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Cardiovascular Manifestations of HIV Infection

Giuseppe Barbaro, MD

S tudies published over the past 3 years have tracked the incidence and course of human immunodeficiency virus (HIV) infection in relation to cardiac illness in both children and adults.¹ These studies show that subclinical echocardiographic abnormalities independently predict adverse outcomes and identify high-risk groups to target for early intervention and therapy. The Joint United Nations Program on HIV/AIDS estimates that 36.1 million people were living with HIV infection at the end of the year 2000.² If 8% to 10% of patients develop symptomatic heart failure over a 2- to 5-year period,³ then 3 million cases of HIV-related heart failure will present during that period.¹

Cardiovascular manifestations of HIV have been altered by the introduction of highly active antiretroviral therapy (HAART) regimens. On one hand, HAART has significantly modified the course of HIV disease, lengthened survival, and improved the quality of life of HIV-infected patients. On the other hand, the early data have raised concerns that HAART is associated with an increase in both peripheral and coronary arterial diseases.¹ The HAART-associated changes are relevant only to the minority of HIV-infected individuals worldwide who have access to HAART. Thus, studies conducted before HAART became available remain globally applicable.

In this review article, the principal HIV-associated cardiovascular manifestations will be discussed, with an emphasis on new knowledge about prevalence, pathogenesis, and treatment.

Dilated Cardiomyopathy

HIV disease is recognized as an important cause of dilated cardiomyopathy, with an estimated annual incidence of 15.9 in 1000 before the introduction of HAART³ (Table 1). The importance of cardiac dysfunction is demonstrated by its effect on survival in acquired immunodeficiency syndrome (AIDS). Median survival to AIDS-related death is 101 days in patients with left ventricular dysfunction and 472 days in patients with a normal heart as shown by echocardiography at a similar infection stage.1 The unadjusted hazard ratio for death in HIV-related cardiomyopathy compared with idiopathic cardiomyopathy is 4.0; the ratio adjusted after multivariate analysis is 5.86.4 In the multicenter Pediatric Pulmonary and Cardiovascular Complications of HIV study (P²C² HIV), children with vertically transmitted HIV infection (median age 2.1 years) had a 5-year cumulative survival of 64%.5 Mortality was higher in children with baseline depressed left ventricular fractional shortening or increased left ventricular dimension, thickness, mass, wall stress, heart rate, or blood pressure. Decreased left ventricular fractional shortening and increased wall thickness were also predictive of survival after multivariate adjustment.⁵

Myocarditis

Myocarditis and HIV-1 myocardial infection are still the most studied causes of dilated cardiomyopathy in HIV disease.^{3,6} HIV-1 virions appear to infect myocardial cells in patchy distributions^{3,6} without a clear direct association between HIV-1 and cardiac myocyte dysfunction. It is unclear how HIV-1 may enter CD4-receptor–negative cells such as myocytes. Reservoir cells (ie, dendritic cells) may play a pathogenic role in the interaction between HIV-1 and the myocyte and in the activation of multifunctional cytokines (ie, tumor necrosis factor- α [TNF- α], interleukin [IL]-1, IL-6, IL-10) that contribute to progressive and late tissue damage.⁴

Autoimmunity

Cardiac-specific autoantibodies (anti- α myosin autoantibodies) have been reported in up to 30% of patients with HIV-associated cardiomyopathy.⁷ The finding supports the theory that cardiac autoimmunity plays a role in the pathogenesis of HIV-related heart disease and suggests that cardiac autoantibodies may be markers of left ventricular dysfunction in HIV-positive patients with previously normal echocardiographic findings.⁷

Relationship to Encephalopathy

Several studies have reported that patients with encephalopathy were more likely to die of congestive heart failure than were patients without encephalopathy^{5,8,9}; the hazard ratio after multivariate analysis was 3.4.⁹ The reservoir cells in the myocardium and the cerebral cortex, which are not susceptible to treatment, may hold HIV-1 on their surfaces for extended time periods and may chronically release cytotoxic cytokines, contributing to progressive and late tissue damage in both systems independently of HAART regimens.⁹

