Heart Failure in Patients With Human Immunodeficiency Virus Infection

Epidemiology, Pathophysiology, Treatment, and Future Research

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With the advent of highly active antiretroviral therapy (HAART), human immunodeficiency virus type 1 (HIV-1) infection has become a chronic disease with longer life expectancy. The HIV Outpatient Study showed that, with the addition of antiretroviral therapy (ART), mortality declined from 29.4 to 8.8 per 100 person-years. More recent data indicate that the proportions of patients expected to survive 5, 10, and 15 years after seroconversion in the HAART era are 99%, 93%, and 89%, respectively. With the increased life expectancy and decreased morbidity from opportunistic infections, the recognition and importance of chronic complications associated with HIV-1 infection are becoming more evident. Cardiac diseases are common complications found in these patients. The spectrum of heart diseases varies significantly between developed and developing countries and, in developed countries, between pre-HAART and post-HAART eras. Among them, HIV-associated cardiomyopathy, broadly defined as a decreased left ventricular (LV) ejection fraction or dilated LV by imaging studies, with or without symptoms of heart failure, is currently recognized as a major long-term complication of HIV-1 infection in developing countries; however, it is still prevalent in developed countries. Many questions regarding its pathogenesis and treatment remain unanswered.

Epidemiology

The epidemiology of HIV-associated cardiomyopathy has changed since the first report in 1986. The advent of HAART has significantly altered both the incidence and prevalence of this disease, and the definition of HIV-associated cardiomyopathy has also evolved from one of primarily systolic dysfunction to now reflect the growing recognition of diastolic dysfunction in these patients.

Incidence

The incidence of HIV-associated cardiomyopathy is difficult to ascertain because very few studies actually evaluated this measure. In the pre-ART era, HIV-associated cardiomyopathy was defined as symptomatic, systolic dysfunction with a dilated LV and was seen almost exclusively in patients with advanced HIV disease and AIDS. These older studies, which are listed in Table 1, generally concluded that there was a high incidence of HIV-associated cardiomyopathy. However, these data are not very useful in the current, post-ART era because the phenotype of the disease has changed. The few studies in the post-ART era that have evaluated the incidence of HIV-associated cardiomyopathy have focused on the incidence of either asymptomatic systolic dysfunction or diastolic dysfunction (Table 1).

Prevalence

Far more studies have examined the prevalence of HIV-associated cardiomyopathy. Again, with the advent of ART, the disease has changed from severe, dilated cardiomyopathy to often minimally symptomatic, mildly reduced LV systolic function or various degrees of impaired diastolic function. In addition, with the spread of ART, the prevalence of systolic dysfunction has decreased, and the number of patients with severely impaired ejection fractions is quite low. On the contrary, the number of HIV-infected patients with abnormal diastolic parameters has increased significantly (Table 1). A meta-analysis of 11 studies in the HAART era assessed 2242 well-controlled, asymptomatic HIV-1–infected patients who nevertheless had a prevalence of systolic dysfunction of 8.3% and diastolic dysfunction of 43.4%. Risk factors for systolic dysfunction included high-sensitivity C-reactive protein >5 mg/L, tobacco use, and past myocardial infarction; for diastolic dysfunction, risk factors were hypertension and older age.

The data discussed above and listed in Table 1 represent studies examining patients in the United States and Europe. However, more than two thirds of HIV-infected people live in Sub-Saharan Africa, where <20% of patients who need ART actually receive it. The Heart of Soweto Study was undertaken to investigate the impact of the HIV/AIDS epidemic on de novo manifestations of heart disease. In that analysis, 518 of 5328 cases (9.7%) of newly diagnosed heart disease were identified as HIV positive. Of those, almost one third presented
**Table 1. Epidemiology of HIV-Associated Cardiomyopathy**

