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Cardiovascular Manifestation of HIV: Review

Anju Bhardwaj[1], Rupen Parikh[2], Joseph Daoko[2], Luv Singh[3], Fayez E. Shamoon[2], Jihad Slim[3,*]

[1]Department of Medicine, St.Joseph's Regional Medical Center, Paterson, New Jersey
[2]Division of Cardiology
[3]Infectious Diseases, St.Michael's Medical Center & Seton Hall University, Newark, New Jersey -07102

Abstract

HIV infection is a leading health problem across the entire world, including United States. Recent advances in medicine have led to a significant decline in mortality associated with HIV infection and hence increased life expectancy in HIV-infected individuals. Cardiovascular complications represent an increasingly important health concern in HIV-infected population especially after the introduction of anti-retroviral therapy. Numerous research studies have demonstrated the increased prevalence of cardiovascular disease in HIV infected individuals. The etiology of the preponderance of cardiovascular manifestations associated with HIV is still not well established. It may be attributed to virus itself, the effects of anti-retroviral medications; or altered immune mechanisms associated with the infection. The stratification of cardiovascular risk and cardiovascular monitoring in HIV patients poses a challenge to the physicians in the modern age. The cardiovascular lesions reported in HIV infection include pericardial disease with effusion and tamponade, myocarditis, dilated cardiomyopathy with left ventricular dysfunction, endocarditis, coronary artery disease, pulmonary hypertension, cardiac autonomic dysfunction and certain rare neoplasms. HIV infection in itself can be a potential risk factor for accelerated coronary artery disease. The advent of anti-retroviral therapy has witnessed an increased risk of metabolic syndrome, hyperlipidemia and insulin resistance in HIV patients on HAART. Thorough understanding of the course of cardiac related illnesses in HIV infection helps in early diagnosis, appropriate intervention and therapy. The following review overviews the cardiac abnormalities associated with HIV infection focusing on early diagnosis, therapy and prognosis.

Introduction

Acquired Immunodeficiency Syndrome (AIDS) caused by infection with human immunodeficiency virus (HIV) is characterized by profound immunosuppression that predisposes a patient to wide array of opportunistic infections, malignant neoplasm and multi-organ dysfunction. It is a leading health problem in the entire world, including United States. An estimated 44,087 persons were newly diagnosed with HIV in 2007 in the 34 states and 5 U.S. dependent areas, which is substantially higher than the previous estimate. The first cardiac manifestation to be reported in AIDS patient was myocardial kaposi sarcoma on autopsy back in 1983 (Autran et al., 1983). Despite the fact that cardiac involvement was recognized early in AIDS epidemic, the heart and great vessels were not so frequently affected by opportunistic infections and neoplastic processes in HIV-infected patients. According to the recent data, the number of people living with HIV is on the rise secondary to the advent of highly active antiretroviral agents, which have greatly reduced morbidity and mortality associated with HIV infection (Boccara et al., 2005). This highly active anti retroviral treatment (HAART) regimen and the increased life span of infected individuals on HAART have led to an increased incidence of cardiovascular complications, which were often unrecognized in the early days of the epidemic (Letts and Lopez-Candales, 2004; Milei et al., 1998). (Table 1.) About 50% of AIDS cases reported some cardiac abnormalities (Milei et al., 1998). These cardiovascular manifestations include but are not limited to dilated cardiomyopathy (CMP), pericardial effusion, endocarditis, myocarditis, pulmonary hypertension, and atherosclerotic heart disease. (Table 1) Potential mechanisms of cardiac complications in AIDS include but are not limited to direct cardiotoxicity by the HIV itself, immune mediated particularly cytokines, nutritional deficiencies and HAART (Khunnawat et al., 2008). HIV-1 is known to be one of the leading causes of dilated cardiomyopathy in the United States associated with biventricular dilatation (Twagirumukiza et al., 2007). After the advent of HAART, there has been increased propensity toward metabolic syndrome secondary to hyperlipidemia and atherosclerotic heart disease (Zareba et al., 2005). Whether treatment with protease inhibitors increase the risk of premature coronary artery disease (CAD) has always been debatable. Recent studies indicate that protease inhibitor and certain nucleoside reverse transcriptase inhibitors (NRTI) accelerate the CAD related events and metabolic disorders (Boccara et al., 2005; Barbaro et al., 2003).

