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.[1] 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.[2] More recent data indicates that the proportion of patients expected to survive 5, 10, and 15 years after seroconversion in the HAART era are 99%, 93% and 89% respectively.[3] With the increased life expectancy and decreased morbidity from opportunistic infections, the recognition and importance of chronic complications associated with HIV-1 infection is becoming more evident. Cardiac diseases are very common complications met 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.[4] Among them, HIV-associated cardiomyopathy, broadly defined as a decreased left ventricular ejection fraction or dilated left ventricle 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.[4] Many questions regarding its pathogenesis and treatment remain unanswered.

Epidemiology

The epidemiology of HIV-associated cardiomyopathy has changed since the first report in 1986.[5] 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

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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 as very few studies actually evaluated this measure. In the pre-ART era, HIV-associated cardiomyopathy was defined as symptomatic, systolic dysfunction with a dilated left ventricle, and seen almost exclusively in patients with advanced HIV disease and acquired immunodeficiency syndrome (AIDS). These older studies, which are listed in Table 1,[6–14] generally concluded that there was a high incidence of HIV-associated cardiomyopathy. However, this data is not all that useful in the current, post-ART era, since 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 and/or diastolic dysfunction (Table 1).[15–22]

Prevalence

Far more studies have studied the prevalence of HIV-associated cardiomyopathy. Again, with the advent of ART, not only has the disease changed from a severe, dilated cardiomyopathy to one of often minimally symptomatic, mildly reduced LV systolic function or various degrees of impaired diastolic function. What is clear is that 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%.[22] Risk factors for systolic dysfunction included high sensitivity C-reactive protein >5 mg/L, tobacco use, and past myocardial infarction, whereas for diastolic dysfunction, risk factors were hypertension and older age.

It is important to point out that the data discussed above and listed in Table 1, represent studies looking at patients in the United States and Europe. However, more than two-thirds of HIV-infected people live in Sub-Sarahan 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.[23] In their analysis, 518 of 5328 (9.7%) of newly diagnosed heart disease were identified as HIV-positive. Of those, almost one-third presented 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 one study, 28 young HIV-1-infected patients age 7–29 years were compared to 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 to controls. Asymptomatic HIV-1 infection and the use of ARTs are associated with left ventricular 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 a far greater experience with HIV-1 infection than HIV-2 with regard to cardiovascular disease. Some older evidence supports a different clinical expectation with regard to infection by HIV-2 compared to HIV-1. Left ventricular function was evaluated by echocardiography in a prospective study that included 98 consecutive HIV-infected patients and 40 HIV-seronegative controls. Only 8 (8%) of infected patients had symptomatic heart failure. In general cardiovascular function was better in earlier stages of the infection (fractional shortening in acquired immunodeficiency syndrome 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 al demonstrated a median survival among patients with AIDS with cardiomyopathy of 101 versus 472 days in those without,[28] whereas another study showed an adjusted hazard for death of 5.86 compared to patients with idiopathic cardiomyopathy.[29] However, with the widespread use of ARTs, not only has the epidemiology of the disease changed, but so has the prognosis. Cardiac diseases account for a quarter of deaths in the post-ART era compared to less than 10% in the pre-ART era. Furthermore, symptoms of heart failure or echocardiographic evidence of cardiomyopathy are associated with 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 4.5 times higher rate than expected. Furthermore, of those who died, 43% (N=13) had echocardiograms prior to death and half had known systolic and/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%/year); all due 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%/year vs.

3.4%/year, p<0.0001). Furthermore, those with contractile reserve were more likely to improve ejection fraction over time (80% vs. 33%, P=0.003) from 30±11% to 44±11%, p<0.0001, vs. from 24±11% to 30±17%, despite no difference in use of anti-remodeling 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, extrapolating evidence from studies in non-HIV-positive patient populations, diastolic dysfunction is a predictor of mortality, though 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 though, other imaging modalities such as MRI and even strain echocardiography need further research to determine what 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 1). The proposed causes include direct infection of the myocardium by the HIV-1 virus with or without myocarditis, toxicity from the medications used to treat HIV-1 infection, opportunistic infections, as well as nutritional disorders, and others.[35, 36] When HIV-associated cardiomyopathy was only thought of in terms of severe, dilated cardiomyopathy, the pathobiology was felt to be from opportunistic infections or as a result of myocarditis. However, as the disease has changed and grown to include more nuanced forms of myocardial involvement, the understanding of the mechanisms too has evolved.