Nutritional Deficiencies

Nutritional deficiencies are common in HIV infection, particularly in late-stage disease, and may contribute in inducing ventricular dysfunction independently of HAART regimens. Deficiencies of trace elements have been associated directly or indirectly with cardiomyopathy.¹⁰ Selenium replacement

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Туре	Possible Causes and Associations	Incidence		
Dilated cardiomyopathy	Infectious:	15.9 patients in 1000 asymptomatic HIV-infected persons before the introduction of HAART. ³		
	HIV, toxoplasma gondii, coxsackievirus group B, Epstein-Barr virus, cytomegalovirus, adenovirus			
	Autoimmune response to infection			
	Drug related			
	Cocaine, possibly nucleoside analogues, IL-2, doxorubicin, interferon			
	Metabolic/endocrine			
	Nutritional deficiency/wasting: selenium, B12, carnitine			
	Thyroid hormone, growth hormone			
	Adrenal insufficiency, hyperinsulinemia			
	Cytokines			
	TNF- α , nitric oxide, TGF- β , endothelin-1			
	Hypothermia			
	Hyperthermia			
	Autonomic insufficiency			
	Encephalopathy			
	Acquired immunodeficiency			
	HIV viral load, length of immunosuppression			
Coronary heart disease	Protease-inhibitor-induced metabolic and coagulative disorders; arteritis	Mostly limited to case reports after the introduction of protease inhibitors containing HAART		
Systemic arterial hypertension	HIV-induced endothelial dysfunction; vasculitis in small, medium, and large vessels in the form of leukocytoclastic vasculitis; atherosclerosis secondary to HAART; aneurysms of the large vessels such as the carotid, femoral, and abdominal aorta with impairment of flow to the renal arteries; PI-induced insulin resistance with increased sympathetic activity and sodium retention	20%–25% of HIV-infected persons before the introduction of HAART. ²⁹ Up to 74% in HIV-infected persons with HAART-related metabolic syndrome ³⁰		
Pericardial effusion	Bacteria	11% per year in asymptomatic AIDS		
	Staphylococcus, Streptococcus, Proteus, Nocardia, Pseudomonas, Klebsiella, Enterococcus, Listeria	patients before the introduction of HAART		
	Mycobacteria			
	Mycobacterium tuberculosis, Mycobacterium avium intracellulare, Mycobacterium kansaii			
	Viral pathogens			
	HIV, herpes simplex virus, herpes simplex virus type 2, cytomegalovirus			
	Other pathogens			
	Cryptococcus, toxoplasma, histoplasma			
	Malignancy			
	Kaposi's sarcoma			
	Malignant lymphoma			
	Capillary leak/wasting/malnutrition			
	Hypothyroidism			
	Prolonged acquired immunodeficiency			
HIV-associated pulmonary hypertension	Recurrent bronchopulmonary infections, pulmonary arteritis, microvascular pulmonary emboli due to thrombus or drug injection, plexogenic pulmonary arteriopathy, mediator release from endothelium	1/200 of HIV-infected persons before the introduction of HAART ¹		
AIDS-related tumors	Kaposi's sarcoma	12%–28% of AIDS patients before the introduction of HAART ^{1,6}		
	Non-Hodgkin lymphomas	Mostly limited to case reports before the introduction of HAART		

TABLE 1. Principal HIV-Associated Cardiovascular Abnormalities

may reverse cardiomyopathy and restore left ventricular function in nutritionally depleted patients.¹⁰ Levels of vitamin B_{12} , carnitine, and growth and thyroid hormone may also be altered in HIV disease; all have been associated with left ventricular dysfunction.¹⁰

