Cardiovascular Disease in HIV Infection

REINALDO J. SÁNCHEZ-TORRES, MD*; MARIO R. GARCÍA-PALMIERI, MD†

Cardiovascular disease has been well documented in patients with Human Immunodeficiency Virus infection, especially after the introduction of highly active antiretroviral therapy. At present, HIV infection is one of the leading causes of acquired cardiovascular disease including heart failure. Some of the changes observed in these patients include left ventricular systolic dysfunction, dilated cardiomyopathy, congestive heart failure, myocarditis, lipodystrophy, dyslipidemia, insulin resistance, accelerated atherosclerosis including myocardial infarction, prothrombotic state, pericardial effusion, pulmonary hypertension, autonomic dysfunction, and malignancy. This article summarizes the main findings in the principal HIV-associated cardiovascular manifestations in order to stimulate its early recognition so helping in early intervention and therapy.

Key words: HIV, Dilated cardiomyopathy, Myocarditis, Lipodystrophy, Dyslipidemia, Insulin resistance, Vasculitis, Infective endocarditis, Malignancy.

The estimated population of Human Immunodeficiency Virus (HIV) infected patients by the end 2003 was 37.8 million (1). There were 4.8 million newly infected patients and 2.9 million AIDS deaths in 2003 (1). Approximately 16/1000 infected patients will develop heart disease which will worsen the prognosis of this condition markedly, and in many cases, accelerating the rate of death. Generally heart disease occurs late in the disease, but in some cases can occur earlier, affecting even more the prognosis of these patients (2). With the introduction of highly active antiretroviral therapy (HAART), patients with HIV infection live longer and are bound to develop cardiovascular disease, which complicates the course of illness, and accelerate death if not recognized early or left untreated. The more common cardiovascular conditions seen in HIV-infected patients are shown in Table 1. In this article we review the principal manifestations of cardiovascular disease in HIV infected patients.

Dilated Cardiomyopathy

HIV disease is recognized as an important cause of dilated cardiomyopathy with an estimated annual incidence of 15.9 per 1000, before the introduction of HAART (3).

*Chief Fellow, Cardiology Section, Department of Medicine, University of Puerto Rico School of Medicine, †Head Cardiology Section, Distinguished Professor of Medicine, Department of Medicine, University of Puerto Rico School of Medicine

Address correspondence to: Cardiology Section, UPR School of Medicine, P.O. Box 365067, San Juan, Puerto Rico 00936-5067; e-mail: dr_sancheztorres@yahoo.com, Telephone: (787) 754-0101 Ext. 3660

Table 1. Cardiovascular Abnormalities in HIV

1. Dilated cardiomyopathy
2. Myocarditis
3. Lipodystrophy
4. Dyslipidemia
5. Insulin resistance
6. Accelerated atherosclerosis
7. Pulmonary hypertension
8. Vasculitis
9. Pericardial effusion
10. Infective endocarditis
11. Autonomic dysfunction
12. Malignancy

Dilated cardiomyopathy is commonly manifested by heart failure due to left ventricular systolic dysfunction (LVSD). The exact cause of LVSD is not completely clear although it is thought to be secondary to the HIV infection affecting the myocardial tissue directly or due to an autoimmune process due to other cardiotropic viruses (4). These viruses include Epstein-barr, coxsackievirus group B, cytomegalovirus (CMV), adenovirus, and others. Also infection with Toxoplasma gondii has been associated with LVSD. HIV also causes alteration in cytokine production, increasing the production of tissue necrosis factor (TNF), tissue growth factor β(TGF-β), and nitric oxide (NO), which in high levels could be cytotoxic to myocytes and have a negative inotropic effect (2). Cytokine levels have an inverse relationship with the CD4 counts. Dilated cardiomyopathy has been closely related to low CD4 levels (below 100 cells/ml) but LVSD has been observed in patients with CD4 levels above 400 cells/ml.

