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Infection Diseases Section *Review Article*

Human Immunodeficiency Virus (HIV) and Cardiomyopathy: A Systematic Review

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Abstract

Human immunodeficiency virus (HIV) infection has been associated with cardiac disease, including anatomical or functional disturbance to the heart. Cardiomyopathy (CMP) is one of these disturbances that have been associated with high rates of morbidity and mortality. In this review article, several aspects of potential relationships between HIV infection and cardiomyopathy development have been issued. Most studies indicated increased prevalence, incidence and mortality rates for CMP in the HIV infected patients, especially in more advanced grades of the infection. CD4 cell count has been shown to be associated with both incidence and outcome of HIV-related CMP. In children, also similar findings have been observed with high incidence and mortality rates associated with CMP-HIV have been observed. However, prepartum CMP burden in HIV infected mothers was not different than that in HIV-negative ones. However, evidence about the effects of ART on the development and progression of HIV-related CMP was very controversial. While is some studies, no associations have been found in some others, ART has been associated with either a better or worse disease incidence or condition. We propose more studies with prospective approach and large patient populations to be conducted for better understanding of the effects of different ART agents on the incidence and outcome of HIV-related CMP.

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Introduction

According to the latest report by the World Health Organization (WHO) in 2011, there were approximately 34.0 million people (3.3 million children under 15) globally living with HIV infection, 2.5 million of them were newly infected people, and 1.7 million died of AIDS [1]. After the introduction of highly active antiretroviral therapy (HAART) in 1996, the mortality associated with the HIV-infection has dramatically decreased [2]; therefore, HIV-infected patients live longer. Nevertheless, this survival advantage was not free from complications, and cardiovascular diseases have become more common and a major problem in this patient population. Evidence indicates significant increase in the rates of myocardial infarction [3], stroke events [4], and cardiomyopathy [5].

According to reports of clinical and autopsy studies, the reported prevalence of cardiomyopathy in HIV-positive patients constitutes a broad range from about 4% [6] to as high as 75% [7] in different studies. Mortality in HIV patients has also been reported to be substantially due to cardiomyopathy with up to 6 fold higher rate of death even in HIV+ children [8]. Even having minimal left ventricular dysfunction in children was associated with over 55% mortality in 5 years follow up [9]. The same rates have been reported in adult populations [reff344], although controversial reports also exist [10].

The effect of antiretroviral therapy (ART) on the incidence and prevalence of HIV-related cardiovascular disease has also been not well demonstrated. A large study of over 23 thousand HIV positive patients reported that use of ART is associated with increased risk of acute cardiovas-

cular and cerebrovascular events [11,12]. However, having a more chronic process, cardiomyopathy seems to benefit from ART with declining the incidence and mortality of HIV-related mortality in these patients [8], although strong controversies exist. In this review article, we tried to systematically review the existing literature regarding HIV infection and its association to the incidence and outcome of cardiomyopathy in these patients.

Methods

This systematic review was conducted using the primary search terms including "HIV" and “cardiomyopathy” as the keywords within the timespan of 1990-2013. The search has been repeated using terms “cardiac dysfunction” instead of “cardiomyopathy”. The literature search was performed using the Pubmed database as the main search engine, which we believe provides relatively the largest published data of the most relevant studies in the fields of microbiology and cardiology. We also boosted our search protocol using the citations of the found articles, which was available through Google Scholar database, to find potential reports which either have not been indexed in Pubmed or not been retrieved through Pubmed search.

Overall, 466 studies were found upon a search of the literature by Pubmed using the mentioned keywords. The found titles were screened to obtain the appropriate studies associated with the main purpose of our systematic review. Despite the keywords used to find them, the majority of the studies, were not associated with our review article principle. For example, several studies were analyzing effects of HIV infection on myocardial infarction which was not part of our systematic review protocol; so, we “only” included studies that had investigated cardiomyopathy separately in their analyses. Finally, 54 studies have been remained, and reviewed according to the following categorization of the research: Incidence and prevalence of HIV-induced cardiomyopathy, risk factors of cardiomyopathy in HIV infected patients, cardiac dysfunction and HIV infection, correlation between CD4 count and cardiac dysfunction in HIV infection, mortality associated with HIV-cardiomyopathy, HIV positive children and cardiomyopathy, pregnancy in HIV positive women, and the effects of antiretroviral therapy on HIV-CMP.