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Incidence, %</th>
<th>Systolic Dysfunction, % (EF, %, If Reported)</th>
<th>Diastolic Dysfunction, % (Stage, If Reported)</th>
<th>Antiretroviral Therapy</th>
<th>Mean CD4, cells/mm³</th>
<th>Viral Load, Copies/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-HAART</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Levy, 1989⁶</td>
<td>60</td>
<td>NR</td>
<td>16</td>
<td>NR</td>
<td>None</td>
<td>NR (majority &lt;100)</td>
<td>NR</td>
</tr>
<tr>
<td>De Castro, 1992⁷</td>
<td>72</td>
<td>NR</td>
<td>16.6 (all with EF &lt;50; mean EF 35)</td>
<td>NR</td>
<td>Zidovudine</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Herskowitz, 1993⁸</td>
<td>69</td>
<td>18/y</td>
<td>14.5 (all with EF &lt;45; mean EF 34)</td>
<td>NR</td>
<td>None</td>
<td>30</td>
<td>NR</td>
</tr>
<tr>
<td>De Castro, 1994⁹</td>
<td>93</td>
<td>2/3 mo</td>
<td>7.5 (all with EF &lt;45)</td>
<td>NR</td>
<td>69% on zidovudine</td>
<td>56</td>
<td>NR</td>
</tr>
<tr>
<td>Akhras, 1994¹⁰</td>
<td>101</td>
<td>NR</td>
<td>20 (all EF &lt;35)</td>
<td>NR</td>
<td>Zidovudine</td>
<td>67</td>
<td>NR</td>
</tr>
<tr>
<td>Coudray, 1995¹¹</td>
<td>51</td>
<td>NR</td>
<td>4/6 diastolic function parameters worse in HIV patients vs controls (no difference between symptomatic and asymptomatic HIV patients)</td>
<td>None</td>
<td>≈60% on zidovudine</td>
<td>172±198 in symptomatic patients and 422±308 in asymptomatic patients</td>
<td></td>
</tr>
<tr>
<td>Barbaro, 1996¹²</td>
<td>1236</td>
<td>NR</td>
<td>Mean EF=48 in HIV patients vs 59 in controls</td>
<td>NR, but E/A, IVRT, and LA parameters all significantly worse in HIV patients vs controls</td>
<td>None</td>
<td>670</td>
<td>NR</td>
</tr>
<tr>
<td>Lipshultz, 1998¹³</td>
<td>196</td>
<td>4.7/2 y</td>
<td>31</td>
<td>NR</td>
<td>63% on zidovudine</td>
<td>906±890</td>
<td>NR</td>
</tr>
<tr>
<td>Pugliese, 2000¹⁴</td>
<td>1042</td>
<td>NR</td>
<td>8.1 in NRTI- and 1.8 in ART-treated patients</td>
<td>NR</td>
<td>544 on NRTI alone; 498 on ART</td>
<td>42±15 in NRTI- and 92±52 in HAART-treated patients</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Post-HAART</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Bijl, 2001¹⁵</td>
<td>105</td>
<td>NR</td>
<td>3</td>
<td>NR</td>
<td>91% on ART</td>
<td>Median 340</td>
<td>Median 1.15×10⁴ (78% fully suppressed)</td>
</tr>
<tr>
<td>Kristofferson, 2008¹⁶</td>
<td>63</td>
<td>&lt;1% over 4.5 y</td>
<td>&lt;1</td>
<td>NR</td>
<td>95% on ART</td>
<td>710±350</td>
<td>16 300±35 800 (79% fully suppressed)</td>
</tr>
<tr>
<td>Schuster, 2008¹⁷</td>
<td>30</td>
<td>NR</td>
<td>13 (lowest EF= 39)</td>
<td>64 (27% stage I, 37% stage II)</td>
<td>100% on ART</td>
<td>591±314</td>
<td>60% fully suppressed</td>
</tr>
<tr>
<td>Hsue, 2010¹⁸</td>
<td>196</td>
<td>NR</td>
<td>4 (EF range 33–49)</td>
<td>49 (48% stage I, 1% stage II)</td>
<td>82% on ART</td>
<td>Median 420</td>
<td>63% fully suppressed</td>
</tr>
<tr>
<td>Reinsch, 2011¹⁹</td>
<td>803</td>
<td>NR</td>
<td>34 (32% with EF 45–54; 19% with EF 30–44; 0.4% with EF 20–29)</td>
<td>48 (36% stage I, 9% stage II, 3% stage III)</td>
<td>85% on ART</td>
<td>509±301</td>
<td>66% fully suppressed</td>
</tr>
<tr>
<td>Mondy, 2011²⁰</td>
<td>656</td>
<td>NR</td>
<td>18 (17% with EF 35–50; 1% with EF &lt;35)</td>
<td>26 (15% stage I, 2% stage II, 9% stage III)</td>
<td>73% on ART</td>
<td>Median 462</td>
<td>91% fully suppressed</td>
</tr>
<tr>
<td>Blaylock, 2012²¹</td>
<td>60</td>
<td>8.2/100 person-years</td>
<td>NR</td>
<td>47 (40% stage I, 7% stage II)</td>
<td>78% on ART</td>
<td>Median 570</td>
<td>60</td>
</tr>
<tr>
<td>Cerrato, 2013 (meta-analysis)²²</td>
<td>2242</td>
<td>NR</td>
<td>8.33</td>
<td>43.4 (31.85% stage I, 8.53% stage II, 3.02% stage III)</td>
<td>98.5% on ART</td>
<td>Median 489</td>
<td>74% fully suppressed</td>
</tr>
</tbody>
</table>

