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HIV Infection and the Cardiovascular System

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Abstract

Better treatment and supportive care are prolonging the lives of patients with HIV, which is resulting in a higher prevalence of long-term effects of HIV. Autopsy and echocardiography studies support frequent involvement of the heart in advanced stages of HIV infection. The most common cardiac manifestations of HIV are dilated cardiomyopathy, myocarditis, pulmonary hypertension, pericardial effusion, endocarditis, HIV-associated malignant neoplasms, and drug-related cardiotoxicity. Highly active antiretroviral therapy (HAART) has prolonged many patients' lives, but many cardiac sequelae of HIV are not affected by HAART and continue to develop even with treatment. In addition, HAART itself may be associated with an increase in peripheral artery and coronary artery diseases. This review focuses on the most recent knowledge about HIV-associated cardiovascular disease. Careful cardiovascular evaluation in the course of HIV disease can identify cardiac complications early enough to treat. In addition, the study of HIV-related cardiovascular disease may shed light on the mechanisms of non-HIV-related cardiovascular disease.

Key words

HIV. Coronary heart disease. Cardiovascular disease. Antiretroviral therapy. Cardiomyopathy. Myocarditis.

Introduction

Observations of the cardiovascular manifestations of HIV infection for >15 years have been substantiated by prospective studies[1]. Reports from the past 2-3 years have tracked the incidence and course of HIV infection in relation to both pediatric and adult cardiac illnesses[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 introduction of highly active antiretroviral therapy (HAART) regimens has significantly modified the course of HIV disease, with longer survival and improved quality of life. Though inconclusive at this time, early data raised concerns about an increase in both peripheral and coronary arterial disease with HAART. A variety of potential etiologies have been postulated for HIV-related heart disease, including myocardial infection with HIV itself, opportunistic infections, viral infections, autoimmune response to viral infection, drug-related cardiotoxicity, nutritional deficiencies, and prolonged immunosuppression (Table 1).

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Table 1. *Principal HIV-associated cardiovascular abnormalities*[1]

Type	Possible etiologies and associations	Incidence
Dilated cardiomyopathy	– Infectious: 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 and Hyperthermia – Autonomic insufficiency – Encephalopathy – Acquired immunodeficiency – HIV viral load, length of immunosuppression	Estimated 15.9 patients/1000 asymptomatic HIV-infected persons.
Coronary heart disease	Protease inhibitor-induced metabolic and coagulative disorders. Arteritis	Mostly limited to case reports
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%[59]
Pericardial effusion	– Bacteria: *Staphylococcus*, *Streptococcus*, *Proteus*, *Nocardia*, *Pseudomonas*, *Klebsiella*, *Enterococcus*, *Listeria* – 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	11%/year
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[23]
AIDS-related tumors	Kaposi's sarcoma	12-28%[7,23]
	Non-Hodgkin lymphomas	Mostly limited to case reports

Dilated cardiomyopathy

The estimated annual incidence of dilated cardiomyopathy with HIV infection before the introduction of HAART was 15.9/1000 persons[2]. Symptoms of heart failure may be masked in HIV-infected patients by concomitant illnesses such as diarrhea or malnutrition, or may be disguised by bronchopulmonary infections. The gross and microscopic findings with HIV-associated dilated cardiomyopathy are similar to those for idiopathic dilated cardiomyopathy in immunocompetent persons, with four-chamber dilation and patchy myocardial fibrosis. Additional echocardiographic findings include diffuse left ventricular hypokinesis and decreased fractional shortening[3].

Compared to patients with idiopathic dilated cardiomyopathy, those with HIV infection and dilated cardiomyopathy have markedly reduced survival (hazard ratio for death from congestive heart failure: 5.86)[4]. The median survival to AIDS-related death is 101 days in patients with left ventricular dysfunction and 472 days in patients with a normal heart at a similar stage of HIV infection[5]. There is no evidence from prospective studies to suggest that HAART has a beneficial effect on HIV-associated cardiomyopathy. However, some retrospective studies suggest that, by preventing opportunistic infections and improving the immunologic parameters, HAART might reduce the incidence of HIV-associated heart disease and improve its course[6,7].