Incidence and Prevalence of HIV-induced Cardiomyopathy

The incidence and prevalence of cardiomyopathy (CMP) in HIV positive patients has been reportedly high. Different studies from all over the world have demonstrated the HIV infected patients are at high risk of developing different types of CMP especially dilated CMP (DCMP) and suffering their consequences. Jain et al. [13] in their cross-sectional study of 100 HIV positive patients demonstrated a 67% rate of abnormality in the echocardiography of their patients with DCMP comprising 17.6% of them. In a case-control study, Olusegun-Joseph et al. [14] showed that 5% of HIV+ patients represented DCMP, while none of non infected matched controls demonstrated this abnormality. Chillo et al. [15] reported that about 10% of HIV+ patients attending their clinic with cardiac complains were diagnosed with CMP. Another study but with a prospective approach on the same subject reported the following prevalence among HIV positive patients with cardiac complains: Structural dilatation of the left ventricle in 10%; interventricular septum in 18% and posterior wall thickness increase in 11% [16]. In another approach, from 5328 cases of heart disease in a high prevalence area in South Africa, 518 (9.7%) of patients were HIV positive [17]. In another study, HIV+ patients overally showed an 18% rate of CMP [18]. Pozzan et al. [19] investigating myocardial necropsies of 94 HIV+ patients found cardiac alterations in as high as 94% of patients with cardiac dilatation in 74%, 82% of which having biventricular dilatation and myocarditis in 29%. MRI analysis of 12 HIV positive patients with elevated BNP showed that 25% had left ventricular hypertrophy, while myocarditis was detected in 17% and DCMP and right ventricular failure was available in one patient each [20]. A cross-sectional study of 79 black Africans admitting cardiology clinic in Burkina Faso reported that the clinical presentation was principally heart failure (79%), followed by myocarditis or CMP was in 45 (57%); isolated pericarditis in 25 (32%); and pulmonary hypertension in 4 (5%). 70% of the patients were in stage C Atlanta CDC [21]. In a series of 15 AIDS patients from the USA, 3 had CMP [reff275].

Table 1. Incidence and Prevalence of Cardiomyopathy (CMP) in HIV Infected Patients (compared to none-infected individuals)

Study ref.	Population	Methodology	Prevalence of cardiomyopathy
[10]	157 HIV+	Prospective cohort	Cardiac lesions had occurred in 87(55%) patients during 7-year follow up.
[13]	100 HIV infected>13yr	Cross-sectional	Cardiomegaly (15%), abnormal electrocardiogram (18%), abnormal echocardiography (67%); and diastolic dysfunction (42.8%), dilated cardiomyopathy (17.6%).
[14]	150: 100 HIV+; 50 HIV-	Case-control	Systolic dysfunction (30 vs 8%); diastolic dysfunction (32 vs 8%); DCMP in 5% vs. 0
[15]	102 HIV+ with cardiac complains	Cross-sectional	Pericardial effusion (in 41.2%); hypertensive heart disease (34.3%); pulmonary hypertension (12.7%) and DCMP (9.8%)
[16]	803 HIV+	Prospective case-control	Structural dilatation of the LV in 10.1%; interventricular septum and posterior wall thickness were increased in 18.0% and 11.1%; systolic and diastolic dysfunction was 34.3% and 48.0%, respectively
[17]	5328 heart disease patients (518 HIV+)	Prospective case-control	518/5328 (9.7%) of heart disease cases were identified as HIV-positive; the most common primary diagnosis was HIV-related CMP (196 cases, 38%)
[18]	238; 158 HIV+ (90 AIDS; 68 asymptomatic HIV+); 80 HC	Case-control	28/156 HIV+ (17.7%) had CMP: 24/90 (26.6%) in the AIDS group and 4/68 (2.8%) in the asymptomatic HIV+group ($p<0.01$) and none in the HIV (-) group. LV diastolic dysfunction was noted among 88 out of 158 (55.7%) infected patients.
[19]	94 HIV myocardial necropsies	Observational	Cardiac alterations were observed in 94.4%; 74% cardiac dilation with no relation to known cardiovascular diseases. 82% of patients with biventricular dilation. Myocarditis was diagnosed in 27 (28.7%) cases, 16 (59.3%) of known etiology.
[20]	12 HIV+ with elevated BNP	Prospective cohort	MRI diagnosis of LV hypertrophy in 3(25%), myocarditis in 2 (17%), chronic myocardial infarction 2(17%), DCMP in 1(8%) and right ventricular failure in 1(8%) was made.
[21]	79 HIV+ black Africans admitted to cardiology dep.	Cross-sectional	Heart failure (79%), myocarditis or CMP 45(57%); isolated pericarditis 25 (32%); and pulmonary hypertension 4(5%). 70% of the patients were in stage C Atlanta CDC.
[22]	15 AIDS patients		3 (20%) CMP
[23]	47: 27 HIV+; 20 HC	Case-control	LV mass index was significantly higher and LV fractional shortening was significantly lower in patients with HIV after weight loss than in lean, normal controls.
[24]	64: 32 HIV+; 32 HC		Myocarditis was detected histologically in 11/32 (34.3%) HIV-infected patients and borderline myocarditis was diagnosed in another 13 (40.6%) cases. Controls were negative
[25]	952 asymptomatic HIV+ patients	Prospective cohort	During a mean±SD follow-up of 60±5.3 months, DCMP was detected in 76 (8%) patients, with a mean annual incidence rate of 15.9 cases per 1000 patients. Myocarditis detected in 63 (83%) of patients with DCMP.
[26]	440 AIDS autopsy	Cross-sectional	82(18.6%) had cardiac involvement. DCMP detected in 12 (2.7%), myocarditis in 30(6.8%), pericardial effusion in 53(12%)

Left ventricular mass index was significantly higher in HIV infected patients compared to healthy controls in a case control study of 47 subjects [22]. In a series of 32 HIV+ patients myocarditis was detected histologically in 11/32 (34.3%) HIV-infected patients and borderline myocarditis was diagnosed in another 13 (40.6%) cases, while none of HIV negative patients represented any of the mentioned pathologies [23]. A prospective cohort of 952 asymptomatic HIV positive patients, during a follow up of 60±5.3 months, DCMP was detected in 76 (8%) patients, with a mean annual incidence rate of 15.9 cases per 1000 patients [24]. Autopsy analysis of 440 AIDS patients revealed 82(19%) rate of cardiac involvement with DCMP and myocarditis complicating 12(3%) and 30(7%) of patients [25]. In a prospective cohort of 157 HIV+ patients, cardiac lesions had occurred in 87(55%) patients during 7-year follow up [10]. The summary of studies investigating the incidence and prevalence of CMP in HIV infected patients is presented in table 1.