ART indicates antiretroviral therapy; E/A, E to A ratio of mitral inflow; EF, ejection fraction; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; IVRT, isovolumic relaxation time; LA, left atrium; NR, not reported; and NRTI, nucleoside reverse transcriptase inhibitors.
with LV systolic dysfunction (n=148; 29%), and 196 (38%) had HIV-related cardiomyopathy (which encompassed both systolic and diastolic dysfunction in both symptomatic and asymptomatic patients). Furthermore, the incidence of coronary disease, which is rising in ART-treated HIV patients, was low, occurring in just 2.7% of patients. This study has important implications from a global health perspective, but it also reinforces the changing nature of HIV-associated heart disease in the era of widespread ART use.

With the high prevalence of diastolic abnormalities in HIV-infected patients, additional imaging modalities have been used to detect other impairments in cardiac function. In 1 study, 28 young HIV-1–infected patients aged 7 to 29 years were compared with 28 controls and showed no abnormalities in gross systolic or diastolic parameters,24 but the HIV-1–infected patients had impaired radial strain and longitudinal and circumferential strain and strain rate compared with controls. Asymptomatic HIV-1 infection and the use of ARTs are associated with LV hypertrophy and diastolic dysfunction independent of blood pressure.25 More recently, cardiac magnetic resonance imaging and spectroscopy found high rates of cardiac steatosis, altered myocardial function, and a high rate of myocardial fibrosis in almost all 90 HIV-positive patients studied.26 The authors hypothesize that the cardiac steatosis, which is presumably secondary to ART, and the myocardial fibrosis, possibly representing subclinical myocarditis, may underlie the increased morbidity and mortality seen in HIV-infected patients with cardiac disease.

**HIV-2 and Cardiomyopathy**

There is far greater experience with HIV-1 infection than with HIV-2 with regard to cardiovascular disease. Some older evidence supports a different clinical expectation with regard to infection by HIV-2 compared with HIV-1. LV function was evaluated by echocardiography in a prospective study that included 98 consecutive HIV-infected patients and 40 HIV-seronegative controls. Only 8 infected patients (8%) had symptomatic heart failure. In general, cardiovascular function was better in earlier stages of the infection (fractional shortening in the AIDS cohort was 30±6% and in asymptomatic HIV-seropositive patients was 34±5%; P<0.005) and in HIV-2–infected patients, but more specific information about the smaller HIV-2 cohort was lacking.27