Myocarditis and viral myocardial infection as causes of cardiomyopathy. Myocarditis and myocardial infection with HIV are the best-studied causes of dilated cardiomyopathy in HIV disease[2,8]. HIV-1 virions appear to infect myocardial cells in a patchy distribution with no direct association between the presence of the virus and myocyte dysfunction[2,8]. The myocardial fiber necrosis is usually minimal, with accompanying mild-to-moderate lymphocytic infiltrates (Fig. 1)[3]. It is unclear how HIV-1 enters myocytes, which do not have CD4 receptors, although dendritic reservoir cells may play a role by activating multifunctional cytokines that contribute to progressive and late tissue damage, such as tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), and interleukin-10 (IL-10)[4]. Co-infection with other viruses (usually coxsackievirus B3 and cytomegalovirus) may also play an important pathogenetic role[2,8].

Autoimmunity as a contributor to cardiomyopathy. Cardiac-specific autoantibodies (anti-alpha-myosin autoantibodies) are more common in HIV-infected patients with dilated cardiomyopathy than in HIV-infected patients with healthy hearts[9]. Also, Currie, et al. recently reported that HIV-infected patients were more likely to have specific cardiac autoantibodies than were HIV-negative controls[10]. Those with echocardiographic evidence of left ventricular dysfunction were particularly likely to have cardiac autoantibodies, supporting the theory that cardiac autoimmunity plays a role in the pathogenesis of HIV-related heart disease and suggesting that cardiac autoantibodies could be used as markers of left ventricular dysfunction in HIV-positive patients with previously normal echocardiographic findings[10].

In addition, monthly intravenous immunoglobulin in HIV-infected pediatric patients minimizes left ventricular dysfunction, increases left ventricular wall thickness, and reduces peak left ventricular wall stress, suggesting that both impaired myocardial growth and left ventricular dysfunction may be immunologically mediated[11]. These effects may be the result of immunoglobulins inhibiting cardiac autoantibodies by competing for Fc receptors, or they could be the result of immunoglobulins dampening the secretion or effects of cytokines and cellular growth factors[11]. These findings suggest that immunomodulatory therapy might be helpful in adults and children with declining left ventricular function, although further study of this possible therapy is needed.

Myocardial cytokine expression as a factor in cardiomyopathy. Cytokines play a role in development of HIV-related cardiomyopathy[4]. Myocarditis and dilated cardiomyopathy are associated with markedly elevated cytokine production, but the elevations may be highly localized within the myocardium, making peripheral cytokine levels uninformative[4].

When myocardial biopsies from patients with HIV-associated cardiomyopathy are compared to samples from patients with idiopathic dilated cardiomyopathy, the former stains more intensely for both TNF-α and inducible nitric oxide synthase (iNOS). Staining is particularly intense in samples from patients with a myocardial viral infection, independently of antiretroviral treatment[4]. Staining is also more intense in samples from patients with HIV-associated cardiomyopathy co-infected with coxsackievirus B3, cytomegalovirus, or other viruses[4]. Moreover, staining for iNOS is more intense in samples from patients co-infected with HIV-1 and coxsackievirus B3 or cytomegalovirus than in samples from patients with idiopathic dilated cardiomyopathy and myocardial infection with coxsackievirus B3 or who had adenovirus infection alone[12].

In patients with HIV-associated dilated cardiomyopathy and more intense iNOS staining, the survival rate was significantly lower: those whose samples stained more than 1 optical density unit had a hazard ratio of mortality of 2.57 (95% confidence interval: 1.11 to 5.43). Survival in HIV-infected patients with less intense staining was not significantly different from survival in patients with idiopathic dilated cardiomyopathy[4].