The increased incidence of heart disease in HIV population poses a diagnostic and therapeutic challenge to the residents, internists, cardiologists, radiologists and infectious disease specialists. In this article we review the various cardiovascular manifestations of HIV infection, including its causes and pathogenesis.

***Corresponding author:** Jihad Slim, M.D, Div. of Infectious Diseases, 6th Floor, St. Michael's Medical Center, 268 Dr. MLK Jr BLVD, Newark, NJ 07102, Tel: 973-877-5160; Fax: 973-877-5124; E-mail: jsmdsmmc@aol.com

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Cardiaovascular Disorders	Level of Risk with HIV-1 infection	Effect of HAART on Incidence (Increase or Reduce)
Pericardial Disease (Restrepo et al., 2006)	11-17%/year	Decrease
Myocardial Disease (Khunnawat et al., 2008; Sani, 2008)	16/1000 HIV patients	Seven fold reduction in incidence
Infective Endocarditis (Valencia and Miro, 2004)	5-20% of hospital admission in HIV	Decrease
Coronary artery disease (Sabin et al., 2008; Barbaro et al., 2003)	6-15% of total death in HIV patients	Increase
Hypertension (Thompson et al., 1992)	20-25% prevalence	Increase
Pulmonary Hypertension (Humbert et al., 1998)	1 in 200 HIV patients	Decrease
Thrombosis & Embolism (Witz et al., 2000; Sugerman et al., 1996)	2% of HIV patients	Increase with Protease Inhibitors

HAART= highly active anti retroviral treatment

Table 1: Level of Risk with HIV-1 infection on different cardiovascular disorders and effect of HAART on incidence.

Pericardial disease

Pericardial disease in AIDS can be symptomatic or asymptomatic; acute or chronic and can be attributed to various opportunistic infections or malignancies, but most of the times etiology is unidentified. Pericardial effusion is the most common cardiovascular complication of HIV infection, particularly more in patients with advanced disease. Before the introduction of HAART regimen, frequency of this complication ranged from 5% - 46% with incidence of about 11-17% per year (Restrepo et al., 2006). HIV associated pericardial effusion might be associated with a low CD4 count and low albumin indicating pericardial effusion to be a marker of shortened survival (Heidenreich et al., 1995). However, it still remains unclear whether HIV is a direct cause of effusion. In African countries, tuberculosis is implicated as most common cause of pericarditis in HIV patients (Sa et al., 2006). Other causes of the effusion include viral, bacterial (most commonly Staph aureus), fungal and certain malignancies like lymphoma, etc. Cardiac tamponade can also occur as a result of compression of heart by the effusion. Regardless of the modality of treatment, tamponade associated with HIV associated pericardial effusion carries a poor prognosis (Restrepo et al., 2006).

Mycordial disease

Myocardial abnormalities occur in about 25-75% of patients infected with HIV, the wide range being attributed to patient risk factors, stage of disease and environmental factors (D'Amati et al., 2001). Various patterns of myocardial involvement in HIV /AIDS are myocarditis; non-inflammatory myocardial necrosis; dilated cardiomyopathy, isolated right or left ventricular dysfunction and infiltrative myocardial disease (Yunis and Stone, 1998).