**Prognosis**

The severe systolic dysfunction that was a hallmark of pre-ART HIV-associated cardiomyopathy carried a grim prognosis (Table 2).28–34 Currie et al28 demonstrated a median survival among patients with AIDS with cardiomyopathy of 101 days versus 472 days in those without, whereas another study showed an adjusted hazard ratio for death of 5.86 compared with patients with idiopathic cardiomyopathy.29 However, with the widespread use of ARTs, not only has the epidemiology of the disease changed, but the prognosis has changed as well. Cardiac diseases account for a quarter of deaths in the post-ART era compared with <10% in the pre-ART era. Furthermore, symptoms of heart failure or echocardiographic evidence of cardiomyopathy is associated with a 6.5 and 4.0 times higher risk for death, respectively.32 Some studies have tried to further elucidate this increased risk. One such study looked at the risk of sudden cardiac death in HIV-1–infected patients.34 Sudden cardiac death in this population occurred at a 4.5 times higher rate than expected. Furthermore, of those who died, 43% (n=13) had echocardiograms before death, and half had known systolic or diastolic dysfunction. Another study of HIV-infected patients with systolic dysfunction (mean ejection fraction 28±11%) undergoing dobutamine stress echocardiography found 11 cardiac deaths (event rate 7.6%/y), all attributable to either worsening heart failure or arrhythmias.33 The presence of inotropic contractile reserve was associated with improved prognosis. Those without contractile reserve had a 7 times higher event rate (24%/y versus 3.4%/y; P<0.0001). Furthermore, those with contractile reserve were more likely to have an improved ejection fraction over time (80% versus 33%; P=0.003), from 30±11% to 44±11% (P<0.0001) versus from 24±11% to 30±17%, despite no difference in use of antiremodeling medication therapy between groups.33

It is important to recognize that no studies have evaluated the prognosis in HIV-infected patients with diastolic abnormalities. However, when evidence is extrapolated from studies in non–HIV-positive patient populations, diastolic dysfunction is a predictor of mortality, although not to the degree that systolic dysfunction is. Therefore, it seems reasonable to suggest that a screening echocardiogram should be performed on HIV-infected patients, particularly if they have any other cardiovascular risk factors, given the high prevalence of diastolic abnormalities as well as asymptomatic systolic dysfunction. The cost-effectiveness of such a strategy would need to be evaluated, especially given the lack of data supporting any treatments to reduce mortality in patients with diastolic dysfunction. At this time, however, other imaging modalities such as magnetic resonance imaging and even strain echocardiography need further research to determine the impact they may have on prognosis and how they should be used in daily practice. Table 2 presents the studies that have addressed prognosis.28–34

**Pathophysiology**

The pathophysiology of HIV-associated cardiomyopathy remains uncertain and is likely multifactorial (Figure). The proposed causes include direct infection of the myocardium by HIV-1 with or without myocarditis, toxicity from the medications used to treat HIV-1 infection, opportunistic infections, nutritional disorders, and others.35,36 When HIV-associated cardiomyopathy is thought of only in terms of severe, dilated cardiomyopathy, the pathobiology was believed to be from opportunistic infections or as a result of myocarditis. However, as the concept of the disease has changed and grown to include more nuanced forms of myocardial involvement, the understanding of the mechanisms has evolved as well.

**Direct HIV-Induced Myocardial Damage**

Infection of the heart with HIV-1 has been postulated as one of the key mechanisms for the development of impaired systolic function.35,37–41 In situ hybridization of HIV-1 in
myocardial samples from humans with AIDS\textsuperscript{41,42} and in primates with simian immunodeficiency virus\textsuperscript{43} revealed that the cytological identity of cardiac infection was the macrophage rather than the myocyte. These facts are compatible with the notion that cardiomyocytes lack HIV-1 receptor proteins (gp120 or gp24). However, Wang et al\textsuperscript{44} demonstrated that human cardiac fetal myocyte cell lines were capable of ingesting HIV-1 via specific Fc receptors despite the absence of CD4 receptors. Furthermore, HIV-1 infection within cardiac interstitial cells (dendritic cells or endothelial cells) rather than myocytes may play an important pathogenic role because these infected cells serve as viral reservoirs as well as antigen-presenting cells mediating inflammation.\textsuperscript{45} Gene products of HIV-1 may also contribute, and HIV-related proteins expressed in response to infection may lead to the development of cardiomyopathy.\textsuperscript{46,47} As proof of principle, it was shown experimentally that HIV-1 Tat expressed transgenically in the mouse causes systolic dysfunction, which could be relieved by antioxidants.\textsuperscript{48,49}