The inflammatory response may be enhanced by HIV-1 myocardial infection, by the interaction between HIV-1 and cardiotropic viruses, and by immunodeficiency. These factors may increase both the expression and the cytotoxic activity of specific cytokines such as TNF-α and iNOS and blunt the expected increase of anti-inflammatory cytokines such as IL-10[13].

Relationship between HIV-associated cardiomyopathy and encephalopathy. HIV-infected patients with encephalopathy are more likely to die of congestive heart failure than are those without encephalopathy (hazard ratio: 3.4)[14-16]. Cardiomyopathy and encephalopathy may both be traceable to the effects of HIV reservoir cells in the myocardium and the cerebral cortex. These cells may hold HIV-1 on their surfaces for extended time periods even after antiretroviral treatment. HIV-infected macrophages may chronically release cytotoxic cytokines (TNF-α, IL-6, and endothelin-1), which contribute to progressive and late tissue damage in both systems[16]. Because the reservoir cells are not affected by treatment, the effect is independent of whether the patient receives HAART.

Nutritional deficiencies as a factor in left ventricular dysfunction. Nutritional deficiencies are common in HIV infection and may contribute to ventricular dysfunction independently of HAART. Malabsorption and diarrhea can both lead to trace element deficiencies which have been directly or indirectly associated with cardiomyopathy[17-19]. Selenium replacement may reverse cardiomyopathy and

restore left ventricular function in selenium-deficient patients[17-19]. HIV infection may also be associated with altered levels of vitamin B12, carnitine, growth hormone, and thyroid hormone, all of which have been associated with left ventricular dysfunction[19].

Left ventricular dysfunction caused by drug cardiotoxicity. Studies of transgenic mice suggest that zidovudine is associated with diffuse destruction of cardiac mitochondrial ultrastructure and inhibition of mitochondrial DNA replication[20]. This mitochondrial dysfunction may result in lactic acidosis, which could also contribute to myocardial cell dysfunction[9]. However, in a study of infants born to HIV-positive mothers followed from birth to age 5, perinatal exposure to zidovudine was not found to be associated with acute or chronic abnormalities in left ventricular structure or function[21]. Other nucleoside reverse transcriptase inhibitors, such as didanosine and zalcitabine, do not seem to either promote or prevent dilated cardiomyopathy[2].

Treating HIV-associated cardiomyopathy. Standard heart failure treatment regimens are generally recommended for HIV-infected patients with dilated cardiomyopathy and congestive heart failure, even though these regimens have not been tested in this specific population. Patients with systolic dysfunction and symptoms of fluid retention should receive a loop diuretic and an aldosterone antagonist as well as an angiotension-converting enzyme (ACE) inhibitor. ACE-inhibitors are recommended based on general heart failure studies, but may be poorly tolerated due to low systemic vascular resistance from diarrheal disease, infection, or dehydration. Digoxin may be added to therapy for patients with persistent symptoms or rapid atrial fibrillation. In euvolumic patients, a beta-blocker may be started for its beneficial effects on circulating levels of inflammatory and anti-inflammatory cytokines[22].