Risk Factors of Cardiomyopathy in HIV Infected Patients

In the previous section, we described studies investigating the incidence and prevalence of cardiac abnormalities including CMP in HIV infected patients, and demonstrated that the incidence is increased in this population compared to non-infected individuals. Nevertheless, despite the valuable properties of this finding, to have clues to better understanding of the pathogenesis of this correlation as well as inventing preventive strategies, we need to know factors that significantly affect this elevated risk in HIV infection.

CMP: cardiomyopathy; DCMP: dilated cardiomyopathy; HC: healthy controls; HIV: human immunodeficiency virus; AIDS: acquired immunodeficiency syndrome; LV: left ventricularOne of the most important factors which has been demonstrated as a well-recognized factor in the severity and prognosis of the disease is the total CD4 count. Although there are controversial data regarding any associations between these two, most studies are in favor of such a correlation. Jain et al. [reff13] in a recent study from India found no relationship between CMP and CD4 count in their series of 100 HIV infected adults. On the other hand, Patel et al. [reff18] reported that a nadir CD4 percentage less than 15% were independently associated with a higher rate of CMP in children. Similarly, Sliwa et al. [reff35]also found a lower CD4 count in CMP patients with HIV infected patients. El Hattaoui et al. [reff90] reported comparable results with a significant lower CD4 cell count in HIV positive patients with CMP. Table 2 summarizes data of the studies reporting correlations between CD4 count and CMP.

HIV viral load is also another important factor that has been accused to play a major role in the incidence of CMP in HIV positive patients. Sliwa et al. [reff35] reported that viral load in HIV infected patients with CMP was significantly higher than those without it. Similar findings have been reported by Twagirumukiza et al. [reff124] in a study on 416 african HIV infected patients with a higher viral load detection in infected patients with DCMP. However, this was not also a global observation, and controversial reports also exist. Shah [reff137] in a study on children from India found no association between viral load and the stage of CMP.

Anthropometric measures such as body mass index (BMI) have also been associated with CMP in HIV infected patients. In a study from South Africa, Lemmer et al. showed significant relationship between lower mean BMI (21 v. 27 kg/m^2, $p = 0.02$), mid-upper arm circumference (26.2 vs. 27.3 cm, $p = 0.02$), and bone-free arm muscle area (26.7 vs. 32.8 cm^2, $p = 0.02$) in univariate analysis, while after multivariable analysis, a lower BMI remained the only independent anthropometric risk factor for CMP (OR, 0.76, 95%CI, 0.64 - 0.97) [reff42]. In a study of 416 HIV positive patients, both univariate and multivariate analyses revealed that low socio-economic status, estimated duration of HIV-1 infection, CD4 count, HIV-1 viral load, CDC stage B and C of HIV disease and low plasmatic level of selenium were factors significantly associated with the development of cardiomyopathy [reff124]. HIV viral load is also another important factor that has been accused to play a major role in the incidence of CMP in HIV positive patients. Sliwa et al. [reff35] reported that viral load in HIV infected patients with CMP was significantly higher than those without it. Similar findings have been reported by Twagirumukiza et al. [reff124] in a study on 416 african HIV infected patients with a higher viral load detection in infected patients with DCMP.

Table 2. Studies Reporting Correlations between CD4 Count and CMPA prospective cohort study of 174 HIV