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[41, 42] and in primates with Simian immunodeficiency virus[43] revealed the cytologic identity of cardiac infection was the macrophage as compared to the myocyte. These facts are compatible with the notion that cardiomyocytes lack HIV-1 receptor proteins (gp 120 or gp 24). However, Wang et al. demonstrated that human cardiac fetal myocyte cell lines were capable of ingesting HIV-1 via specific Fc receptors despite the absence of CD4 receptors.[44] Furthermore, HIV-1 infection within cardiac interstitial cells (dendritic cells or endothelial cells) rather than myocytes may play an important pathogenic role as these infected cells serve as viral reservoirs as well as antigen presenting cells mediating inflammation.[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.[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.[48, 49]

Autoimmune Mechanisms

There is evidence that common cardiotropic viruses may alter surface antigens leading to an autoimmune reaction to endogenous epitopes[50] and cardiac specific autoantibodies are more common in HIV-1 infected people, especially those with some degree of myocardial disease, than in HIV-negative controls.[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.[52] Interestingly, there is experimental evidence that blocking some of these proteins may be cardioprotective,[47, 51, 53, 54] and monthly intravenous immunoglobulin(s) in pediatric HIV-1 infected patients was shown to minimize left ventricular dysfunction and improve other markers of myocardial injury.[13, 30]

Inflammation

Pro-inflammatory 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] Tumor necrosis factor in autopsies of HIV-associated cardiomyopathy patients suggest that it is a potent inducer of apoptosis.[58] Some suggest that treatment to reduce oxidative stress may impact 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 (mtDNA) replication and decreased energetics are caused by zidovudine (3′-azido-2′,3′-deoxythymidine, AZT)[61, 62] as well as other nucleoside reverse transcriptase inhibitors (NRTIs), specifically fialuridine (FIAU; (1-[2-deoxy-2-fluoro-β-D-arabinofuranosyl]-5-iodouracil)[63] clevudine (L-FMAU) and lodenosine, a purine NRTI (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 to study the pathophysiologic 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 NIH-funded Pediatric HIV/AIDS Cohort Study's Adolescent Master Protocol 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 were not as normal as those in an HIV-exposed uninfected control group.[65] Children

exposed perinatally to either multi-drug 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 showed that 16% of them had at least one abnormal echocardiographic measure.[66] 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. Also, in HIV-exposed uninfected children, serum cardiac biomarker measurements suggested that perinatal exposure to multiple ART agents might have subclinical myocardial inflammation. Specifically, abacavir exposure was potentially associated with deleterious cardiac effects.[67]

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's Disease.[68, 69] However, the data on nutritional deficiencies resulting in cardiomyopathy are more closely related to socio-economic status rather than presence or absence of HIV-associated cardiomyopathy.[50]

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, though similar in many respects to non-HIV-1 infected patients.[70] In a recent analysis, the prevalence of diabetes mellitus and hypertension—two 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 (AMI) compared to AMI patients who were not infected with HIV.[71] Furthermore, the authors showed similar 30-day and 1-year mortality and MACE in the HIV-positive patients with AMI compared to those without the disease. One of the more compelling findings of the study by Lorgis was that there 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 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 hs-CRP levels and prior myocardial infarction.[20, 22] In contrast, the risk factors that seem to be associated with the development of diastolic abnormalities include higher body mass index and hypertension.[20–22] The obvious next step would be to study whether aggressive control of these risk factors will delay or prevents 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 the privacy concerns and regulations, data on HIV status is not collected in clinical trials and registries and therefore no definitive data exists in this regard. Consequently, therapy is driven by

consensus and data is 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 for the benefits of beta-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-cardiomyopathy patients. Unfortunately neither the rate nor the effectiveness of implantable devices have been reported in the HIV-cardiomyopathy population. It has been suggested that HIV-1 infected patients may be less likely to receive an implantable defibrillator or cardiac resynchronization therapy due to either a belief that they have higher mortality and thus shorter lifespans or for fear of infectious complications.[72] This concern is not without some merit, as a recent analysis showed a higher rate of bacteremia despite ART in HIV-1 infected patients as compared to the general population.[73] 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.[34]