Pericardial effusion

The prevalence of pericardial effusion in asymptomatic AIDS patients prior to HAART was estimated at 11%[23]. 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 etiology is not found[24]. The effusion is typically serous, and there is minimal or no lymphocytic epicardial inflammation. The effusion may be part of a generalized serous effusive process involving pleural and peritoneal surfaces. This "capillary leak" syndrome is likely related to enhanced cytokine expression in the later stages of HIV infection[23,24]. Pericardial effusion spontaneously resolves in up to 42% of patients[23]. Pericardiocentesis is currently recommended only with symptomatic effusions, for diagnostic evaluation of systemic illness, or with cardiac tamponade[24]. Mortality is 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 for patients in other risk groups, such as intravenous drug users[25]. The prevalence of endocarditis varies from 6.3% to 34% in HIV-infected patients who use intravenous drugs independently of HAART regimens[8]. Right-sided endocarditis is more common, and the most frequent agents isolated are *Staphylococcus aureus* (>75% of cases), *Streptococcus pneumoniae, Haemophilus influenzae, Candida albicans, Aspergillus fumigatus,* and *Cryptococcus neoformans*[8]. The vegetations are grossly large and friable, with valve destruction; microscopically there are numerous neutrophils, mixed with bacterial colonies, platelets, and fibrin. These vegetations often produce septic emboli. The presentation and survival (85 vs 93%) with infective endocarditis is similar to patients without HIV infection[25]. However, patients with late-stage HIV disease have about 30% higher mortality with endocarditis than asymptomatic HIV-infected patients, which may be related to the degree of immunodeficiency[25]. Surgical management is indicated in selected patients, especially when valvular dysfunction resulting in acute heart failure becomes intractable to medical therapy[26]. Hospital morbidity and mortality rates are higher than usual in this group of patients[26].

Non-bacterial thrombotic endocarditis (marantic endocarditis) occurs in 3 to 5% of AIDS patients, mostly in patients with HIV-wasting syndrome[8]. The friable endocardial vegetations are usually smaller than 0.5 cm and are composed of platelets, fibrin, and few inflammatory cells. They affect predominantly left-sided valves. Systemic embolization from marantic endocarditis is a rare cause of death in AIDS patients in the HAART era.

HIV-associated pulmonary hypertension

The incidence of HIV-associated pulmonary hypertension is 1 in 200, much higher than the 1 in 200,000 found in the general population[27]. The pathogenesis of primary pulmonary hypertension in HIV infection is multifactorial and poorly understood[24]. Primary pulmonary hypertension has been found in hemophiliacs receiving lyophilized factor VIII, intravenous drug users, and patients with left ventricular dysfunction, obscuring any relationship with HIV-1[24]. HIV-1 is frequently identified in alveolar macrophages on histology[28]. These macrophages release TNF-α, oxide anions, and proteolytic enzymes in response to infection.

Clinical symptoms and outcome 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[24]. Activation of α-1 receptors and genetic factors (increased frequency of HLA DR6 and DR52) have also been involved in the pathogenesis of HIV-associated pulmonary hypertension[24]. Therapy includes anticoagulation (based on individual risk/benefit analysis) and

vasodilator agents. Currently, 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 patients[29] because of its cost and of the need for continuous intravenous infusion with associated risk of infection[30]. Effects of HAART regimens on the clinical course of HIV-associated pulmonary hypertension are unknown.

HIV infection, opportunistic infections, and vascular disease

A wide range of inflammatory vascular diseases including polyarteritis nodosa, Henoch-Schonlein purpura, and drug-induced hypersensitivity vasculitis may develop in HIV-infected individuals. Kawasaki-like syndrome[31] and Takayasu's arteritis[32] have also been described. The course of vascular disease may be accelerated in HIV-infected patients because of atherogenesis stimulated by HIV-infected monocyte-macrophages, possibly via altered leukocyte adhesion or arteritis[33].

Some patients with AIDS have a clinical presentation resembling systemic lupus erythematosus (SLE) including vasculitis, arthralgias, myalgias, and autoimmune phenomena with a low titer positive antinuclear antibody, coagulopathy with lupus anticoagulant, hemolytic anemia, and thrombocytopenic purpura. Hypergammaglobulinemia from polyclonal B-cell activation may be present, but often diminishes in the late stages of AIDS. Specific autoantibodies to double-stranded DNA, Sm antigen, RNP antigen, SSA, SSB and other histones may be found in a majority of HIV-infected persons, but their significance is unclear[34].