### Autoimmune Mechanisms

There is evidence that common cardiotropic viruses may alter surface antigens, leading to an autoimmune reaction to endogenous epitopes,\textsuperscript{50} and cardiac-specific autoantibodies are more common in HIV-1–infected people, particularly those with some degree of myocardial disease, than in HIV-negative controls.\textsuperscript{51} This can result in increased myocardial expression of HLA class I antigens, which is seen more commonly in AIDS patients with symptomatic systolic dysfunction.\textsuperscript{52} Interestingly, there is experimental evidence that blocking some of these proteins may be cardioprotective,\textsuperscript{47,51,53,54} and administration of monthly intravenous immunoglobulin(s) in pediatric HIV-1–infected patients was

### Table 2. Prognosis of HIV-Associated Cardiomyopathy

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Length of Study</th>
<th>Definition of Cardiomyopathy</th>
<th>Hazard Ratio for Death</th>
<th>Median Survival</th>
<th>CD4 Count, Mean</th>
<th>Mean Ejection Fraction, %</th>
<th>ART, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Currie, 1994</td>
<td>296 (13 had dilated cardiomyopathy)</td>
<td>4 y</td>
<td>FS &lt;28% with global LV hypokinesia</td>
<td>11.68 for patients with dilated cardiomyopathy vs controls with AIDS</td>
<td>101 d for patients with dilated cardiomyopathy</td>
<td>153 (7.4 in patients with dilated cardiomyopathy)</td>
<td>NR</td>
<td>No</td>
</tr>
<tr>
<td>Felker, 2000</td>
<td>1230 (45 with HIV-associated cardiomyopathy)</td>
<td>4.4 y</td>
<td>NR</td>
<td>5.86 vs idiopathic cardiomyopathy</td>
<td>NR</td>
<td>NR</td>
<td>NR N</td>
<td>NR</td>
</tr>
<tr>
<td>Lipshultz, 2000</td>
<td>193 (mean age 2.1 y)</td>
<td>60 mo</td>
<td>LV contractility (&gt;2 SD) below mean and LV end-diastolic dimension (&gt;2 SD) above mean*</td>
<td>FS: 1.31 RR for each SD decrease; wall thickness: 1.35 for each SD increase</td>
<td>64% at 5 y (38% if FS &lt;2 SD below normal; 45% if wall thickness &gt;1 SD above normal)</td>
<td>690 (normal value for 2-year-old is 2298)</td>
<td>NR N</td>
<td>NR</td>
</tr>
<tr>
<td>Sackoff, 2006</td>
<td>68669</td>
<td>5 y</td>
<td>NR (only evaluated “cardiovascular disease” as a cause of non-HIV-related death)</td>
<td>29.2 age-adjusted mortality per 10,000 persons with AIDS for cardiovascular disease</td>
<td>NR</td>
<td>NR</td>
<td>NR N</td>
<td>NR</td>
</tr>
<tr>
<td>Crum, 2006</td>
<td>4241 (15 total deaths from heart failure or cardiomyopathy in study cohort)</td>
<td>13 y</td>
<td>Heart failure or cardiomyopathy diagnosed on basis of death certificate</td>
<td>6.52 for congestive heart failure; 3.97 for cardiomyopathy</td>
<td>NR</td>
<td>123 pre-HAART era; 202 early-HAART era; 316 late-HAART era</td>
<td>NR N</td>
<td>NR</td>
</tr>
<tr>
<td>Wever-Pinzon, 2011</td>
<td>60</td>
<td>2.4±2.1 y</td>
<td>Patients with EF &lt;45%; DSE performed to assess inotropic contractile reserve</td>
<td>6.6 for absence of contractile reserve; 56% had improvement in EF (mean 48±9%)</td>
<td>NR</td>
<td>243</td>
<td>28±11 77</td>
<td>NR</td>
</tr>
<tr>
<td>Tseng, 2012</td>
<td>2860</td>
<td>Median 3.7 y</td>
<td>Causes of death were obtained from death certificates or National Death Index database</td>
<td>4.46 for SCD (13% of deaths attributable to SCD)</td>
<td>NR</td>
<td>Median 312 for patients who died of SCD</td>
<td>In patients with echo, 23% had moderate to severe low EF</td>
<td>NR</td>
</tr>
</tbody>
</table>

\*LV contractility was defined as the relation between end-systolic LV wall stress and the rate-adjusted velocity of fiber shortening, which incorporates afterload and is independent of preload. Afterload was measured as meridional end-systolic LV wall stress. Peak systolic wall stress was measured as well.