Drug Cardiotoxicity

Studies on transgenic mice suggest that zidovudine is associated with diffuse destruction of cardiac mitochondrial ultrastructures and inhibition of mitochondrial DNA replication.¹¹ Lactic acidosis related to mitochondrial dysfunction may further contribute to myocardial cell dysfunction.¹¹ The P^2C^2 HIV Study monitored infants born to HIV-positive mothers from birth to age 5 with serial echocardiographic studies every 4 to 6 months. No association with acute or chronic abnormalities in left ventricular structure or function was found with perinatal exposure to zidovudine.¹² Other nucleoside reverse transcriptase inhibitors, such as didanosine and zalcitabine, do not seem either to promote or to prevent dilated cardiomyopathy.³

Treating HIV-Associated Cardiomyopathy

No prospective studies have investigated the efficacy of specific therapeutic regimens on HIV-associated cardiomyopathy other than intravenous immunoglobulin.13 Multivariate analysis showed that contractility improved by 10% and that peak wall stress improved by 15% in HIV-infected children who received intravenous immunoglobulin treatment and in those with higher endogenous immunoglobulin G levels, suggesting that both the impaired myocardial growth and the left ventricular dysfunction observed might be immunologically mediated and responsive to immunomodulatory therapy.13 The apparent efficacy of immunoglobulin therapy may be the result of immunoglobulins inhibiting cardiac autoantibodies by competing for Fc receptors or dampening the secretion or effects of cytokines and cellular growth factors.13 There is no evidence from prospective studies to suggest that HAART has a beneficial effect on HIV-associated cardiomyopathy. Some retrospective studies, however, suggest that by preventing opportunistic infections and reducing the incidence of encephalopathy, HAART might reduce the incidence of HIV-associated heart disease and improve its course.14

Pericardial Effusion

The prevalence of pericardial effusion in asymptomatic AIDS patients has been estimated at 11% before the introduction of HAART¹⁵ (Table 1). HIV infection should be included in the differential diagnosis of unexplained pericardial effusion or tamponade. Pericardial effusion in HIV disease may be related to opportunistic infections or to malignancy, but most often a clear pathology is not found.¹ The effusion may be part of a generalized serous effusive process also involving pleural and peritoneal surfaces. This "capillary leak" syndrome is likely related to enhanced cytokine expression in the later stages of HIV disease.^{1,15} Pericardial effusion spontaneously resolves in up to 42% of patients.¹⁵ Pericardiocentesis is currently recommended only in large or poorly tolerated effusions, for diagnostic evaluation of systemic illness, or in

the presence of cardiac tamponade.¹ Mortality remains increased in HIV-infected patients who develop an effusion, even if the effusion resolves over time. The effects of HAART therapy on pericardial effusion are largely unexplored.

Endocarditis

The prevalence of infective endocarditis in HIV-infected patients is similar to that in patients of other risk groups, such as intravenous drug users.⁶ Estimates of endocarditis prevalence vary from 6.3% to 34% of HIV-infected patients who use intravenous drugs independently of HAART regimens.⁶ Right-sided valves are predominantly affected, and the most frequent agents are *Staphylococcus aureus* (>75% of cases), *Streptococcus pneumoniae, Haemophilus influenzae, Candida albicans, Aspergillus fumigatus*, and *Cryptococcus neoformans*.⁶ Patients with HIV generally have presentations and survival from infective endocarditis similar to those without HIV (85% versus 93%).⁶

Patients with late-stage HIV disease, however, have about a 30% higher mortality with endocarditis than asymptomatic HIV-infected patients, which may be related to the degree of immunodeficiency.¹⁶ Surgical management is indicated in selected patients, especially when valvular dysfunction resulting in acute heart failure becomes intractable to medical therapy.¹⁷ Hospital morbidity and mortality rates are higher than usual in this group of patients.¹⁷ Nonbacterial thrombotic endocarditis, also known as marantic endocarditis, occurs in 3% to 5% of AIDS patients, mostly in patients with HIVwasting syndrome.⁶ It is characterized by friable endocardial vegetations, affecting predominantly the left-sided valves and consisting of platelets within a fibrin mesh with few inflammatory cells. Systemic embolization from marantic endocarditis is a rare cause of death in AIDS patients in the HAART era.