Endothelial dysfunction. Endothelial dysfunction and injury have been described in HIV infection[35]. Circulating markers of endothelial activation, such as soluble adhesion molecules and procoagulant proteins, are elaborated in HIV infection[35]. HIV may enter endothelium via CD4 or galactosyl-ceramide receptors[24]. Other possible mechanisms of entry include chemokine receptors[36]. Endothelium isolated from the brain of HIV-infected subjects strongly expresses both CCR3 and CXCR4 HIV-1 coreceptors, whereas coronary endothelium strongly expresses CXCR4 and CCCR2A coreceptors[36]. CCR5 is expressed at a lower level in both types of endothelium. The fact that CCR3 is more common in brain endothelium than in coronary endothelium could be significant in light of the different susceptibilities of heart and brain to HIV-1 invasion[36]. These chemokine receptors could play a role in endothelial migration and repair[36].

Endothelial activation in HIV infection may also be caused by cytokines secreted in response to mononuclear or adventitial cell activation by the virus, or may be a direct effect of the secreted HIV-associated proteins gp120 and tat[35]. Opportunistic agents, such as cytomegalovirus, frequently coinfect HIV-infected patients and may contribute to the development of endothelial damage. Moreover, a retrospective analysis of post-mortem reports revealed a strong correlation between Kaposi's sarcoma, the most frequent AIDS-related neoplasm, and the presence of atheroma[37]. On the basis of this observation and previous experimental data, the authors hypothesize that human herpes virus-8 HHV-8 (a virus that is found in all forms of Kaposi's sarcoma) may trigger or accelerate the development of atheroma in the presence of hyperlipidemia[37]. In spite of all these observations, the clinical consequences of HIV-1 and opportunistic agents on endothelial function has not been elucidated.

HIV infection and coronary arteries. The association between viral infection (cytomegalovirus or HIV-1 itself) and coronary artery lesions is not clear. HIV-1 sequences have recently been detected by *in situ* hybridization in the coronary vessels of an HIV-infected patient who died from acute myocardial infarction[38]. Potential mechanisms through which HIV-1 may damage coronary arteries include activation of cytokines and cell-adhesion molecules and alteration of major histocompatibility complex class I molecules on the surface of smooth muscle cells[38].

Opportunistic infections. *Toxoplasma gondii* can produce a gross pattern of patchy irregular white infil-

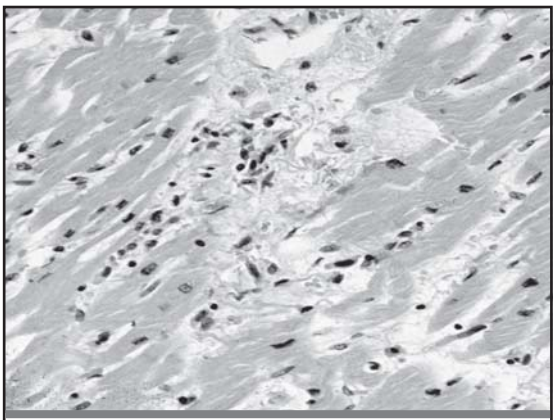

Figure 1. *Myocarditis with HIV is accompanied by small lymphocytes scattered in the myocardium along with minimal myocardial fiber necrosis (200x).*

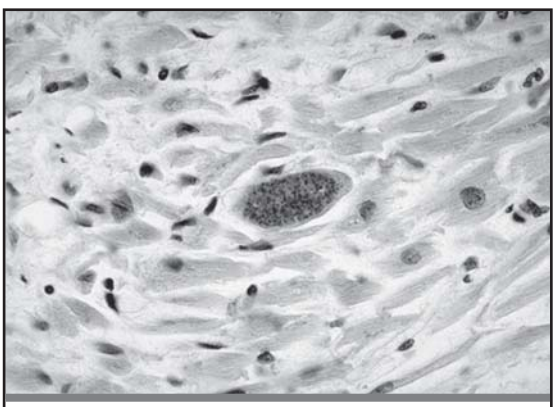

Figure 2. *Toxoplasma gondii infection leads to myocarditis with mixed inflammatory cell infiltrates within the myocardium (100x). A pseudocyst with bradyzoites is seen in the center (400x).*

