Infection of the heart with the HIV causes impaired systolic function. HIV gene products, such as tat, probably also contribute. Proinflammatory cytokines such as tumor necrosis factor and IL-1ß have also been shown to depress LV systolic function. In sub-Saharan Africa and other poor areas, nutritional deficiencies may contribute to HIV-associated cardiomyopathy. Selenium deficiency has been reported in PLWHIV and is associated with a cardiomyopathy in China termed Keshan disease [1].

LEFT VENTRICULAR HYPERTROPHY IN PERSONS LIVING WITH HIV

LV hypertrophy is more common in HIV-infected patients than in controls. In our study, HIV-infected participants had a mean 8 g/m^2 larger LV mass index compared with controls ($P = 0.001$) [3]. Higher LV mass index was independently associated with lower nadir CD4 T-cell count, suggesting that immunodeficiency might play a role in this process. After adjustment for age and traditional risk factors, HIV patients were 2.4 times more likely to have diastolic dysfunction than controls. Overall, 50% of PLWHIV had diastolic dysfunction compared with 29% of uninfected controls.

Another study compared LV mass in patients with and without HIV infection, and with and without hypertension [4]. In normotensive and in hypertensive patients, the HIV-infected group had greater LV mass and more diastolic dysfunction compared with uninfected controls. In older data from the Framingham Study, electrocardiographic evidence of LV hypertrophy was shown to be a strong predictor of cardiovascular death [5]. In our study of PLWHIV, diastolic dysfunction predicted sudden cardiac death (SCD) (hazard ratio 14.8, 95%

Table 1. Features of heart failure in persons living with HIV according to treatment status

	Untreated PLWHIV	PLWHIV receiving ART
Prevalence	Decreasing with increased ART availability	Increasing with improved survival of PLWHIV
Type of HF	Mainly systolic	More often HF with preserved EF
Cause	HIV ± opportunistic infections, inflammatory, and nutritional deficiencies	CAD, LVH, or both
Time course	Acute	Chronic
Treatment	ART + standard HF care	Standard HF care
Prognosis	Poor without ART	Similar to HF in persons without HIV

ART, antiretroviral therapy; CAD, coronary artery disease; EF, ejection fraction; HF, heart failure; LVH, left ventricular hypertrophy; PLWHIV, persons living with HIV.

CI 4.0–55.4, $P < 0.001$), but not as strongly as depressed ejection fraction [6].

PATHOPHYSIOLOGY OF HEART FAILURE IN PERSONS LIVING WITH HIV RECEIVING ANTIRETROVIRAL THERAPY

In contrast to heart failure occurring in PLWHIV not receiving ART, in which the course of the disease plays out over weeks or months, heart failure in PLWHIV who are receiving ART covers a more prolonged course. These patients are older and carry a high cardiovascular risk factor burden, with high prevalence of hypertension, smoking, dyslipidemia, diabetes, and the metabolic syndrome. High alcohol consumption in some PLWHIV may also contribute to heart failure. Similar to recent reports that more than 40% of reported myocardial infarctions (MI) in HIV are actually Type II or demand related as opposed to true atherothrombotic disease [7], it is possible that unrecognized alcohol abuse and/or cocaine or meth abuse contributes to cardiomyopathy in HIV.

Some types of ART adversely affect glucose and lipid metabolism and thus indirectly increase the risk of heart failure. In addition, zidovudine (AZT), a nucleoside reverse transcriptase inhibitor, causes a dose-dependent skeletal and cardiac myopathy that has been attributed to mitochondrial toxicity and has the potential to impair LV function directly [1]. ART has been blamed for the otherwise unexplained LV hypertrophy that is seen in PLWHIV.

On the other hand, ART plays an important role in the prevention of the type of heart failure described above that was so common in the pre-ART era. Recent evidence also suggests that specific types of ART are associated with a lower risk of developing heart failure. In a cohort of 21 435 PLWHIV in the veterans affairs system, 438 incident heart failure events occurred over a median follow-up of 5.4 years. Heart failure risk was markedly lower in current tenofovir disoproxil fumarate (TDF) users (hazard ratio = 0.68; 95% CI 0.53–0.86) compared with never users [8▪]. Speculation as to why TDF might reduce the risk of heart failure includes the possibility that it improves viral control and thus reduces inflammation, or that it might be related to the lipid-lowering effect of TDF. Further studies are needed to confirm this beneficial effect of TDF in heart failure.