Study	Population	Methodology	Prevalence of cardiomyopathy
[6]	296 HIV+ adults	Cross-sectional	Compared to other forms of cardiac dysfunction, DCMP was significantly associated with CD4 cell count < 100 mm3.
[8]	335 HIV+ children	Cohort	Among HAART users, a nadir CD4 percentage less than 15% were independently associated with a higher rate of CMP.
[13]	100 HIV infected>13yr	Cross-sectional	No relationship between diastolic dysfunction & CD4 count has been detected
[17]	5328 heart disease patients: 518 HIV+	Prospective case-control	CMP cases were more likely to have a lower CD4 count [median 180 (71-315) vs. 211 (96-391); P = 0.019] than the rest.
[18]	238; 158 HIV+ (90 AIDS; 68 asymptomatic HIV+); 80 HC	Case-control	CMP was significantly higher in the HIV+ low CD4 (<100/mm3; n=16 [57%]) than those with CD4 100-200/mm3, n=6 (21.42%). [reff90]
[27]	416 HIV+ African	Cross-sectional	By multivariate analysis, DCMP was associated with lower CD4 count.
[28]	92 HIV+ ART naïve children	Cross-sectional	Patients with HIV cardiomyopathy (n = 4) had lower CD4 counts (mean 182 cells/mm3, p = 0.04). CD4 count and CD4% did not correlate with the stage of the disease as per the CDC classification.
[33]	90: 45 HIV+ART naïve; 45 HC	Case-control	Low CD4 count was significantly associated with pericardial effusion (p= 0.048) but not with diastolic or systolic dysfunction. (no numbers regarding each group provided!)
[37]	20 HIV+:12 with LV hypokinesis; 8 autopsy from patients without cardiac disease	Case-control	All specimens with unexplained congestive heart failure had CD4 counts less than 100/mm^3
[38]	138 HIV+: 41 AIDS; 49 AIDS related complex (ARC); 32 with chronic lymphoadenopathy syndrome (LAS) and 16 with asymptomatic HIV infection	Case-control	LV shortening fraction was lower in the subgroup with CD4 lymphocyte count less than 100/mm^3 (31 +/- 7 vs 34 +/- 5; p=0.055).
[39]	196 vertically HIV-infected children (median age: 2.1 years)	Prospective cohort	No association was seen between longitudinal changes in LV fractional shortening and CD4 cell count z score.
[40]	75: 30 AIDS; 24 HIV+; 21 HIV negative		DCMP occurred in 6(31.6%) of the patients with a CD4 cell count < or =100/mm(3) and two (6.1%) in those with absolute CD4 counts >100/mm(3) ($\chi 2$ = 4.02, p = 0.03).
[41]	952 asymptomatic HIV+ patients	Prospective cohort	The incidence of DCMP was higher in patients with a CD4 count< 400 cells/mm3
[42]	173 HIV+	Cross-sectional, follow up in 71 patients	Median CD4 cell count in DCMP patients was 38 cells/mm^3

However, this was not also a global observation, and controversial reports also exist. Shah [reff137] in a study on children from India found no association between viral load and the stage of CMP.

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ciated with the development of cardiomyopathy [reff124].

Cardiac Dysfunction and HIV Infection

Aside from anatomical injuries to the myocardium by the HIV infection, this infection has been widely reported to be able to disturb cardiac function as well. Lubega et al. [reff155] in a study from Uganda showed that the prevalence of left ventricular systolic dysfunction in HIV infected patients was 17%. The prevalence was 22% in a cross-sectional study of 151 HIV positive patients from Zimbabwe [reff363]. Reinsch et al. [reff30] in a prospective case-control study reported that the prevalence of systolic and diastolic dysfunction among HIV infected individuals were 34% and 48%, respectively. The prevalence of diastolic dysfunction has been shown 43%, in a series of 100 HIV infected patients from India [reff13]. This rate was 18% in another study of 45 patients from the same country and systolic dysfunction was 7% [reff49].

Olusegun-Joseph et al. [reff15] in a case-control study from Nigeria reported that both systolic and diastolic dysfunction were significantly more prevalent in HIV infected patients. a study from Morocco, however, reported the highest rate of diastolic dysfunction in HIV infected patients with 88 out of 158 (55.7%) infected patients representing left ventricular diastolic dysfunction [reff90]. Table 3 summarizes data of cardiac dysfunction (either systolic or diastolic) in HIV positive patients.

Correlation between CD4 Count and Cardiac Dysfunction in HIV Infection

As mentioned before, the majority of the existing evidence suggests that HIV infection can lead to cardiac dysfunction, either in its systolic or diastolic function. However, this gives us no enough data on the factors associated with HIV infection that can predict cardiac dysfunction in this patient population. Again, like the incidence of CMP, CD4 cell count is one of the main factors that have been investigated for this purpose, and controversial data have been reported.

positive patients, Herskowitz et al. [reff368] reported 9 patients experiencing symptomatic heart disease, all of them having CD4 T cell counts < 200 mm^3, which represented a significant factor in predicting cardiac disease in HIV infected patients. Cardoso et al. [reff382] also reported that HIV infected patients with CD4+ lymphocytes counts < or = 100/mm^3 had more frequent abnormal echocardiograms than those with CD4+ lymphocytes counts > 100/mm3. Similar finding has been reported by Herskowitz et al. [reff412] demonstrating a greater proportion of prospective and referred patients with LV dysfunction to have CD4 counts < 100/mm^3 (62 and 79%, respectively) than did those without LV dysfunction (35%). All of HIV+ patients diagnosed with unexplained congestive heart failure had CD4 counts less than 100/mm^3 in a cross-sectional study [reff423]. An Italian study revealed that left ventricular shortening fraction was lower in the subgroup with CD4 lymphocyte count less than 100/mm3 (31 +/- 7 vs 34 +/- 5) [reff451].

On the other hand, as mentioned before, controversial data also exists in the literature putting strong doubts on the existence of any relationship between CD4 cell counts and cardiac dysfunction in HIV infected patients. Jain et al. [reff13] found no significant association between diastolic dysfunction and CD4 cell count. Similar results have been reported by Guha et al. [reff49] reporting no association between CD4 cell count and either diastolic or systolic dysfunction. Lipshultz et al. [reff341] also reported no association was seen between longitudinal changes in LV fractional shortening and CD4 cell count z score.