Immune Therapy

While sparse data exists, one retrospective review of intravenous immunoglobulin therapy in 49 children with HIV-1 infection found that it was associated with significant improvements in left ventricular wall thickness and decreases in peak wall stress.[74] 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.[75] In an animal study, monkeys infected with simian immunodeficiency virus as well as killed Mycobacterium avium complex bacteria developed severe left ventricular dysfunction.[57] 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 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 higher incidence of coronary disease, which is a risk factor for myocardial impairment. Some case reports have been published that showed regression and normalization of cardiomyopathy in adults[76] and children[77] that were treated with HAART. In the largest study to date of pediatric patients, over 3,000 children with HIV infection were longitudinally followed for incident cardiomyopathy and to assess the effect of HAART.[78] Over a median of 5.5 years of follow-up, 99 cases of cardiomyopathy were observed, yielding an incidence of 5.6 cases per 1,000 person years. The authors noted that the incidence decreased dramatically in the post-HAART era from 25.6 cases per 1,000 person-years to 3.9 cases per 1,000 person-

years. While this study did not specifically address the effect of HAART on "curing" HIV-cardiomyopathy (specifically LV systolic dysfunction), it did demonstrate 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 100,000 children from the US Pediatric Cardiomyopathy Registry.[79] Thus, the question of whether HAART can actually reverse HIV-cardiomyopathy is not answered and warrants further investigation,

Transplant and Mechanical Circulatory Assist Devices

HIV-1 infection has generally been considered a contraindication for cardiac transplant due to historically poor survival and concerns over progression to AIDS with immunosuppression,[80] despite recent evidence that suggests that immunosuppressant medications can actually increase the efficacy of HAART in treating HIV infection.[81] A survey of cardiac transplant programs revealed that the 70% considered infection with HIV-1 an absolute contraindication to transplant. Indeed, early reports of cardiac transplant in patients subsequently found to have HIV-1 infected after transplantation showed poor outcomes.[82] However, since 2003 when the first cardiac transplant was performed in a known HIV-positive patient[83], outcomes have generally been favorable.[84] No increase in rejection or worsening of HIV status with immunosuppression have been reported. Larger case-series in the US[85] and Europe[86] have shown similar results. Hence calls for re-evaluation of HIV-1 infection as an absolute contraindication have been made.[80]

In 2009, 2 reports of destination therapy with HeartMate XVE implanted in HIV-1 infected patients were published.[87, 88] Both patients did well and did not suffer complications much different from those by non-HIV-1 infected left ventricular assist device recipients. A subsequent case demonstrated no major infectious related complications[89] and no significant increased risk of allosensitization.[90] Thus, while 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 the HIV-associated cardiomyopathy has evolved, but nevertheless remains inadequate. What was once thought of as strictly systolic dysfunction and associated with poorly controlled HIV-1 infection, the widespread use of ART in the Western world has changed the disease from a severe, dilated cardiomyopathy to one of less severe LV systolic function and one with various degrees of impaired diastolic function, often independent of traditional cardiac risk factors. The prevalence of systolic dysfunction has decreased in developed countries and unfortunately in the parts of the world where HIV is most prevalent, ART is not widespread and so the disease remains one of severe systolic impairment with high rates of morbidity and mortality. While the exact incidence, prevalence and pathophysiology remain to be elucidated, it is clear that these patients have poor prognosis if they develop systolic dysfunction. The exact significance of diastolic abnormalities among these patients is not known, necessitating further research to

determine their prognosis and how best to prevent its development. Related to the fact that its pathophysiology is poorly understood, the therapeutic approach to these patients remains unknown as well. Whether or not 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 to the same degree, is unknown. Considering the epidemiologic significance of cardiac functional abnormalities among HIV-1 infected individuals and the lack of definitive data on how to treat these patients, further research is urgently needed in this group particularly in sub-Saharan Africa