Coronary artery disease is an important contributor to heart failure in PLWHIV, as it is in other populations. Survivors of MI with HIV infection are on average a decade younger compared with uninfected post-MI patients and thus have better short-term survival, as age is such an important predictor of mortality post-MI. However, in an age-matched and sex-matched analysis from a large contemporary French database, hospitalizations for heart failure were more common during 1 year of follow-up in HIV-infected compared with uninfected patients, 3.3 versus 1.4%, ($P = 0.02$) [9]. HIV status was an independent predictor of heart failure in this post-MI cohort. Significantly, newer biomarkers often used in heart failure such as ST2 as well as markers of fibrosis such as GDF-15 are higher among HIV-infected individuals; in addition, these markers are associated with structural abnormalities on echo and are better predictors of mortality in HIV [10▪].

Table 2. Cardiac MRI results in persons living with HIV compared with uninfected controls

	Control patients, $n = 92$	HIV-Infected patients, $n = 103$	*P* value
LVEDV indexed (ml/m^2)	78 ± 14	76 ± 14	0.39
LVESV indexed (ml/m^2)	22 ± 7	25 ± 8	0.02
LVEF (%)	72 ± 5	68 ± 6	<0.001
LV mass indexed (g/m^2)	54 ± 11	58 ± 11	0.02
Pericardial effusion	19 (21%)	58 (57%)	<0.001
Late-gadolinium enhancement	15 (16%)	84 (83%)	<0.001

LV, left ventricular; LVEDV, left ventricular end diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume. Adapted from [11▪▪].

Cardiac MRI provides insight into the subtle LV abnormalities that contribute to heart failure in PLWHIV. A recent study compared the results of cardiac MRI between 103 PLWHIV without known cardiovascular disease, mean age 45 ± 10 years, and 92 uninfected controls of a similar age [11▪▪]. As shown in Table 2, LV ejection fraction, while still in the normal range, was 6% lower and LV mass was 7% higher in the HIV-infected patients. A pericardial effusion was present in more than half of the PLWHIV, much more common than the frequency in controls. Late-gadolinium enhancement, a marker of myocardial fibrosis was observed in 83% of HIV-infected patients and 16% of uninfected controls. Examples of an HIV-infected and a control patient from this study are shown in Fig. 1. As fibrosis in the general population is associated with SCD, whether or not higher levels of myocardial fibrosis underlie SCD in the setting of HIV remains unknown [12].

ATRIAL FIBRILLATION IN PERSONS LIVING WITH HIV

Advanced age and LV hypertrophy are strong risk factors for the development of atrial fibrillation, so it is not surprising that the incidence of atrial

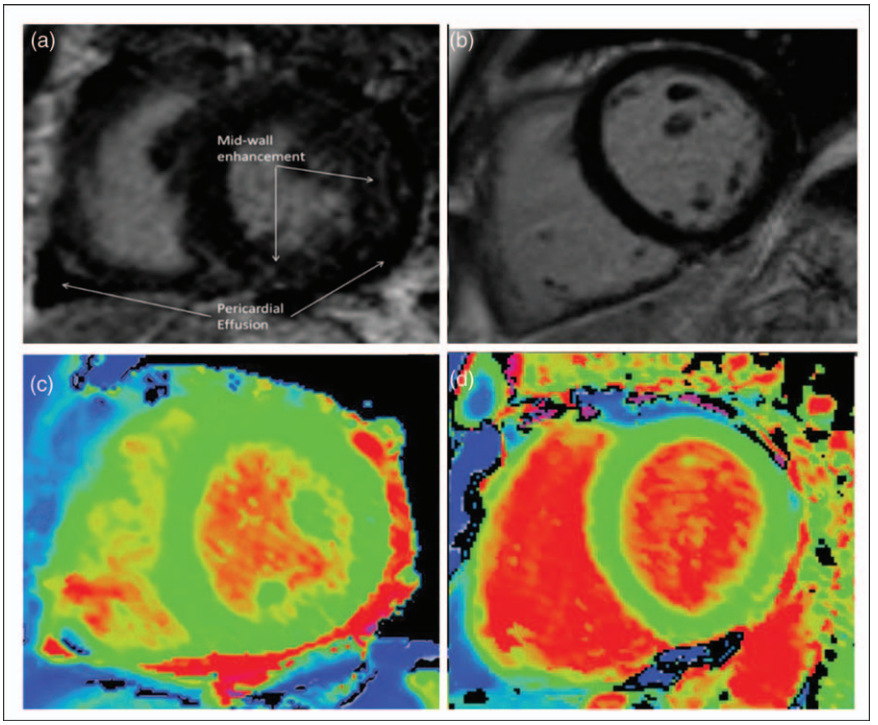

FIGURE 1. Pericardial effusions, late-gadolinium enhancement, and native T1 mapping in HIV-infected individuals and controls. (a) Cine image from a patient with HIV, with arrows demonstrating midwall fibrosis and a small pericardial effusion, compared with a normal control patient (c). (b) The corresponding T1 map, from a patient with HIV, with associated pericardial effusion (red) compared with a normal control patient (d). Adapted with permission from [11▪▪].