HIV-Associated Pulmonary Hypertension

The pathogenesis of primary pulmonary hypertension in HIV infection is multifactorial and poorly understood.¹ Primary pulmonary hypertension has been found in hemophiliacs receiving lipophilized factor VIII, intravenous drug users, and patients with left ventricular dysfunction, obscuring any relationship with HIV-1. HIV-1 is frequently identified in alveolar macrophages on histology.¹⁸ These macrophages release TNF- α , oxide anions, and proteolytic enzymes in response to infection. Clinical symptoms and outcomes of patients with right ventricular dysfunction are related to the degree of pulmonary hypertension, varying from a mild asymptomatic condition to severe cardiac impairment with cor pulmonale and death.¹⁸ Activation of α -1 receptors and genetic factors (increased frequency of HLA-DR6 and DR52) have also been hypothesized in the pathogenesis of HIVassociated pulmonary hypertension.1 Therapy includes anticoagulation (on the basis of individual risk/benefit analysis) and vasodilator agents as tolerated. At present, it is not clear whether early administration of epoprostenol could substantially improve the prognosis of HIV-infected patients with pulmonary hypertension. Epoprostenol therapy is generally limited to seriously ill patients¹⁹ because of its cost and the need for continuous intravenous infusion with an associated risk of infection. Effects of HAART regimens on the clinical course of HIV-associated pulmonary hypertension are unknown.

Vasculitis and Coronary Artery Disease

A wide range of inflammatory vascular diseases, including polyarteritis nodosa, Henoch-Schönlein purpura, and druginduced hypersensitivity vasculitis, may develop in HIVinfected individuals.¹ Kawasaki-like syndrome²⁰ and Takayasu's arteritis²¹ have been also described.

Before the introduction of HAART, coronary heart disease in HIV infection had been postulated to be linked to cytomegalovirus or HIV-1 itself, even though controversy remains and the association between viral infection and coronary artery lesions is not clear.²² Acute coronary syndromes may be observed with increasing frequency among HIV patients receiving therapy with protease inhibitors as part of HAART regimens. Protease inhibitors are designed to target the catalytic region of HIV-1 protease. This region is homologous with regions of 2 human proteins that regulate lipid metabolism, cytoplasmic retinoic-acid binding protein 1 and low-density lipoprotein-receptor-related protein.23 It has been hypothesized, although without strong experimental support, that this homology may allow protease inhibitors to interfere with these proteins, which may be the cause of the metabolic and somatic alterations that develop in protease inhibitors-treated patients (ie, dyslipidemia, insulin resistance, increased C-peptide levels, and lipodystrophy).23 Recent data indicate that dyslipidemia may be, at least in part, caused either by protease inhibitors-mediated inhibition of proteasome activity and accumulation of the active portion of sterol regulatory element-binding protein-1c in liver cells and adipocytes²⁴ or to apo-CIII polymorphisms in HIV-infected patients.25 Endothelial dysfunction has been recently described in protease inhibitors recipients, further supporting the idea of increased risk of coronary artery disease in these patients.26

The patients with preexisting cardiovascular risk factors or a family history of cardiovascular disease may have a higher risk of developing acute coronary syndromes. Data on the incidence of coronary artery disease among HIV-infected subjects receiving protease inhibitors, however, are largely limited to case reports,²⁷ and controlled prospective studies are lacking. In the retrospective analysis of the Frankfurt HIV-Cohort Study, Rickerts et al²⁸ reported a 4-fold increase in the annual incidence of myocardial infarction among HIV infected patients after introduction of HAART regimens including protease inhibitors compared with patients from the pre-HAART period. In this study, previous HAART therapy that included protease inhibitors was significantly associated with the incidence of myocardial infarction in univariate analysis and in a multiple regression model.²⁸