Mortality Associated with HIV-Ardiomyopathy

In the previous sections we described the incidence of CMP and cardiac dysfunction in HIV infected patients as well as any potential interfering factors that may affect these rates; but the clinical significance of these issues would become most highlighted when they can be attributed to the survival of patients. In HIV non-infected individuals, CMP has been associated with an increased risk of death [Elliott PM, Poloniecki J, Dickie S, Sharma S, Monserrat L, Varnava A, Mahon NG, McKenna WJ. Sudden death in hypertrophic cardiomyopathy: identification of high risk patients. J Am Coll Cardiol. 2000 Dec;36(7):2212-8.].

Table3. Cardiac dysfunction (either systolic or diastolic) in HIV positive patients

Study	Population	Methodology	Major findings
[6]	296 HIV+ adults	Cross-sectional	Cardiac dysfunction was identified in 44 (14.9%) subjects (dilated cardiomyopathy in 13 (4.4%); isolated right ventricular dysfunction in 12(4.1%); borderline left ventricular dysfunction in 19(6.4%)).
[7]	8 HIV+children with cardiac dysfunction	Cross-sectional/COHORT	Decreased left ventricular function in all eight were detected
[9]	185 vertically HIV+children	Prospective cohort	The 5-year cumulative incidence of congestive heart failure was 12.3%. Mild LV dysfunction was present in 29 (18%) of 158 children with 2 echocardiography within the first year.
[13]	100 HIV infected>13yr	Cross-sectional	Diastolic dysfunction (42.8%)
[14]	150: 100 HIV+; 50 HIV-	Case-control	Systolic dysfunction (30 vs 8%; p = 0.024); diastolic dysfunction (32 vs 8%; p = 0.002)
[15]	102 HIV+ with cardiac complains	Cross-sectional	pulmonary hypertension diagnosed in 13 (12.7%)
[16]	803 HIV+	Prospective case-control	Systolic and diastolic dysfunction was 34.3% and 48.0%, respectively
[18]	238; 158 HIV+ (90 AIDS; 68 asymptomatic HIV+); 80 HC	Case-control	Left ventricular diastolic dysfunction was noted among 88 out of 158 (55.7%) infected patients.
[21]	79 HIV+ black Africans admitted to cardiology Dep.	Cross-sectional	Pulmonary hypertension in 4 (5%)
[30]	230 HIV+ children: 32HIV+; 156 AIDS related complex; 42 AIDS	Case-control	Left ventricular systolic dysfunction (17%), congenital heart disease (4.8%) and cor pulmonale (1.3%).
[31]	157 HIV+ acutely ill	Cross-sectional	Left ventricular dysfunction in 33/151 (9%)
[33]	90: 45 HIV+ART naïve; 45 HC	Case-control	In HIV+ patients, diastolic dysfunction (18%), systolic dysfunction (7%). Compared to the controls the study population had statistically higher rate of diastolic dysfunction (p = 0.035) but not systolic dysfunction (p = 0.61)
[34]	174 HIV+	Prospective cohort	55(31.6%) patients had global left ventricular dysfunction, with 84% of them having advanced disease (New York Heart Association Class III or IV) on presentation.
[39]	196 vertically HIV-infected children (median age: 2.1 years)	Prospective cohort	2 year cumulative incidence of CHF was 4.7%.
[43]	60 women with peripartum cardiomyopathy (PPCMP): 20 HIV+; 40 HIV-	Prospective cohort	No statistically significant difference in LVEF was observed between cases and controls
[44]	84 children born to infected mothers: 43 HIV seroreverted; 41 HIV+	Cross-sectional	In HIV+ patients: congestive heart failure diagnosed in 12(14.3%), pulmonary hypertension in 2(2.4%)
[45]	84 HIV+	Cross-sectional	6 (7.1%) had congestive heart failure
[46]	332 heart disease: 166 HIV+; 166 HIV-	Case-control	Systolic function was very severely impaired at the higher stages of AIDS compared to HIV stage A infection or normal controls.
[47]	136 HIV+: 17 asymptomatic; 26 AIDS related complex; 93 AIDS	Prospective Cohort	During a mean follow-up period of 415 +/- 220 days, 7(5.2%) patients, all in the AIDS subgroup (7.5%), developed clinical and echocardiographic findings of acute global left ventricular dysfunction.
[48]	124 HIV+; 101 AIDS (A); 23 HIV+ (B)		In Group A, left ventricular dilatation and/or dysfunction were found in 20(20%) patients. 10 patients had tachyarrhythmias compared to only two in Group B.
[36]	1819 HIV+: 69 HIV+ were prospectively followed	Prospective cohort	During a mean follow-up duration was 11 months, 14.5% developed global LV hypokinesia with an incidence of 18% per patient-year. After 18-months of follow-up period, 4 prospective patients (5.8%) developed symptoms of congestive heart failure.
[42]	173 HIV+	Cross-sectional, follow up in 71 patients	26(15%) patients with abnormalities of ventricular size or function or both were identified. Left ventricular dilatation without loss of function in 6(3.5%) patients. 18/71(25%) of whom had myocardial dysfunction.