Before the introduction of HAART, the incidence of cardiomyopathy was estimated to be 15.9 per 1000 patients annually. But after the introduction of HAART and consequent reduction in opportunistic infections the prevalence of cardiomyopathy has been reduced by 30% in developed countries (Khunnawat et al., 2008). Various etiologies include cardiomyopathy due to infections like coxsackie, toxoplasma, epstein-barr virus, etc; drug-related e.g, zidovudine; nutritional deficiencies, and cytokine-mediated (Khunnawat et al., 2008); (Barbaro and Klatt, 2002). Recent studies suggest an important role of proinflammatory cytokines in the progression of cardiomyopathy in HIV-infected individuals. Markers like tumor necrosis factor-alpha (TNF-alpha), interleukin (IL) 1and IL-6 activate p38 mitogen-activated protein kinase (p38 MAPK) and nuclear factor kappa-B (NFKB) which promotes expression of inducible nitric oxide synthase (iNOS) in cardiomyocytes. This high concentration of nitric oxide (NO) and TNF-alpha induces cardiomyocyte apoptosis by TNF type 1 receptor activation. This effect is more pronounced in HIV infected individuals, especially in patients with low CD4 count, which accounts for the worse outcomes of heart failure in HIV patients (Monsuez et al., 2007).

Severity of the disease ranges from incidental microscopic findings on autopsy to clinically significant heart disease causing severe cardiac dysfunction (Sani, 2008). On gross examination, the findings may vary from eccentric hypertrophy, with increased wall thickening and chamber dilatation to thinning of ventricular wall (Restrepo et al., 2006). There is evidence of cardiac dysfunction in asymptomatic HIV infected patients. Left ventricular diastolic dysfunction is presumed to precede systolic dusfunction and can be diagnosed early by means of echocardiography (El hattaoui et al., 2008). Echocardiography is a specific and sensitive mean of diagnosis but endomyocardial biopsy remains the gold standard for diagnosis (Khunnawat et al., 2008). There is no clinical evidence to suggest any specific therapeutic regimen or modulation of TNF production for the treatment of HIV associated cardiomyopathy, but HAART regimens have reduced the prevalence of HIV related cardiomyopathy by almost seven-fold compared to the pre-HAART era (Khunnawat et al., 2008; Sani , 2008).

Endocarditis

Endocarditis in AIDS patients can be infective or nonbacterial e.g. marantic endocarditis. Infective endocarditis is responsible for about 5-20% of hospital admissions and about 5-10% of total deaths in HIV infected intravenous drug abusers (Valencia and Miro, 2004). In intravenous drug abusers tricuspid valve involvement is strikingly frequent (Valencia and Miro, 2004). The major organisms causing endocarditis in HIV infected patients are staph aureus and streptococcus viridians. The symptoms include fever, chills, sweats, weight loss, and septic emboli. Left sided endocarditis may cause perforation of valve leaflets or rupture of chordate tendinae which may cause acute

valvular insufficiency and heart failure. Pulmonary sequelae of right sided endocarditis are septic emboli, abscess and infarction of the lung (D'Amati et al., 2001). However, treatment of infective endocarditis in the HIV infected population is same as in those without HIV (Khunnawat et al., 2008). Nonbacterial infective endocarditis is seen in advanced stages of the disease and is associated with significant mortality in late stages of HIV infection (Restrepo et al., 2006). It can involve any cardiac valves. On gross inspection, the vegetations are similar to those found in infective endocarditis; the differentiating feature being the absence of infection with negative blood cultures and no destruction orerosions of cusp edges or tears and perforations through the body of cusp. Histologically, they consist of platelets within a fibrin mesh with few inflammatory cells; no infective organisms can be visualized in non bacterial thrombotic endocarditis (D'Amati et al., 2001). Also, the incidence of non bacterial infective endocarditis has decreased after the introduction of HAART (Khunnawat et al., 2008).