Hypertension and Coagulative Disorders

The prevalence of hypertension in HIV disease has been estimated to have been about 20% to 25% before the introduction of HAART.²⁹ Recent reports indicate that elevated blood pressure may be related to protease inhibitorinduced lipodystrophy and metabolic disorders, especially fasting triglyceride, with a prevalence of hypertension in up to 74% of patients with HAART-related metabolic syndrome.³⁰ HIV-infected patients, especially those with fat redistribution, may develop coagulation abnormalities such as increased levels of fibrinogen, D-dimer, plasminogen activator inhibitor-1, and tissue-type plasminogen activator antigen, or a deficiency of protein S.^{31,32} These abnormalities have been associated with documented thromboses involving both veins and arteries and seem to be related to protease inhibitor-containing HAART.32 The routine evaluation of coagulation parameters is probably not advisable until the benefit of widespread screening is assessed in prospective studies. However, clinicians should be aware of the increased risk of coagulative disorders in HIV-infected patients receiving HAART.

Risk Stratification for Patients on HAART

For patients taking HAART, it may be important to evaluate the traditional vascular risk factors and to try to intervene on those that can be modified. Existing guidelines for the management of dyslipidemia in the general population, such as those of the National Cholesterol Education Program, currently represent the basis for therapeutic recommendations also in HIV-infected individuals.33 In the absence of specific trial data, HIV patients presenting with acute coronary syndromes should be treated according to international guidelines. Diet and exercise should not be overlooked, because both can be effective in managing these complications without causing further side effects.33 Fibric acid derivatives and statins can lower HIV-associated cholesterol and triglyceride levels, although further data are needed on interactions between statins and protease inhibitors.33 Most statins are metabolized through the CYP3A4 pathway, raising concern over the potential interactions with protease inhibitors. The inhibition of CYP3A4 by protease inhibitors could potentially increase by several-fold the concentrations of statins, thus increasing the risk of skeletal muscle toxicity or hepatic toxicity. Pravastatin appears to be the safest agents at this time because it is least influenced by the CYP3A4 metabolic pathway.33 An approach to the treatment of dyslipidemia in patients treated with protease inhibitors is to switch to protease inhibitors-free combination regimens. Although large randomized trials are lacking, some favorable effects have been shown. Of interest are data indicating that patients never treated with HAART who started a protease inhibitorssparing regimen including nevirapine showed a significant increase of HDL cholesterol.34

Common HIV Therapies and the Heart

In AIDS patients with Kaposi's sarcoma, reversible cardiac dysfunction was associated with prolonged, high-dose therapy with interferon- α .¹ Doxorubicin, which is used to treat AIDS-related Kaposi's sarcoma and non-Hodgkin's lymphoma, has a dose-related effect on dilated cardiomyopathy, as does foscarnet sodium when used to treat cytomegalovirus esophagitis.¹ Cardiac arrhythmias have been described with the administration of amphotericin B, ganciclovir, trimethoprim-sulfamethoxazole, and pentamidine.¹ The prin-