fibrillation is rising as PLWHIV in the ART era age. In a national sample of 30 533 HIV-infected veterans followed in the Veterans Affairs HIV Clinical Case Registry from 1996 to 2011, 780 (2.6%) patients developed atrial fibrillation during a median follow-up of 6.8 years [13]. Markers of HIV disease severity, specifically low CD4 count and high viral load, were independently associated with development of atrial fibrillation, as were older age, white race, coronary disease, heart failure, alcoholism, proteinuria, reduced kidney function, and hypothyroidism.

Drug treatment of atrial fibrillation aims to control the ventricular rate to preserve exercise tolerance, and in patients at high risk, to prevent embolic events. Drugs commonly used for rate control (digitalis, diltizem, and verapamil) are metabolized by the same hepatic enzyme system as some forms of ART. Caution is therefore warranted in dose selection, and a dose adjustment of ART may be indicated. Scores to assess embolic risk have not been validated in PLWHIV who have atrial fibrillation, but recent studies suggest that these thrombotic risk calculators do not perform well in the setting of HIV (Chau, K, JAIDS in press). Newer anticoagulants have not been well studied in PLWHIV. Atrial fibrillation increases a pill burden that may already be onerous and nearly intolerable for some PLWHIV.

TREATMENT OF HEART FAILURE

Treatment recommendations for heart failure in PLWHIV are based upon trials done in uninfected heart failure patients and from guidelines based upon these trials [1]. Thus, angiotensin-converting enzyme inhibitors, β-blockers, and aldosterone antagonists should be used, although trials of these drugs have not been done in PLWHIV with heart failure.

ART is not specific therapy for heart failure; however, the incidence of heart failure declined dramatically after the introduction of ART. Whether ART can reverse heart failure caused by an established cardiomyopathy is not known. On the other hand, ART drugs such as AZT have direct myocardial toxicity, and ART may accelerate coronary atherosclerosis, ultimately leading to LV dysfunction. The role of inflammation and immune response in HIV-associated heart failure is highlighted by a study in HIV-infected children with LV dilation, in which better LV contractility was seen in those with higher endogenous IgG levels and those treated with intravenous immunoglobulin [14]. However, in the

absence of HIV-specific trials, using the same guidelines and therapies to treat congestive heart failure (CHF) among individuals with HIV appears reasonable. These medications include ACE-inhibitors, beta blockers, digoxin, aldactone, biventricular pacemakers, and AICDs. Although many studies have highlighted echocardiographic abnormalities in the setting of HIV, the utility of screening asymptomatic individuals with HIV remains uncertain.

Heart transplantation with excellent long-term survival has been reported in small numbers of HIV-infected patients [1]. The fear that immunosuppression in such patients might lead to AIDS has proved unfounded, and the notion that HIV infection should be a contraindication to cardiac transplantation is no longer tenable.

PROGNOSIS

HIV-associated cardiomyopathy with heart failure in the pre-ART era carried a grim prognosis. In one study, median survival among patients with AIDS and cardiomyopathy was 101 days compared with 472 among patients with AIDS alone [15]. In another study, the adjusted hazard ratio for patients with cardiomyopathy associated with AIDS was 5.86 compared with patients with idiopathic cardiomyopathy [16].

Since the advent of ART, the epidemiology and prognosis of heart failure in PLWHIV has improved dramatically. However, symptoms of heart failure or echocardiographic evidence of cardiomyopathy greatly increase the risk of death [1]. SCD in HIV patients occurs at 4.5 times the expected rate, and systolic and diastolic dysfunction are known to be present in more than half of such deaths. The presence of contractile reserve as assessed by dobutamine stress echocardiography has been reported to be a marker for improved survival in HIV patients with cardiomyopathy. Patients with contractile reserve were also more likely to experience an improvement in ejection fraction.