The symptoms of heart failure may be obscured by the presence of other frequent conditions such as pulmonary infections, malignancy, malnutrition, anemia, and pulmonary hypertension, among others (2). For this reason a good history and physical examination is needed during the evaluation of these patients, in addition to a high index of suspicion. 2D echocardiography and ECG will help in the diagnosis of LVSD and dilated cardiomyopathy. Diastolic dysfunction, which usually precedes the LVSD and is related to the high number of patients with arterial hypertension, could also be evaluated by 2 D echocardiography (2).

Some of the possible etiological agents of this condition include HIV infection itself, an autoimmune response to HIV, other viral infections, nutritional deficiencies including selenium and other trace elements deficiencies, cardiotoxicity from therapeutic drugs, use of illicit drugs in some cases, and cytokine over expression (2). Up to 30% cardiac-specific antibodies have been reported in patients with HIV associated cardiomyopathy (5). Levels of vitamin B 12, carnitine, growth hormone and thyroid hormone may be altered in HIV and all have been associated with LVSD (5). Table 2 illustrates the recognized etiologies in dilated cardiomyopathy associated to HIV infection.

Patients with LVSD and dilated cardiomyopathy have an increased mortality, and this is independent of sex, age, or CD4 levels, especially if the ventricular dysfunction is developed early in the disease. In general, treatment is similar to the standard therapy that patients receive for CHF. Also it is important to correct the nutritional status, and to treat opportunistic infections. Myocardial biopsy is recommended in patients with no clinical improvement after adequate treatment is implemented (2). A case report of a successful orthotopic heart transplant was published in the New England Journal of Medicine in 2003 but, at present, this option is still controversial and is generally not recommended (6).

Myocarditis

Myocardial infection occurs in patchy distribution and there is no clear association between the infection and the cardiac functional disability (2). It is a cause of dilated cardiomyopathy in HIV. There is involvement of several cytokines including TNF – á, interleukin (IL) – 1, IL – 6, IL – 10, that may contribute to progressive and late tissue damage (5). IV immunoglobulins have had some success in the management of cases of nonspecific myocarditis and in acute congestive cardiomyopathy (2).

Lipodystrophy

Body fat abnormalities have been reported to occur in 40 – 50% of patients receiving combination therapy or HAART (7). These include central and visceral fat accumulation, subcutaneous lipoatrophy, dyslipidemia and insulin resistance which markedly affects the metabolic profile of these patients. Subcutaneous lipoatrophy is seen in the face, limbs, buttocks, and trunk. Deposition of excess fat in the neck and upper back may cause a double chin and buffalo hump.

It is well known that protease inhibitor therapy (PI) may induce lipodystrophy. It develops in approximately 40% of patients receiving PI therapy for more than one year (8). In addition the combination of stavudine and didanosine is strongly associated with the development of lipoatrophy.

The mechanism involved in lipodystrophy is related to the inhibition of the sterol regulatory enhancer-binding protein 1(SREBP-1)-mediated activation of the heterodimer consisting of adipocytes retinoid x receptor and peroxisome proliferator-activated receptor γ(PPAR γ) or related transcription factors such as PPAR γ coactivator 1(7). Metformin and rosiglitazone are clinically used to improve glycemic control in patients with type 2 diabetes. A comparison between rosiglitazone and metformin for the treatment of lipodystrophy associated to HAART therapy showed that although rosiglitazone partly correct the lipoatrophy, metformin improves the visceral fat accumulation, fasting lipid profile, and endothelial function (9).