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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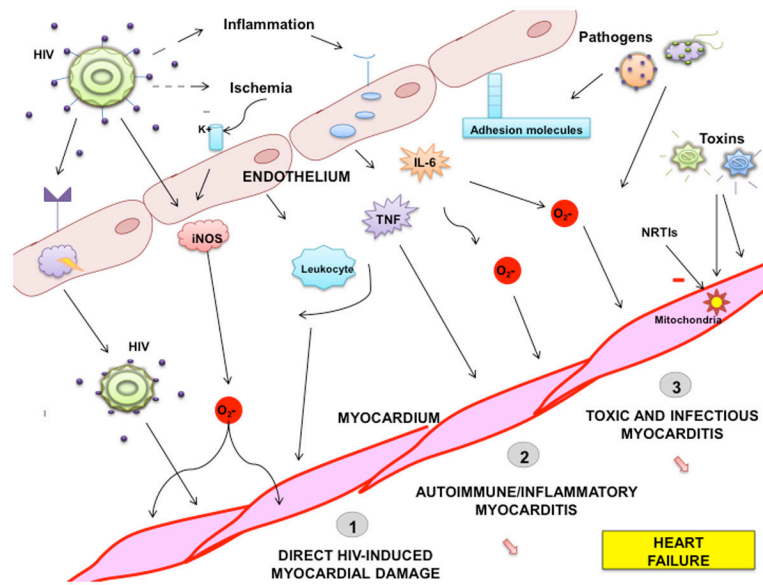
Figure 1.
Pathophysiology of HIV Associated Heart Failure. HIV causes damages myocardium directly and also indirectly through inflammation and increased susceptibility to infections, toxins and eventually, ischemia. The endothelium serves as a reservoir of HIV and also acts to elaborate cytokines, such as tumor necrosis factor and interleukin-6, and free radicals in response to increased inflammation. Other causes of myocardial dysfunction among HIV infected individuals include mitochondrial damage resulting from HIV therapy such as NRTIs and other toxins. HIV=human immunodeficiency virus; TNF=tumor necrosis factor; IL-6=Interleukin-6; iNOS=inducible nitric oxide synthase; NRTIs=nucleoside reverse transcriptase inhibitors.

Table 1

Epidemiology of HIV-Associated Cardiomyopathy.

Study	N	Incidence	Prevalence		Anti-retroviral therapy	Mean CD4 (cells/mm³)	Viral Load (copies/mL)
			Systolic Dysfunction (EF, if reported)	Diastolic Dysfunction (Stage, if reported)			
Pre-HAART							
Levy 1989 [6]	60	NR	16%	NR	None	NR (majority <100)	NR
DeCastro 1992 [7]	72	NR	16.6% (all with EF <50%; mean EF 35%)	NR	Zidovudine	NR	NR
Herskowitz 1993 [8]	69	18% per year	14.5% (all with EF <45%; mean EF 34%)	NR	None	30	NR
DeCastro 1994 [9]	93	2% per 3 months	7.5% (all with EF <45%)	NR	69% on Zidovudine	56	NR
Akhras 1994 [10]	101	NR	20% (all EF <35%)	NR	Zidovudine	67	NR
Coudray 1995 [11]	51	NR	NR	4/6 diastolic function parameters worse in HIV vs. controls (no difference between symptomatic and asymptomatic HIV patients)	~60% on Zidovudine	172±198 in symptomatic- and 422 ±308 in asymptomatic patients	NR
Barbaro 1996 [12]	1236	NR	Mean EF = 48% in HIV vs. 59% in controls	NR, but E/A, IVRT and LA parameters all significantly worse in HIV patients vs. controls	None	670	NR
Lipshultz 1998 [13]	196	4.7% per 2 years	31%	NR	63% on Zidovudine	906 +/− 890	NR
Pugilese 2000 [14]	1042	NR	8.1% in NRTI and 1.8% in ART treated patients	NR	544 on NRTI alone 498 on ART	42±15 in NRTI and 92±52 in HAART treated patients	NR
Post-HAART							
Bijl 2001 [15]	105	NR	3%	NR	91% on ART	Median 340	Median 1.15 x10⁴ (78% fully suppressed)
Kristofferson 2008 [16]	63	<1% over 4.5 years	<1%	NR	95% on ART	710 +/− 350	16300±35800 (79% fully suppressed
Schuster 2008 [17]	30	NR	13% (lowest EF= 39%)	64% (27% stage I, 37% stage II)	100% on ART	591 +/− 314	60% fully suppressed
Hsue 2010 [18]	196	NR	4% (EF range 33%– 49%)	49% (48% stage I, 1% stage II)	82% on ART	Median 420	63% fully suppressed