Coronary artery disease

CAD accounts for about 6–15% of all deaths in HIV-infected patients (Boccara et al., 2008). HIV patients with CAD are known to have a histologically distinctive form of accelerated atherosclerosis, with diffuse and circumferential vessel involvement (Khunnawat et al., 2008). Both immunodeficiency and immune reconstitution are known to accelerate atherosclerosis (Hsue et al., 2004). HIV associated CAD is characterized by hyper proliferation of smooth muscle cells, mixed with abundant elastic fibres (Khunnawat et al., 2008). Also HIV is associated with accelerated T- cell proliferation and activation, high levels of inflammatory markers and immunologic disturbances, which persist even after initiation of anti retroviral therapy (Hsue et al., 2004). Study by Boccara et al. (2005) showed an increased trend of acute myocardial infarction in HIV-infected patients as compared to the general population, especially those on HAART, particularly those on protease inhibitors (Boccara et al., 2005). One explanation for this can be the deleterious metabolic effects of protease inhibitors that include dyslipidemia and insulin resistance. Recent French hospital database (Costagliola, 2009) showed no such impact on risk of myocardial infarction from non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors. (Table-2) Also there are studies suggesting that use of certain NRTI like abacavir and didanosine are associated with increase in incidence of myocardial infarction without the evidence of a direct effect on metabolic factors (Sabin et al., 2008; Lundgren et al., 2009). (Table-3) It is noticed that HIV infected patients with coronary events are young, male, heavy smokers, and have low HDL cholesterol levels as opposed to other patients with acute coronary syndrome (Barbaro et al., 2003). However, HIV infected patients with acute coronary syndrome have less extensive coronary disease, usually single vessel disease, but percutaneous intervention (PCI) in these patients is associated with higher restenosis rates. It is recommended that HIV patients with CAD should be considered high risk and undergoes PCI with drug eluting stents (Segev et al., 2006). This might be attributed to higher levels of inflammatory markers like C-reactive protein (CRP) at time of PCI, as patients with HIV infection have higher levels of CRP (Hsue et al., 2004). Coronary artery bypass grafting is a suitable revascularization procedure in HIV patients with multi vessel coronary artery disease with similar immediate postoperative outcomes when compared with general population. However, there is increased rate of repeated revascularization using PCI of native coronary arteries but not of grafts (Boccara et al., 2008). Also there is enough evidence to suggest that there is an increased risk of cardiovascular and cerebrovascular events in HIV patients on antiretroviral therapy (de Azevedo et al., 2007).

NNRTI	Cumulative Exposure OR (95% CI)
Efavirenz	1.01 (0.87-1.16)
Nevirapine	1.01 (0.88-1.15)
Protease Inhibitors	
Indinavir	1.07 (0.95-1.21)
Lopinavir	1.37 (1.13-1.65)
Nelfinavir	1.09 (0.96-1.25)
saquinavir	0.94 (0.81-1.09)

NNRTI = Non nucleoside reverse-transcriptase inhibitors; CI = confidence interval

Table 2: Risk of Myocardial Infarction after Exposure to NNRTIs and Protease Inhibitors.

NRTI	Relative Risk (95% CI) Recent use	Relative Risk (95% CI) Cumulative/Year
Abacavir	**1.68 (1.33-2.13)**	**1.07 (1.01-1.14)**
Didanosine	**1.41 (1.09-1.82)**	**1.00 (0.94-1.06)**
Lamivudine	1.21 (0.95-1.55)	0.99 (0.94-1.05)
Tenofovir	1.14 (0.85-1.52)	1.05 (0.92-1.19)
Stavudine	1.02 (0.78-1.32)	1.03 (0.98-1.09)
Zidovudine	0.99 (0.78-1.26)	1.04 (0.99-1.08)

NRTI= non nucleoside nucleoside reverse-transcriptase inhibitors; CI=confidence interval

Table 3: Risk of Myocardial Infarction for NRTIs.

Cardiotoxicity associated with cocaine use is another area of concern in HIV patients. The seroprevalence of HIV in cocaine users is well known and increasing alarmingly (Kloner et al., 1992). Cocaine use, both acute and chronic, has potential cardiotoxic effects. Acute doses of cocaine are associated with myocardial ischemia/infarction and life threatening arrhythmias. Chronic cocaine use can cause accelerated coronary artherosclerosis. Cocaine also has a direct toxic effect on myocardium, thereby, causing myocyte necrosis and fibrosis, which leads to cardiomyopathy (D'Arminio et al., 2004).