Table 4. Mortality associated with CMP in HIV positive patients

Study	Population	Methodology	Major findings
[6]	296 HIV+ adults	Cross-sectional	During the study 12/13 (92%) subjects with DCMP, 5/12 (42%) with right ventricular dysfunction, and 8/19 (42%) with borderline left ventricular function died of AIDS-related conditions. Subjects with DCMP had a significantly decreased survival than those with normal hearts. The median survival from the index echocardiogram was 101 days (95% CI, 42 to 146) for the subjects with cardiomyopathy compared with 472 days (383 to 560) for those with normal hearts and a CD4 cell count of < 20 mm3.
[7]	8 HIV+children with cardiac dysfunction	Cross-sectional/CHOHORT	All patients subsequently died of noncardiac causes. Results of autopsies on four of eight patients showed focal myocarditis in two (25%) and DCMP in 2(25%) others.
[8]	335 HIV+ children	Cohort	CMP was associated with a 6-fold higher death rate.
[9]	185 vertically HIV+children	Prospective cohort	For these 29 children, the 5-year mortality was 55.4%. In the 8 children with LV mass z score of > 2 SD on both initial and follow-up echocardiograms, the 5-year mortality was 75%.
[10]	157 HIV+	Prospective cohort	During 7-year follow up, in a multivariate analysis the lowest socioeconomic status and the pericardial effusion were the independent predictors of death, while DCMP was associated with longer survival.
[21]	79 HIV+ black Africans admitted to cardiology Dep.	Cross-sectional	The overall hospital mortality rate was 15%.
[34]	174 HIV+	Prospective cohort	Sudden cardiac death in 1; 3 died of heart failure.
[43]	60 women with peripartum cardiomyopathy (PPCMP): 20 HIV+; 40 HIV-	Prospective cohort	No statistically significant difference in LVEF and 2 years of mortality was observed between cases and controls
[47]	136 HIV+: 17 asymptomatic; 26 AIDS related complex; 93 AIDS	PROSPECTIVE Cohort	During a mean follow-up period of 415 +/- 220 days, 6/7(85%) AIDS patients with left ventricular dysfunction died of congestive heart failure with a mean survival time from symptom onset of 41 ± 13 days; the only surviving patients was diagnosed with left ventricular dysfunction reversible with treatment
[51]	2,860 HIV+	Retrospective cohort	230 deaths over a median of 3.7 years of follow-up; the mean sudden cardiac death (SCD) rate was 2.6 per 1,000 person-years (95% CI: 1.8 to 3.8), 4.5-fold higher than expected; Compared with other deaths, SCDs had a higher prevalence of CMP (23% vs. 3%), heart failure (30% vs. 9%), and arrhythmias (20% vs. 3%).
[52]	127 HIV+ with Heart disease suspicion: 96 had AIDS (A); 31 pre-AIDS (B)	Prospective cohort	65 patients (51%) died during follow-up (group A only). There were 19 cardiac deaths (15%). 9(47%) of cardiac death were in patients with CMP. Total mortality was 85% in patients with DCMP, 73% in myocarditis cases, 71% in pericarditis cases, 66% in right ventricular dilatation cases, 34% in normal cases.
[53]	114 HIV+: 31 asymptomatic; 11 AIDS related complex; 72 AIDS	Prospective case-control; survival mean follow up: 44 months	29 (40.2%) AIDS patients died. Death was attributed to a cardiac event in 4/29(13.8%) patients.
[54]	2030 HIV+ (A):201 (10%) had suspected cardiovascular inv. (B)	Cross-sectional	Among B patients, mortality was increased in patients with CMP or myocarditis (OR 2.72, 95% CI 1.09-6.81), and right ventricular dysfunction and/or pulmonary hypertension (OR 4.67, 95% CI 1.44-15.2). Patients in group B had a significantly increased cardiac death rate than group A patients (0.114 vs 0.018, p < 0.001).
[55]	1230 CMP: 45 HIV CMP	Cohort	HIV infection was associated with higher mortality (adjusted HR, 5.86; 95%CI, 3.92 to 8.77, in multivariate Cox regression)
[56]	164: 82 HIV DCMP; 82 IDCM	Case-control	The staining intensity of iNOS correlated to mortality rate, because it was higher in HIV-DCM patients and, in particular, in those with an optical density unit >1.
[57]	28 HIV+Myocardial injury+(A); 46 HIV+ myocardial injury negative(B); 52 HIV-low risk; 14 HIV-drug users	Case control	On follow up, 6 subjects with normal echocardiograms but raised autoantibody concentrations had died after a median of 298 days, three with left ventricular abnormalities at necropsy. This compared with a median survival of 536 days for 21 HIV positive patients with normal cardiological and immunological results.
[58]	96: 60 male HIV+; 36 HC	Prospective cohort of 36 months	Within the three-year observation period, 28 (46.7%) of the patients died from HIV-related disease.
[59]	74 AIDS patients died	Cross-sectional	32 had cardiac pathology. 6 (18.7%) had cardiomegaly. The most common pathological finding was nonspecific myocarditis.
[60]	12 AIDS died	Cross-sectional	7/12 (58.3%) were positive for HIV-1; 6/7 (85.7%) patients represented pathological signs of myocarditis.