Table 2. Etiology of Dilated Cardiomyopathy in HIV

1. Infectious agents	a.	HIV, Epstein-barr, Coxsackie group B, CMV, Adenovirus, Toxoplasma gondii
	b.	Autoimmune response to HIV
2. Metabolic/Endocrine	a.	Nutritional deficiencies – selenium, vitamin B12, carnitine
	b.	Thyroid and growth hormonesc. Adrenal insufficiency, hyperinsulinemia
3. Drug cardiotoxicity	a.	Nucleoside analogs
	b.	Cocaine
	c.	Interleukin – 2
	d.	Interferon
	e.	Doxorubicin
4. Cytokine overexpression	a.	TNF – α
	b.	TGF – β
	c.	NO
	d.	Endothelin –1

HIV = human immunodeficiency virus; CMV = cytomegalovirus; TNF α = tissue necrosis factor α; TGF β = tissue growth factor β; NO = nitric oxide

Dyslipidemia

Dyslipidemia is a frequent problem after starting HAART. Administration of PI's to HIV patients is associated with marked, compound specific dyslipidemia (10). It is known that the protease inhibitor ritonavir increases hepatic triglyceride synthesis and plasma triglyceride and cholesterol levels (2). At the time of seroconversion, total cholesterol, HDL cholesterol, and LDL cholesterol levels decreases. After HAART is started, the total cholesterol and LDL cholesterol increases but the HDL cholesterol remains low (7). It is believed that dyslipidemia could be secondary to the effects of the viral infection, acute phase reactants, and circulating cytokines including interferon α(7).

Whenever treatment with statins is used it should be carefully done because most protease inhibitor drugs are metabolized by the cytochrome P450 system (CYP 3A4 subfamily) and increase the levels of statins and other cardiovascular drugs (12). Pravachol has been used mostly for this reason. Other treatment option is the use of fibrates and carnitine for hypertriglyceridemia. The optimal approach to the management of dyslipidemia in infected persons has not been defined. At this moment it seems that dyslipidemia in this patients should be managed as in HIV negative patients as long as therapy is individualized (12). Table 3 summarizes the most frequently used non-pharmacologic and pharmacologic measures when dealing with HIV patients with dyslipidemia.

Table 3. Treatment Options for Dyslipidemia in HIV

1. Diet	Low in saturated fats and sugarOmega – 3 rich foods Fish oils
2. Exercise	Regular aerobic exercise program
3. Statins	Pravastatin 20 mg qdAtorvastatin 10 mg qd
4. Fibrates	Fenofibrate 48-145 mg qdGemfibrozil 600 mg bid
5. Nicotinic acid	Niacin 250 mg qd up to 1-2g/day
6. Carnitine	Carnitor 330-990 mg tid

Insulin Resistance

Impaired glucose tolerance (insulin resistance) and diabetes mellitus are known risk factors for CAD. The identification of an increased incidence of insulin resistance among HIV infected patients has raised the concern that this population may be at increased risk for developing diabetes and cardiovascular disease. Protease inhibitors indinavir and lopinavir used in HIV patients may affect insulin sensitivity as well (7). Antiretroviral therapy contribute to altered glucose homeostasis, altered flux of free fatty acids, and accumulation of intramyocellular lipid, alteration in adipokine levels (low level of adiponectin), and reduced PPARγ expression in subcutaneous adipocytes (7)

The pathogenesis of metabolic complications in HIV is most likely multifactorial, with changes resulting from fat distribution and from the direct effect of medications like PIs (13). Table 4 presents the metabolic alterations occurring in organs and tissues during HIV infection related to insulin resistance and lipodystrophy. Studies done in HIV-infected patients have demonstrated that there is significant fasting hyperinsulinemia even in the presence of normal fasting glucose levels, which is indicative of insulin resistance, and place these patients at an increase risk for cardiovascular disease (13). These factors should be recognized and treated because these patients have an elevated 10-year cardiovascular risk.