Vasculitis

HIV infected patients manifest a variety of peripheral vascular abnormalities ranging from gross wall deformities to endothelial cellular derangements of proliferation, apoptosis, and Activation (Zietz et al., 1996). Various inflammatory vascular diseases have been described in HIV infected adults, which include polyarteritis nodosa, henoch-schonlein purpura, hypersensitivity vasculitis and kawasaki-like syndrome, even though these are more common in HIV infected children. One study indicated that coronary arteriopathy is a noninflammatory lesion that involves fragmentation and calcification of internal elastic lamina with less prominent intimal fibrosis, while large vessel arteriopathy affecting aorta is inflammatory being centered on the vasa vasorum (Thompson et al., 1992). In another series of patients with biopsy proven transmural inflammation, histopathologic features included necrotizing and non necrotizing arteritis, neutrophilic and mononuclear inflammatory vascular disease and other small-vessel inflammatory changes (Restrepo et al., 2006). The therapeutic approach for HIV asso-

ciated thrombotic angiopathy is similar to the therapy for patients uninfected by HIV. Prognosis is related to the stage of HIV infection and is particularly poor in patients with advanced AIDS (Thompson et al., 1992).

Systemic arterial hypertension

The prevalence of systemic hypertension in HIV population is estimated to be about 20-25% before introduction of HAART (Restrepo et al., 2006). The Multicenter AIDS Cohort Study (MACS) showed a significantly higher systolic blood pressure in those using HAART for greater than five years (Seaberg et al., 2005). Prolonged use of HAART might predispose patients to other metabolic complications, which in turn, increase the risk of hypertension (Perez-Atayde et al., 2004). Hypertension is one of the contributing factors to the preexisting risk of premature cardiovascular disease. Also HIV infection with hypertension poses an increased risk of overt proteinuria which can be explained by hypertensive nephrosclerosis along with renal manifestation of HIV infection itself (Jung et al., 2004).

Pulmonary hypertension

The incidence of HIV associated pulmonary arterial hypertension (PAH) is estimated to be much higher in HIV patients, about 1 in 200 as compared to about 1 in 200,000 in general population (Seoane et al., 2001). Patients with HIV associated PAH tend to die from the deleterious consequences of PAH rather than the HIV infection itself. HIV associated PAH is associated with decreased survival and a poorer prognosis as compared with HIV infected patients without this complication (Humbert et al., 1998). Histopathologic findings of lung tissue of patients of HIV related PAH are similar to that of primary PAH, most common finding being plexogenic pulmonary arteriopathy, seen in about 78-85% of patients (Restrepo et al., 2006). It is hypothesized that this increased incidence of pulmonary hypertension in HIV infection might be secondary to increased production of platelet derived growth factor , but the exact mechanism is still not clear (Humbert et al., 1998). It appears that PAH has multifactorial etiology that leads to pulmonary vascular dysfunction. A wide range of growth factors and cytokines along with mediators involved with vasodilatation and vasoconstriction have been implicated in pulmonary vascular remodeling contributing to the progression of disease (Humbert, 2008). It is also controversial whether HAART has a beneficial effect on HIV associated pulmonary hypertension or it exacerbates HIV associated PAH by causing endothelial proliferation by increasing endothelin-1 production (Humbert, 2008). There is no considerable difference between the treatment algorithms for treatment of PAH and that of HIV associated PAH. Clinical evidence suggests that bosentan is the first line of therapy in patients with WHO functional class III. In patients with more severe disease (WHO functional class IV), epoprostenol should be considered as a first line therapy. Calcium channel antagonists are not indicated secondary to the rarity of vasodilator response with HIV associated PAH.