\textsuperscript{ART indicates antiretroviral therapy; BSA, body surface area; DSE, dobutamine stress echocardiography; EF, ejection fraction; FS, fractional shortening; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; LV, left ventricle; NR, not reported; NYHA, New York Heart Association; RR, relative risk; and SCD, sudden cardiac death.}

\textsuperscript{*LV contractility was defined as the relation between end-systolic LV wall stress and the rate-adjusted velocity of fiber shortening, which incorporates afterload and is independent of preload. Afterload was measured as meridional end-systolic LV wall stress. Peak systolic wall stress was measured as well.
shown to minimize LV dysfunction and improve other markers of myocardial injury.13,30

Inflammation
Proinflammatory cytokines, particularly interleukin-1β and tumor necrosis factor (TNF), have been shown to exert a negative inotropic effect and likely play a role in HIV-associated cardiomyopathy, specifically the form associated with depressed systolic function.55–57 Other investigators showed that TNF and inducible nitric oxide synthase expression was higher in patients with HIV-associated cardiomyopathy.45 Autopsies of HIV-associated cardiomyopathy patients suggest that TNF is a potent inducer of apoptosis.58 Some suggest that treatment to reduce oxidative stress may affect the development and outcome of impaired systolic function in these patients.59

Side Effects of HIV Medications
Some of the medications used to treat HIV infection may have a deleterious effect on myocardium. Mitochondrial toxicity is an acknowledged side effect of ART.60 Defects in mitochondrial DNA replication and decreased energetics are caused by zidovudine (3′-azido-2′,3′-dideoxythymidine)61,62 as well as other nucleoside reverse transcriptase inhibitors, specifically fialuridine (1-[2-deoxy-2-fluoro-β-D-arabinofuranosyl]5-iodouracil),63 clevudine (L-FMAU), and lodenosine, a purine nucleoside reverse transcriptase inhibitor (2′-fluoro-2′,3′-dideoxyadenosine), which had been used in the treatment of hepatitis B.64

Children infected with HIV are exposed to ART for many years, including in utero exposure to HAART while the cardiovascular system is still developing. There may be an interaction between the effects of ART and HIV on the cardiovascular system of children; however, the direction and magnitude of such effects are unknown. Children and adolescents are unique populations in which to study the pathophysiological mechanisms of HIV-associated cardiomyopathy because they are less likely than adults to be exposed to other cardiovascular risk factors. HIV infection and ART exposure lead to subclinical abnormalities of cardiac structure and function in children that may eventually result in symptomatic cardiomyopathy in adulthood. Specifically, it has been reported that long-term HAART
exposure may have cardioprotective properties early in life, but this cardioprotection decreases as HIV-infected children age into adolescence and early adulthood. Echocardiographic data from the National Institutes of Health–funded Adolescent Master Protocol of the Pediatric HIV/AIDS Cohort Study showed that measures of LV structure and function were better in the long-term HAART-exposed group than in the relatively HAART-unexposed vertically transmitted HIV infection cohort, but they were not as normal as those in an HIV-exposed uninfected control group. Children exposed perinatally to either multidrug ART or HAART had below-normal LV mass, LV dimension, and septal wall thickness. In a larger cohort of HIV-exposed, uninfected, perinatally HAART-exposed children, 16% of them had at least 1 abnormal echocardiographic measure. First-trimester exposure to various ART agents has been associated with specific echocardiographic abnormalities. For instance, first-trimester exposure to abacavir has been associated with decreased LV wall thickness. In addition, in HIV-exposed uninfected children, serum cardiac biomarker measurements suggested that perinatal exposure to multiple ART agents might have led to subclinical myocardial inflammation. Specifically, abacavir exposure was potentially associated with deleterious cardiac effects.

Nutritional Effects
Selenium deficiency has been described in HIV-1–infected patients and is associated with a form of cardiomyopathy in China known as Keshan disease. However, the data on nutritional deficiencies resulting in cardiomyopathy are more closely related to socioeconomic status rather than presence or absence of HIV-associated cardiomyopathy.