Study	N	Incidence	Prevalence		Anti-retroviral therapy	Mean CD4 (cells/mm^3)	Viral Load (copies/mL)
			Systolic Dysfunction (EF, if reported)	Diastolic Dysfunction (Stage, if reported)			
Reinsch 2011 [19]	803	NR	34% (EF=32% 45–54%, 1.9% 30–44%, 0.4% 20–29%)	48% (36% stage I, 9% stage II, 3% stage III)	85% on ART	509+/−301	66% fully suppressed
Mondy 2011 [20]	656	NR	18% (EF=17% 35–50%, 1% <35%)	26% (15% stage I, 2% stage II, 9% stage III)	73% on ART	Median 462	91% fully suppressed
Blaylock 2012 [21]	60	8.2 per 100 person years	NR	47% (40% stage I, 7% stage II)	78% on ART	Median 570	60 copies/mL
Cerrato 2013 (meta-analysis) [22]	2242	NR	8.33%	43.4% (31.85% stage I, 8.53% stage II, 3.02% stage III)	98.5% on ART	Median 489	74% fully suppressed

ART=Anti-Retroviral Therapy, EF=Ejection fraction, IVRT=Isovolumic Relaxation Time, LA=Left Atrium, NR = Not Reported, NRTI=Nucleoside Reverse Transcriptase Inhibitors

Table 2

Prognosis of HIV-Associated Cardiomyopathy.

Study	Number of Patients	Length of Study	Definition of Cardiomyopathy	Hazard Ratio for Death	Median Survival	CD4 count (mean)	Mean Ejection Fraction	ART
Curie 1994 [28]	296 (13 had dilated cardiomyopathy)	4 years	FS <28% with global LV hypokinesia	11.68 for patients with dilated cardiomyopathy vs. controls with AIDS	101 days for patients with dilated cardiomyopathy	153 (7.4 in patients with dilated cardiomyopathy)	NR	No
Felker 2000 [29]	1230 (45 with HIV-cardiomyopathy)	4.4 years	NR	5.86 vs. idiopathic cardiomyopathy	NR	NR	NR	NR
Lipshultz 2000 [30]	193 (mean age 2.1 years old)	60 months	LV contractility >2SD below the mean and LV end diastolic dimension >2 SD above mean*	FS: 1.31 RR for each SD decrease Wall thickness: 1.35 for each SD increase	64% at 5 years (38% if FS <2 SD below normal) (45% if wall thickness >1 SD above normal)	690 (normal value for 2 year old is 2298)	NR	NR
Sackoff 2006 [31]	68,669	5 years	NR (only evaluated "cardiovascular disease" as a cause of non-HIV related death	29.2 age-adjusted mortality per 10,000 persons with AIDS for cardiovascular disease	NR	NR	NR	NR
Crum 2006 [32]	4241 (15 total deaths from HF or Cardiomyopathy in study cohort)	13 years	Heart failure or cardiomyopathy diagnosed based on death certificate	6.52 for Congestive Heart Failure 3.97 for Cardiomyopathy	NR	123 pre-HAART era 202 early-HAART era 316 late-HAART era	NR	NR
Wever-Pinson 2011 [33]	60	2.4 +/- 2.1 years	Patients with EF<45%; DSE performed to assess for inotropic contractile reserve	6.6 for the absence of contractile reserve 56% had improvement in EF (mean 48±9%)	NR	243	28 +/- 11%	77%
Tseng 2012 [34]	2860	Median 3.7 years	Causes of death were obtained from death certificates or National Death Index database	4.46 for SCD (13% of deaths due to sudden cardiac death)	NR	Median 312 for patients who died of SCD	Patients with echo, 23% had moderate to severe low EF	NR

ART= Anti-Retroviral Therapy, BSA= Body Surface Area, EF = Ejection fraction, FS= Fractional Shortening, LV= Left Ventricle, NR = Not Reported, NYHA= New York Heart Association, SCD= Sudden Cardiac Death, SD= Standard Deviation.

*
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.