In HIV positive patients, the rate of cardiac deaths in a cohort of 60 patients was 11 with an event rate of 7.6%/year, after 2.4 ± 2.1 years of follow [reff31]. Tseng et al. [reff23] in a prospective cohort study of 2860 HIV positive patients reported that compared to other deaths, sudden cardiac deaths had a higher prevalence of CMP (23% vs. 3%) [reff23]. Patel et al. [reff18] reported a 6-fold higher mortality rate in patients with CMP than in other HIV infected individuals. Cecchi et al. [reff344] also reported the highest mortality rate in HIV patients with DCMP comprising 85% of patients, followed by myocarditis cases (73%), pericarditis cases (71%), right ventricular dilatation cases (66%), and normal heart cases (34%) after 6-36 months of follow up. In contrast, Longo-Mbenza et al. [reff340] reported a significantly higher survival for HIV infected patients with DCMP compared to those with the lowest socioeconomic status and the pericardial effusion. Table 4 summarizes data of CMP-associated mortality reviewed in this study.

HIV Positive Children and Cardiomyopathy

HIV positive children like adults are at a substantial risk of morbidities and mortality associated with the infection [Judd A, Doerholt K, Tookey PA, Sharland M, Riordan A, Menson E, Novelli V, Lyall EG, Masters J, Tudor-Williams G, Duong T, Gibb DM; Collaborative HIV Paediatric Study (CHIPS); National Study of HIV in Pregnancy and Childhood (NSHPC). Morbidity, mortality, and response to treatment by children in the United Kingdom and Ireland with perinatally acquired HIV infection during 1996-2006: planning for teenage and adult care. Clin Infect Dis. 2007 Oct 1;45(7):918-24.]. HIV-related CMP is one of these complications that has the potential to induce a high rate of deaths. In a cohort of 335 HIV positive children, Patel et al. [reff18] reported that 99 children (29.5%; 5.6/1000 person years) were diagnosed with CMP, at a median age of 9.4 year for diagnosis of CMP. In a case-control study of 230 HIV infected patients, children having AIDS were significantly at higher risk of developing CMP compared to asymptomatic infection (76% vs. 25%, respectively)[reff155]. In a cohort of 185 vertically infected children, the 5-year cumulative incidence of congestive heart failure was 12.3% [reff160]; mild LV dysfunction was present in 29 (18%) of 158 children who had follow up echocardiograms within the first year. For these 29 children, the 5-year mortality was 55.4%; in the 8 children with LV mass z score of > 2 SD on both initial and follow-up echocardiograms, the 5-year mortality was 75% [reff160]. Another prospective cohort of 196 vertically infected children reported that 2 year cumulative incidence of CHF was 4.7% [reff341] Heart rate and LV mass significantly showed progressive abnormalities; no association was seen between longitudinal changes in LV fractional shortening and CD4 cell count z score [reff341]. Data of studies investigating CMP in children is summarized in table 5.

Pregnancy in HIV Positive Women

Pregnancy in HIV infected women might be troublesome both to the mother and the fetus. Moreover, treatment of the infection in the mother might have some side effects on the fetus. In a case control of 82 pregnant women (41 HIV infected and 41 non-infected), authors reported that the only echocardiographic measure different in the two maternal groups was mean right ventricular systolic pressure (18 vs. 22.6), no other difference in the fetal or maternal measures found. Moreover, no difference in the cardiac defects regarding ART therapy within the first trimester of pregnancy has been observed in a cohort of 1414 pregnant women [reff53]. In a cohort of 60 women with with peripartum CMP, o statistically significant difference in left ventricular ejection fraction and 2 years of mortality has been observed between the HIV-positive cases and -negative controls [reff70]. So, our review suggests no additional risk of pregnancy problems in HIV infected mothers than non-infected ones.

Effects of antiretroviral therapy on HIV-CMP

Antiretroviral therapy (ART) in HIV infected patients has the potential to induce either beneficial or hazardous effects to the cardiac health of the patients, so it is crucial to have a proper view on the effects of ART on the development or treatment of CMP in HIV infected patients. There are controversial evidence regarding the effects of ART on the heart of patients. In a cross sectional study of 100 patients, Jain et al. [reff13] reported no relation between ART and diastolic dysfunction.