Coronary Artery Disease
The growing burden of coronary artery disease in HIV-1–infected individuals may also significantly modify the risk for HIV-associated cardiomyopathy. It is well known that coronary disease can predispose patients to the development of cardiomyopathy, and the mechanisms of coronary disease in this population are complex, although they are similar in many respects to those in non–HIV-1–infected patients. In a recent analysis, diabetes mellitus and hypertension, 2 of the most common and recognized risk factors for coronary artery disease, were found less frequently in HIV-infected patients who suffered an acute myocardial infarction than in patients with acute myocardial infarction who were not infected with HIV. Furthermore, the authors showed similar 30-day and 1-year mortality and major adverse cardiac events rates in the HIV-positive patients with acute myocardial infarction compared with those without the disease. One of the more compelling findings of the study by Lorigs et al was a 2-fold increased risk of hospitalization for heart failure in the year after the acute event in the HIV-positive group. The presence of diabetes mellitus conferred an almost 5-fold increased risk for the development of heart failure, as did the presence of HIV infection itself. Prior studies have also shown that risk factors for the development of systolic impairment include smoking status, increased high-sensitivity C-reactive protein levels, and prior myocardial infarction. In contrast, the risk factors that seem to be associated with the development of diastolic abnormalities include higher body mass index and hypertension. The obvious next step would be to study whether aggressive control of these risk factors will delay or prevent the development of myocardial dysfunction.

Treatment

Medical Therapy
Little is known about the optimal therapy for HIV cardiomyopathy and the response of known heart failure medications in HIV-1–infected patients. No randomized trials of heart failure medications have been performed in this patient population. With privacy concerns and regulations, data on HIV status are not collected in clinical trials and registries, and therefore no definitive data exist in this regard. Consequently, therapy is driven by consensus, and data are derived from either retrospective analyses/case reports or from extrapolation from non–HIV-1–infected patients. General recommendations include standard, guideline-driven therapy, but no studies have assessed the benefits of β-blockers, angiotensin-converting enzyme inhibitors, or aldosterone antagonists in this specific subset of patients.

Devices
Little is known about the effect of device therapy in HIV-associated cardiomyopathy patients. Unfortunately, neither the rate nor the effectiveness of implantable devices has been reported in the HIV-associated cardiomyopathy population. It has been suggested that HIV-1–infected patients may be less likely to receive an implantable defibrillator or cardiac resynchronization therapy because of either a belief that they have higher mortality and thus shorter life spans or a fear of infectious complications. This concern is not without some merit because a recent analysis showed a higher rate of bacteremia despite ART in HIV-1–infected patients compared with the general population. However, in light of the findings by Tseng et al, the benefit of implantable defibrillator in this population to prevent the high incidence of sudden cardiac death should be studied.

Immune Therapy
Although sparse data exist, a retrospective review of intravenous immunoglobulin therapy in 49 children with HIV-1 infection found that it was associated with significant improvements in LV wall thickness and decreases in peak wall stress. Favorable trends were also noted in fractional shortening and contractility. The therapeutic benefit of intravenous immunoglobulin may result from its ability to inhibit TNF and interleukin production. Etanercept, another immune-modulating agent, has been used in a small study of patients with heart failure with moderate success. In an animal study, monkeys infected with simian immunodeficiency virus as well as killed Mycobacterium avium complex bacteria developed severe LV dysfunction. However, monkeys treated with etanercept did not develop cardiomyopathy, suggesting not only that TNF may play a causative role in the development of HIV cardiomyopathy (as discussed above) but that therapy directed at TNF may treat the cardiomyopathy as well. However, this therapy has not been tested in human HIV-1–infected patients.
HAART Therapy