Class	Drugs	Cardiac Drug Interactions	Cardiac Side Effects	
Antiretroviral				
Nucleoside Reverse Transcriptase Inhibitors (RTI)	Abacavir (Ziagen), zidovudine (AZT, Retrovir)	Dipyridamole	Lactic acidosis (rare), hypotension, skeletal muscle myopathy, (mitochondrial dysfunction hypothesized, but not seen clinically)	
Nonnucleoside RTI	Delavirdine (Rescriptor), efavirenz (Sustiva), nevirapine (Viramune)	Warfarin (class interaction), calcium channel blockers, β -blockers, quinidine, steroids, theophylline	Delavirdine can cause serious toxic effects if given with antiarrhythmic drugs and myocardial ischemia if given with vasoconstrictors	
Protease inhibitors	Amprenavir (Agenerase), indinavir (Crixivan), nelfinavir (Viracept), ritonavir (Norvir), saquinavir (Invirase, Fortovase)	All are metabolized by cytochrome p-450 and interact with: sildenafil, amiodarone, lidocaine, quinadine, warfarin, statins	Implicated in premature atherosclerosis, dyslipidemia, insulin resistance, and lipodystrophy/lipoatrophy	
		Calcium channel blockers, β -blockers (1.5–3× increase), prednisone, quinine, theophylline (decrease concentrations)		
Anti-infective				
Antibiotics	Erythromycin, clarithromycin	Cytochrome p-450 metabolism and drug interactions	Orthostatic hypotension, ventricular tachycardia, bradycardia, dr prolongation	
	Rifampicin	Reduces therapeutic effect of digoxin by induction of intestinal P-glycoprotein		
	Trimethoprim/sulfamethoxazole (Bactrim)	Increases warfarin effects	Orthostatic hypotension, QT prolongation	
Antifungal agents	Amphotericin B	Digoxin toxicity	Hypertension, renal failure, hypokalemia, thrombophlebitis, angioedema, dilated cardiomyopathy, arrhythmias.	
	Ketoconazole, itraconazole	Cytochrome p-450 metabolism and drug interactions; increases levels of sildenafil, warfarin, statins, nifedipine, digoxin		
Antiviral agents	Foscarnet, ganciclovir	Zidovudine	Reversible cardiac failure (dose-related effect), electrolyte abnormalities, ventricular tachycardia (QT prolongation), hypotension	
Antiparasitic	Pentamidine (intravenous)		Hypotension, arrhythmias (torsade de pointes, ventricular tachycardia), hyperglycemia, hypoglycemia, sudden death	
			Note: Contraindicated if baseline QTc>0.48	
Chemotherapy agents	Vincristine, doxorubicin	Decrease digoxin level	Arrhythmias, myocardial infarction, dilated cardiomyopathy (dose-related effect), autonomic neuropathy	
	Recombinant interferon- α		Hypertension, hypotension, dilated cardiomyopathy, ventricular and supraventricular arrhythmias, atrioventricular block	
	IL-2		Hypotension, arrhythmias, myocardial infarction, cardiac failure, capillary leak, thyroid alterations	

TABLE 2. Ca	ardiovascular	Actions/Interactions o	f Common	HIV 1	[herapies]
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cipal cardiovascular actions/interactions of common HIV therapies are reported in Table 2.

Cardiac Involvement in AIDS-Related Tumors Retrospective autopsy studies in the pre-HAART period estimated the prevalence of cardiac Kaposi's sarcoma in AIDS to be from 12% to 28%.⁶ Cardiac Kaposi's sarcoma is not usually obstructive or associated with clinical cardiac dysfunction, morbidity, or mortality. Malignant lymphoma involving the heart is infrequent in AIDS.⁶ Lymphomatous infiltration may be diffuse or may result in discrete isolated lesions, which are usually derived from the Burkitt or immunoblastic type B cells.⁶ The prognosis of patients with HIV-associated cardiac lymphoma is generally poor, although clinical remission has been observed with combination chemotherapy.¹ The introduction of HAART may lead to a reduction in the overall incidence of cardiac involvement by Kaposi's sarcoma and non-Hodgkin lymphomas. The fall may be attributable to the improved immunologic state of the patients and the prevention of opportunistic infections (human herpes virus-8 and Epstein-Barr virus) known to play a pathogenic role in these neoplasms.³⁵

Conclusions

It is hoped that HAART regimens, by improving the clinical course of HIV disease, will reduce the incidence of pericardial effusions and myocardial involvement of HIV-associated malignancies and co-infections. A careful cardiological screening, however, is warranted for patients who are being evaluated for or who are receiving HAART regimens, especially those with other known underlying cardiovascular risk factors, as the atherogenic effects of protease inhibitors may synergistically promote the acceleration of coronary heart and cerebrovascular disease and enhance the risk of death due to myocardial infarction and stroke. A tight collaboration be-tween cardiologists and specialists in infectious diseases may be useful in the decision regarding the use of antiretrovirals and other treatment for a careful stratification of the cardiovascular risk and cardiovascular monitoring.

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