Table 5. HIV-related cardiomyopathy in children

Study	Population	Methodology		Major findings
[7]	8 HIV+children with cardiac dysfunction	Cross-sectional/cohort	Echo	Decreased left ventricular function in all eight, dilated left ventricular myopathy in 6(75%), concentric left ventricular wall thickening in 2(25%), enlarged right ventricle in 2(25%), and pericardial fluid in 3(37.5%). All patients subsequently died of noncardiac causes. Results of autopsies on four of eight patients showed focal myocarditis in two (25%) and DCMP in 2(25%) others.
[8]	335 HIV+ children	Cohort		99 (29.5%; 5.6/1000 person years) were diagnosed with CMP; median age of CMP diagnosis: 9.4 yr; CMP was associated with a 6-fold higher death rate.
[9]	185 vertically HIV+children	Prospective cohort		The 5-year cumulative incidence of congestive heart failure was 12.3%. Mild LV dysfunction was present in 29 (18%) of 158 children with 2 echocardiography within the first year. For these 29 children, the 5-year mortality was 55.4%.
[28]	92 HIV+ ART naïve children	Cross-sectional		Patients with HIV-CMP (n = 4) had lower CD4 counts (mean 182 cells/mm3, p = 0.04).
[30]	230 HIV+ children: 32HIV+; 156 AIDS related complex; 42 AIDS	Case-control		Heart abnormalities were most prevalent among AIDS (76.2%) and least in asymptomatic HIV+ (25%); The abnormalities included; Sinus tachycardia (21%), left ventricular systolic dysfunction (17%), right ventricular dilatation (14%), congenital heart disease (4.8%), dilated cardiomyopathy (3.0%), pericarditis (2.2%) and cor pulmonale (1.3%).
[39]	196 vertically HIV-infected children (median age: 2.1 years)	Prospective cohort		2 year cumulative incidence of CHF was 4.7%. Heart rate and LV mass showed significantly progressive abnormalities.
[44]	84 children born to infected mothers: 43 HIV seroreverted; 41 HIV+	Cross-sectional	PREVALENCE	In HIV+ patients: congestive heart failure (12 cases); DCMP (5 cases), pericardial tamponade (2 cases), pulmonary hypertension (2 cases)
[64]	48 HIV-1+ children: 24 with cardiac impairment; 24 control	Case-control		Conditional logistic regression to test for an association between coxsackievirus antibody titer and the presence or absence of cardiac impairment, by any indicator, showed an OR of 1.11 (95% CI, 0.58-2.10; P=.75), indicating no association between coxsackievirus infection and cardiac impairment.
[65]	9 symptomatic HIV+ children	Clinical trial of 12 weeks ACEI administration		Pulmonary arterial pressure was not decreased, however the fractional shortening and mean velocity of circumferential fiber shortening improved significantly.
[66]	137 HIV+ children	Retrospective cohort of patients under different treatments		The odds that a CMP would develop was 8.4 times greater in children who had previously used AZT than in those who had never taken AZT (95% CI, 1.7 to 42.0).
[62]	34 HIV+ children: 18 ART+; 16 ART-	Case-control		ART was associated with improvements in left ventricular function (fractional shortening; 33.5% vs. 17%), CD4 count (30.5% vs. 12%), viral load suppression;
[63]	Children 18 mo-12 yr	Cross-sectional	Prevalence	Prevalence of cardiac abnormalities in HIV-infected children was 75.9% including: DCMP (33.7%), decreased LVSF of ≤ 25% in 33.7%, increased left ventricular mass (20.5%) and pericardial effusion (14.5%).

However, in a prospective cohort of 335 HIV infected children, Patel et al. [reff18] found that highly active ART (HAART) was associated with a 50% decrease in the risk of CMP, but zalcitabine (ddC) was associated with 80% higher risk of CMP. Among HAART users, older age at HAART initiation, ddC use before HAART initiation, and initiating a HAART regimen containing zidovudine (ZDV) were independently associated with a higher rate of CMP [reff18]. In a case control study of 34 HIV infected patients in which 18 patients received ART (cases) but 16 did not (controls) ART was associated with improvements in left ventricular function (fractional shortening; 33.5% vs. 17%) [reff28]. Cardiac side effects of ART therapy has also been a matter of research. A case control study of 1042 HIV positive patients showed that ART-related cardiac complications (including arrhythmias, pericarditis, ischaemia, dilated cardiomyopathy, endocarditis, pulmonary hypertension, and myocarditis) were observed in 282 of 544 (51.8%) patients treated with NRTI, compared with 93 of 498 (18.6%) patients with HAART ($P < 0.0001$) [reff298].

Conclusion

In this review article, several aspects of potential relationships between HIV infection and cardiomyopathy development have been issued. In the first section, reviewing articles with an overall patient population of 8343, we found that most studies indicate an increased prevalence and incidence rates for CMP in the HIV infected patients, especially in more advanced grades of the infection. In the second section, potential factors affecting the development of HIV-related CMP have been investigated. 10,579 patients in these articles had been studied regarding associations between CD4 cell count and CMP development, and in only 2 articles with a cumulative population of 296, no association between CD4 count and CMP has been found. In the third section, studies regarding cardiac dysfunction and HIV infection comprising 5916 patient population have been reviewed. The rate of cardiac dysfunction was high in HIV infected patients, and in those comparing it between the infected and non-infected patients, only one prospective cohort on pregnant women, reported no significant difference. Then, in the forth section, potential association between HIV-related cardiac dysfunction and CD4 cell count has been investigated and a positive correlation has been observed. The fifth section issued mortality of HIV-related CMP. 7049 patients were reviewed in these studies. Most of them reported high mortality rate associated with HIV-CMP, especially in AIDS patients. The next section investigated the HIV-associated CMP in children. Overall 1358 children have been reviewed, and high incidence and mortality rates associated with CMP-HIV have been observed. The next section studied prepartum CMP in HIV infected patients. Despite the high burden, no difference has been observed than HIV-negative mothers. The last section was related to the effects of ART on the development and progression of HIV-related CMP. In this section, the inconsistencies are highest. While is some studies, no associations have been found in some others, ART has been associated with either a better or worse disease incidence or condition. We propose more studies with prospective approach and large populations to be conducted to better discuss this issue.

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