Table 4. Mechanisms for Metabolic Abnormalities in HIV

1. Vessels	a. Increase in VLDL cholesterol and triglycerides
	b. Increase in systemic apolipoprotein C-II and apolipoprotein E
	c. Accumulation of CD 36-dependent ester in macrophages
	d. Decreased degradation of lipoprotein B
	e. Impaired fibrinolysis
2. Fat	a. Increased lipolysis
	b. Decreased subcutaneous fat differentiation and increased apoptosis
	c. Decreased SREBP-1-activated PPARγ expression
	d. Mitochondrial toxicity and decreased PPARγ expression
3. Liver	a. Increased hepatic glucose production
	b. Decreased mitochondrial fatty acid oxidation
	c. Increased lipid accumulation and hepatic steatosis
4. Muscle	a. Decreased glucose transport
	b. Decreased glucose phospholyration secondary to increase fatty acids
	c. Increased intramyocellular lipids secondary to decreased adiponectin
5. Pancreas	a. Increased insulin secondary to insulin resistance

VLDL = very low density lipoprotein; SREBP-1 = sterol regulatory enhancer-binding protein 1; PPAR γ = peroxisome proliferator-activated receptor γ

Accelerated Atherosclerosis

HIV infected patients may develop accelerated atherosclerosis, which has been observed in young patients without the traditional risk factors for CAD. CMV and hepatitis B virus have been found in autopsy studies and associated with accelerated atherosclerosis. Premature cerebrovascular disease is also common and has been documented from autopsies (estimated 8% prevalence) (2). Studies showed that the intima of carotid arteries thicken over time in patients that receive PIs (11).

PI therapy affects the lipid profile and may be associated with premature atherosclerotic disease. Also a chronic inflammatory state has been associated with the

development of premature atherosclerotic disease. Lipid alteration seen with the use of PI therapy are elevated triglyceride, LDL cholesterol, lipoprotein (a), total cholesterol, c-peptide and insulin levels, and low HDL cholesterol levels which confers an atherosclerotic profile to this patients. Also hypertension is seen more frequently with the use of PI therapy. Ritonavir affects the lipid profile more than other antiretroviral drugs.

HIV patients with acute coronary syndromes (ACS) are younger and usually are male, smokers, and have lower HDL cholesterol levels than other patients with ACS. Usually have single vessel disease but have a higher level of restenosis (14). An incidence of 3.5/1000 person-years for a first myocardial infarction was showed in the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study (14). Combination therapy was found with an independent increase in rate of myocardial infarction during the first years of therapy (15).

Risk stratification in these patients should be done based on traditional risk factors in addition to evaluation of diet, alcohol intake, physical exercise, hypertriglyceridemia, cocaine and heroin use, thyroid disease, renal disease, and hypogonadism. They should be considered for long-term cardiac preventive care (2).

In summary, mechanisms for the development of vascular disease in HIV-infected patients includes dyslipidemia, insulin resistance, diabetes mellitus, chronic inflammation, impaired fibrinolysis, endothelial dysfunction, hypertension and the use of antiretroviral medications (7). Treatment options are adequate diet and exercise, cessation of smoking, careful use of statins or fibrates due to increase risk of hepatic and musculoskeletal damage, surgery for lipodystrophy, although lipodystrophy changes tend to recur with time, and changes in the antiretroviral therapy without compromising the immunological status of the patients (7).

Pulmonary Hypertension

Risk factors for the development of pulmonary hypertension include a history of thromboembolism, IV drug abuse, left ventricular dysfunction and bronchopulmonary infections. Another cause may be pulmonary arteritis that occurs secondary to the immunological effect of the HIV infection itself. Pulmonary hypertension can be diagnosed by 2D echocardiography or right heart catheterization. There have been cases described where HIV-infected patients did not had a previous history of thromboembolism, IV drug abuse, or pulmonary infection (5). Nevertheless, a diagnosis of primary pulmonary hypertension is difficult to establish, since there is always the possibility that the condition is associated to the HIV infection itself.

Clinical findings include dyspnea on exertion, hypoxemia, and restrictive lung disease with decreased diffusing capacity for carbon monoxide. ECG may show evidence of right ventricular hypertrophy. Therapy with vasodilator agents and anticoagulation should be individualized (2). Agents like epoprostenol have been used in some cases but have limitations due to its high cost (5).