The role of HAART in HIV cardiomyopathy is complicated. On the one hand, most studies suggest that systolic dysfunction is more pronounced and prevalent with poorly controlled HIV-1 infection. On the other hand, therapy with ART has been associated with a higher incidence of coronary disease, which is a risk factor for myocardial impairment. Some published case reports showed regression and normalization of cardiomyopathy in adults\(^8\) and children\(^7\) who were treated with HAART. In the largest study to date of pediatric patients, >3000 children with HIV infection were longitudinally followed for incident cardiomyopathy and to assess the effect of HAART.\(^7\)\(^3\) Over a median of 5.5 years of follow-up, 99 cases of cardiomyopathy were observed, yielding an incidence of 5.6 cases per 1000 person-years. The authors noted that the incidence decreased dramatically in the post-HAART era from 25.6 cases per 1000 person-years to 3.9 cases per 1000 person-years. Although this study did not specifically address the effect of HAART on “curing” HIV-associated cardiomyopathy (specifically LV systolic dysfunction), it demonstrated the “protective” effect of HAART in reducing its incidence. Despite this, the incidence of cardiomyopathy in pediatric HIV-1–infected patients is still 40 times higher than the reported annual incidence of 1.13 per 100000 children from the US Pediatric Cardiomyopathy Registry.\(^7\) Thus, the question of whether HAART can actually reverse HIV-associated cardiomyopathy is not answered and warrants further investigation.

Transplantation and Mechanical Circulatory Assist Devices

HIV-1 infection has generally been considered a contraindication for cardiac transplantation because of historically poor survival and concerns over progression to AIDS with immunosuppression.\(^8\)\(^0\) despite recent evidence suggesting that immunosuppressant medications can actually increase the efficacy of HAART in treating HIV infection.\(^8\)\(^1\) A survey of cardiac transplant programs revealed that the 70% considered infection with HIV-1 an absolute contraindication to transplantation. Indeed, early reports of cardiac transplantation in patients subsequently found to have HIV-1 infection after transplantation showed poor outcomes.\(^8\)\(^2\) However, since 2003, when the first cardiac transplantation was performed in a known HIV-positive patient,\(^8\)\(^3\) outcomes have generally been favorable.\(^8\)\(^4\) No increases in rejection or worsening of HIV status with immunosuppression have been reported. Larger case series in the United States\(^8\)\(^5\) and Europe\(^8\)\(^6\) have shown similar results. Hence, calls for reevaluation of HIV-1 infection as an absolute contraindication have been made.\(^8\)\(^0\)

In 2009, 2 reports of destination therapy with HeartMate XVE implanted in HIV-1–infected patients were published.\(^8\)\(^7\)\(^8\) Both patients did well, and they did not suffer complications that were very different from those experienced by non–HIV-1–infected LV assist device recipients. A subsequent case demonstrated no major infection-related complications\(^8\)\(^9\) and no significant increased risk of allosensitization.\(^8\)\(^0\) Thus, although the data on mechanical assist devices in HIV-1–infected patients are limited, case series indicate reasonable outcomes and no significant adverse events attributed to HIV-1 infection. These findings warrant further investigation.

Conclusion

Since the first report in 1986, our understanding of HIV-associated cardiomyopathy has evolved but nevertheless remains inadequate. Whereas the disease was once thought of as strictly systolic dysfunction associated with poorly controlled HIV-1 infection, the widespread use of ART in the Western world has changed the concept of this disease from severe, dilated cardiomyopathy to less severe LV systolic function and various degrees of impaired diastolic function, often independent of traditional cardiac risk factors. The prevalence of systolic dysfunction has decreased in developed countries; unfortunately, in the parts of the world where HIV is most prevalent, ART is not widespread, and therefore the disease remains one of severe systolic impairment with high rates of morbidity and mortality. Although the exact incidence, prevalence, and pathophysiology remain to be elucidated, it is clear that these patients have a poor prognosis if they develop systolic dysfunction. The exact significance of diastolic abnormalities among these patients is not known, necessitating further research to determine the prognosis of these patients and the best way to prevent the development of these abnormalities. Because its pathophysiology is poorly understood, the therapeutic approach to these patients remains unknown as well. It is unknown whether drug- and device-based therapies that have been shown to be of benefit in heart failure patients without HIV-1 infection will benefit those who are infected and whether these therapies will benefit them to the same degree. When one considers the epidemiological significance of cardiac functional abnormalities among HIV-1–infected individuals and the lack of definitive data on treatment for these patients, further research is urgently needed in this group, particularly in Sub-Saharan Africa.

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Disclosures

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