Cardiac tumours

Patients with HIV are at increased risk of developing kaposi's sarcoma and non-hodgkin lymphoma of the heart (Mbulaiteye et al., 2003). The first cardiac complication of HIV to be recognized was Kaposi's sarcoma in 1983 (Autran et al., 1983). It is a low-grade malignancy derived from mesenchymal or endothelial cells. It is the most common cardiac tumor associated with HIV, occurs in about 30% of patients. Usually it is occult, but pericardial involvement may manifest as tamponade (Restrepo et al., 2006). Non-hodgkin's lymphoma is second most common cardiac tumor, about 25 to 60 times more common in HIV-infected patients than in general population (Khunnawat et al., 2008). 80-90% of cardiac lymphomas are high grade B- cell tumors consisting of large cell immunoblastic or small non cleaved lymphomas (Autran et al., 1983). Grossly, it appears as a single mass or multiple firm nodules within the myocardium. Computerized tomography (CT) scan helps identifying cardiac tumors. CT scan of one of our patient with cardiac lymphoma is shown in Figure 1. Patient was not on HAART before the diagnosis. Clinical manifestations of cardiac lymphoma vary from cardiomegaly, pericardial effusion, congestive heart failure, arrhythmias or progressive heart block. Overall prognosis is poor. The incidence of cardiac tumors has decreased after the introduction of HAART. Chemotherapy and radiotherapy remain the main stay of treatment (Khunnawat et al., 2008).

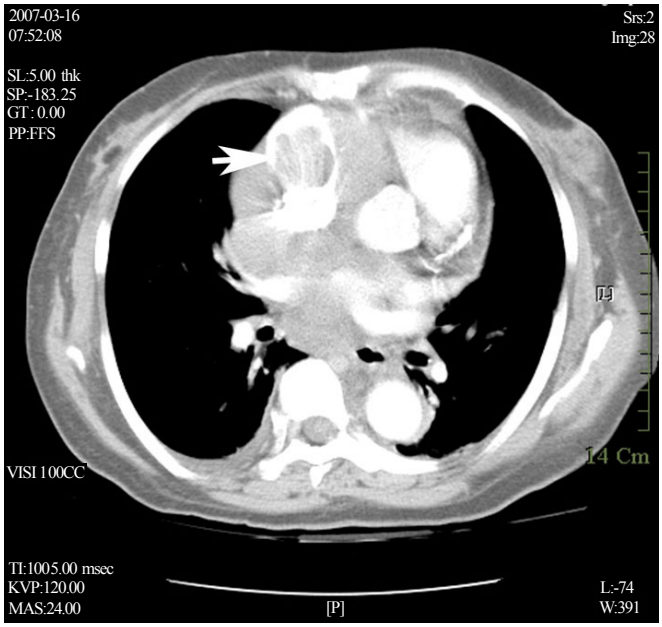

Figure 1: Computerized tomography of the heart with arrow showing mass in the right Atrium.

Thrombosis and embolism

Immunologically mediated diseases, whether autoimmune or immunodeficient have an increased predisposition for development of thrombosis (Witz et al., 2000). HIV patients have an increased propensity to develop coagulation disorders. The mechanism is not clear. But it is attributed to increased levels of fibrinogen, D-dimer, plasminogen activator inhibitor-1 (Restrepo et al., 2006). Other possible contributing factors are endothelial dysfunction and abnormalities of fibrinolytic system. It includes both arterial and venous thrombosis, especially in patients taking protease inhibitors. About 2% of HIV infected patients have been reported to develop clinical thrombosis (Witz et al., 2000). It was also reported that acquired protein C deficiency is significantly more prominent in HIV patients with CD4 count < 200 (Sugerman et al., 1996).

Conclusion

HIV infected population have an increased risk of cardiovascular complications which carry a worse prognosis when compared to that in general population. This can be attributed to the disease itself or even as the adverse effects of certain antiretroviral agents. Physician need to be aware of the course of the cardiovascular manifestations associated with HIV and with the various treatment regimens.

Guidance to the readers

The early diagnosis and risk stratification of cardiovascular disease in HIV patients poses a clinical challenge to the physicians. The advent of anti-retroviral therapy has witnessed an increased risk of metabolic syndrome and coronary artery disease in HIV patients on HAART. Careful cardiovascular evaluation during the course of treatment of HIV can help in early identification and treatment of cardiac complications. All HIV patients on treatment should undergo appropriate cardiovascular risk assessment according to the available guidelines.

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