Vasculitis

Several conditions including polyarteritis nodosa, Henoch-Schönlein purpura, and drug hypersensitivity vasculitis have been described in HIV (5). In addition there are described cases of Kawasaki-like syndrome and Takayasu's arteritis. Vasculitis should be suspected in patients with fever of unknown origin and unexplained multisystemic disease (2). Other conditions include unexplained arthritis or myositis, glomerulonephritis, peripheral neuropathy, and unexplained gastrointestinal, cardiac, or central nervous system ischemia (2). Successful therapy with steroids has been reported in some cases.

Pericardial Effusion

Effusion is a common finding in HIV infection and in many times are asymptomatic. Its presence has been generally associated with low CD4 levels. The presence of pericardial effusion and/or cardiac tamponade in a young patient should alert the possibility of HIV infection (5). Etiology of effusions is variable. Culture of pericardial fluid is often unrevealing. Common causes include opportunistic infections, malignancy, a generalized effusive process, uremia, drug nephrotoxicity, and fibrinous pericarditis (2). It may resolve spontaneously in up to 42% of patients (5). Pericardial effusion may markedly increase the mortality of patients.

Infective Endocarditis

Incidence of infective endocarditis in HIV infected patients is not higher than the rest of patients with similar risk behaviors although it is more common in IV drug abusers (2). They respond well to antibiotics and in some cases the valvular damage is less severe due to the immunosupression itself. One common finding is that these patients are prone to develop Salmonella endocarditis during Salmonella infection (2). Other common organisms are Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, Aspergillus fumigatus, Candida sp., and Cryptococcus neoformans (16). Patients with advance disease may have a fulminant course due to the inability to fight the infection.

Nonbacterial Thrombotic Endocarditis or marantic endocarditis is a rare cause. It involves large friable and

sterile vegetations and is associated with disseminated intravascular coagulation and embolization. Risk vs. benefit of anticoagulation should be made on individual basis only. This condition should be suspected in AIDS patients with systemic embolization (2).

Autonomic Dysfunction

Common signs of autonomic dysfunction in HIV infection include syncope, pre-syncope; diminish sweat, diarrhea, bladder dysfunction, and erectile dysfunction (2). These signs of autonomic dysfunction are more common in patients that have nervous system disease.

Malignancy

Cardiovascular malignancy is usually secondary to metastasis. Autopsy reports show that Kaposi's sarcoma may be present in a large number of patients (12-28%) but many times this is an incidental finding (2). Primary cardiac malignancy is usually lymphoma of the Non Hodgkin type. Both Kaposi's sarcoma and Non Hodgkin's Lymphoma have been found also in the pericardium (16).

Pericardial effusions may be associated to malignancy and cause symptoms of dyspnea, heart failure, chest pain, and arrhythmias. Superior vena cava syndrome and tamponade may also be seen. Prognosis in patients with HIV and cardiac malignancy is usually poor (2).

Conclusions

The principal HIV associated cardiovascular manifestations are discussed. It is clear that cardiovascular disease will be expected to be more prevalent in the HIV infected population as these patents live more due to the success of recent advances made in the newer therapies. The implications of HAART are still unclear for which close follow up and proper evaluation and risk stratification is warranted for these patients. Clinicians should be vigilant in addressing known risk factors for cardiovascular disease in their patients with HIV infection and should be aware of the multiple cardiovascular manifestations of HIV infection. Early screening of cardiovascular conditions is important since the development of heart disease will have an important impact on survival and morbidity and the avoidance of fatal complications that can be prevented in many cases. Traditional risk factors should be evaluated and treatment given on individual basis. High index of suspicion is often needed since other conditions may have similar symptoms for which a good history and physical examination are always needed. The 12-lead electrocardiogram and 2D echocardiography are great tools that aid in the evaluation of these patients, especially when symptoms develop, and should be done periodically.

Traditional treatments for cardiovascular disease may be used on individual basis but the clinicians must be alert to drug incompatibilities due to the possibility of drug interactions and organ damage, if not used with caution.