CONCLUSION

Similar to the uninfected population, heart failure is becoming increasingly more common among HIV-infected individuals and is anticipated to increase in clinical significance as this population ages. Although there are many parallels to the disease entity of HIV-associated atherosclerosis, there are relatively fewer studies and less understanding of this disease process and even fewer studies evaluating treatment in the setting of HIV. Future studies are ongoing to ascertain the underlying pathophysiology of heart failure in HIV, which will be helpful in developing treatment strategies.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Remick J, Georgiopoulou V, Marti C, *et al.* Heart failure in patients with human immunodeficiency virus infection: epidemiology, pathophysiology, treatment, and future research. Circulation 2014; 129:1781–1789.
2. ■■ Freiberg MS, Chang 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. JAMA Cardiol 2017; 2:536–546.

By using epidemiological data from the Veterans Aging Cohort, these investigators previously reported an association between HIV and heart failure. Here, the investigators build on prior work with this large cohort to show that persons living with HIV have a significantly increased risk of heart failure with reduced ejection fraction, heart failure with preserved ejection fraction (HFpEF), and borderline HFpEF events compared uninfected people in the antiretroviral therapy (ART) era.

3. Hsue PY, Hunt PW, Ho JE, *et al.* Impact of HIV infection on diastolic function and left ventricular mass. Circ Heart Fail 2010; 3:132–139.
4. Grandi AM, Nicolini E, Giola M, *et al.* Left ventricular remodelling in asymptomatic HIV infection on chronic HAART: comparison between hypertensive and normotensive subjects with and without HIV infection. J Hum Hypertens 2012; 26:570–576.
5. Haider AW, Larson MG, Benjamin EJ, *et al.* Increased left ventricular mass and hypertrophy are associated with increased risk for sudden death. J Am Coll Cardiol 1998; 32:1454–1459.
6. Moyers BS, Secemsky EA, Vittinghoff E, *et al.* Effect of left ventricular dysfunction and viral load on risk of sudden cardiac death in patients with human immunodeficiency virus. Am J Cardiol 2014; 113:1260–1265.
7. Crane HM, Paramsothy P, Drozd DR, *et al.* Types of myocardial infarction among human immunodeficiency virus-infected individuals in the United States. JAMA Cardiol 2017; 2:260–267.
8. ■ Chen R, Scherzer R, Hsue PY, *et al.* Association of tenofovir use with risk of incident heart failure in HIV-infected patients. J Am Heart Assoc 2017; 6:e005387.

This study was the first to show that heart failure risk was lower with certain ART regimens; specifically, these authors report a significant reduction in heart failure risk with regimens containing tenofovir disoproxil fumarate.

9. Lorgis L, Cottenet J, Molins G, *et al.* Outcomes after acute myocardial infarction in HIV-infected patients: analysis of data from a French nationwide hospital medical information database. Circulation 2013; 127:1767–1774.
10. ■ Secemsky EA, Scherzer R, Nitta E, *et al.* Novel biomarkers of cardiac stress, cardiovascular dysfunction, and outcomes in HIV-infected individuals. J Am Coll Cardiol Heart Failure 2015; 3:591–599.

This was the first study to demonstrate that ST2 and other novel biomarkers of cardiac stress were found to be strongly associated with diastolic dysfunction and mortality in an HIV+ cohort.

11. ■■ Ntusi N, O'Dwyer E, Dorrell L, *et al.* HIV-1-related cardiovascular disease is associated with chronic inflammation, frequent pericardial effusions, and probable myocardial edema. Circ Cardiovasc Imaging 2016; 9:e004430.

This study provides additional evidence that treated HIV is associated with chronic myocardial inflammatory changes, including chronic subclinical myocardial edema and a high incidence of pericardial effusions. By using cardiac MRI, the investigators extend their prior study and report that compared with controls, HIV+ individuals had lower (though still normal) LVEF, higher myocardial mass, and lower peak diastolic strain rate.

12. Holloway CJ, Ntusi N, Suttie J, *et al.* Comprehensive cardiac magnetic resonance imaging and spectroscopy reveal a high burden of myocardial disease in HIV patients. Circulation 2013; 128:814.

13. Hsu JC, Li Y, Marcus GM, *et al.* Atrial fibrillation and atrial flutter in human immunodeficiency virus-infected persons: incidence, risk factors, and association with markers of HIV disease severity. J Am Coll Cardiol 2013; 61:2288–2295.
14. Fisher SD, Starc TJ, Guerra V, *et al.* Declining incidence of systolic left ventricular dysfunction in human immunodeficiency virus-infected individuals treated with highly active antiretroviral therapy. Am J Cardiol 2016; 117:1194–1195.
15. Currie PF, Jacob AJ, Foreman AR, *et al.* Heart muscle disease related to HIV infection: prognostic implications. BMJ 1994; 309:1605–1607.
16. Felker GM, Thompson RE, Hare JM, *et al.* Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. N Engl J Med 2000; 342:1077–1084.