Resumen

La enfermedad cardiovascular se ha documentado en pacientes infectados con el virus de inmunodeficiencia humana, especialmente luego de la introducción de la terapia antiretroviral combinada. Actualmente es una de las causas más comunes de enfermedad cardiovascular adquirida y fallo cardiaco sintomático. Se resumen los aspectos generales de las condiciones cardiovasculares que se asocian a la infección con el virus de inmunodeficiencia humana. Las condiciones que se observan comúnmente son disfunción del ventrículo izquierdo, cardiomiopatía dilatada, lipodistrofia, dislipidemia, resistencia a insulina, ateroesclerosis acelerada, hipertensión pulmonar, disfunción autonómica y malignidad. El artículo presenta los datos más sobresalientes de estas condiciones en un esfuerzo por estimular una intervención y manejo temprano.

References

1. Joint United Nations Programme on HIV/AIDS 2004. Report on the Global AIDS Epidemic, 4th Global Report, available at http://www.unaids.org.

2. Braunwald E, Zipes D, Libby P. Heart Disease seventh edition A Textbook of Cardiovascular Medicine, Philadelphia Elsevier Saunders Company; 2005,p.1719–1730.

3. Barbaro G, Klatt EC. HIV Infection and the Cardiovascular System. AIOS Rev. 2002;4:93-103.

4. Barbaro G, Di Lorenzo G, Grisorio B, Barbarini G. Incidence of Dilated Cardiomyopathy and Detection of HIV in Myocardial Cells of HIV-Positive Patients. N Engl J Med 1998;339(16):1093-99.

5. Barbaro G. Cardiovascular Manifestations of HIV Infection. Circulation 2002;106:1420-25.

6. Calabres LH, Albrecht M, Young J, McCarthy P, Haugh M, Jarcho J, Zackin R. Successful Transplantation in an HIV-1-Infected Patient with Advanced Disease. N Engl J Med 2003; 348:2323-8.

7. Grinspoon S, Carr A. Cardiovascular Risk and Body-Fat Abnormalities in HIV-Infected Adults. N Engl J Med 2005; 352:48-62.

8. Garg A. Acquired and Inherited Lipodytrophies. N Engl J Med 2004;350:1220-34.

9. van Wijk J P.H., de Koning E J.P., Castro M, Roodt J, Joven J, Rabelink TJ, Hoepelman AI. Comparison of Rosiglitazone and Metformin for Treating HIV Lipodystrophy. Ann Intern Med 2005;143:337-46

10. Périard D, Telenti A, Sudre P, Cheseaux JJ, Halfon P, Reymond M, Marcovina S, Glauser M, Nicod P, Darioli R, Mooser V. Atherogenic dyslipidemia in HIV-Infected Individuals Treated with Protease Inhibitors. Circulation 1999;100:700-705.

11. Fichtenbaum CJ. The Evaluation and Management of

Dyslipidemia in HIV-Infected Patients. AIDS Clinical Care 2001; 13 (12): 113-20.

12. Tungsiripat M, Aberg JA. Dyslipidemia in HIV Patients. Cleveland Clinic Journal of Medicine 2005;72(12):1113-20.

13. Hadigan C, Grinspoon S. Insulin Resistance in HIV Lipodystrophy Syndrome. AIDS Clinical Care 2001;13(2):13-22

14. Hsue PY, Giri K, Erickson S, McGregor JS, Younes N, Shergill A, Waters DD. Clinical Features of Acute Coronary Syndromes in Patients with Human Immunodeficiency Virus Infection. Circulation 2004;109:316-19.

15. The Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study Group. Combination Antiretroviral Therapy and the Risk of Myocardial Infarction. N Engl J Med 2003;340:1993-2003.

16. Rakhlin N, Hsue P, Cheitin MD. Cardiac Manifestations of HIV. HIV In Site, available at http://www.hivinsite.ucsf.edu.