trates in myocardium similar to non-Hodgkin lymphoma. Microscopically, the myocardium shows scattered mixed inflammatory cell infiltrates with polymorphonuclear leukocytes, macrophages, and lymphocytes. True *T. gondii* cysts or pseudocysts containing bradyzoites are often hard to find, even if inflammation is extensive (Fig. 2). Immunohistochemical staining may reveal free tachyzoites, otherwise difficult to distinguish, within the areas of inflammation. *T. gondii* myocarditis can produce focal myocardial, fiber necrosis and heart failure can ensue[39].

Other opportunistic infections of the heart are infrequent. They are often incidental findings at autopsy, and cardiac involvement is probably the result of widespread dissemination, as exemplified by *Candida* and by the dimorphic fungi *Cryptococcus neoformans, Coccidioides immitis*, and *Histoplasma capsulatum*. Patients living in endemic areas for *Trypanosoma cruzi* may rarely develop a pronounced myocarditis[40].

Antiretroviral therapy and metabolic disorders

Pathogenesis of protease inhibitor (PI)-related metabolic disorders. PIs are designed to target the catalytic region of HIV protease. This region is homologous with regions of two human proteins that regulate lipid metabolism: cytoplasmic retinoic-acid binding protein 1 (CRABP-1) and low-density lipoprotein-receptor-related protein (LRP)[41]. It has been hypothesized, although without strong experimental support, that this homology may allow PIs to interfere with these proteins, which may be the cause of the metabolic and somatic alterations that develop in PI-treated patients, including a peculiar adipose tissue redistribution known as lipodystrophy. This syndrome is associated with loss of facial fat, dorsocervical tissue accumulation, increased internal abdominal fat accumulation, hyperlipidemia (often exceeding 1000 mg/dl), peripheral insulin resistance and impaired glucose tolerance[41]. There is a wide variation in the severity and clinical presentation of these metabolic side effects. Dyslipidemia is most pronounced with ritonavir[42].

The hypothesis is that PIs inhibit CRABP-1-modified and cytochrome P450-3A-mediated synthesis of cis-9-retinoic acid and peroxisome proliferator-activated receptor type gamma (PPAR-gamma) heterodimer. The inhibition increases the rate of apoptosis of adipocytes and reduces the rate at which preadipocytes differentiate into adipocytes, reducing triglyceride storage and increasing lipid release. PI binding to LRP would impair hepatic chylomicron uptake and endothelial triglyceride clearance, resulting in hyperlipidemia and insulin resistance[41].

Recent data indicate that dyslipidemia may, at least in part, be caused either by PI-mediated inhibition of proteasome activity and accumulation of the active portion of sterol regulatory element-binding protein-1c in liver cells and adipocytes[43] or by apo CIII polymorphisms in HIV-infected patients[44]. Some nucleoside analogues, such as stavudine, may enhance the effects of PIs when given in combination. Experimental studies show that stavudine depletes white adipose tissue and mitochondrial DNA in obese, but not lean, mice[45].

There is also evidence that PIs directly inhibit the uptake of glucose in insulin-sensitive tissues, such as fat and skeletal muscle, by selectively inhibiting the glucose transporter Glut4[46]. The relationship between the degree of insulin resistance and levels of soluble type 2 tumor necrosis factor-alpha receptor suggests that an inflammatory stimulus may contribute to the development of HIV-associated lipodystrophy[24,47]. Endothelial dysfunction has been recently described in PI recipients, further supporting the increased risk of cardiovascular disease in these patients[48].

Mitochondrial damage and metabolic disorders. Similarities between HAART-associated fat redistribution and metabolic abnormalities with both inherited lipodystrophies and benign symmetric lipomatosis could suggest the pathophysiological involvement of nuclear factors like lamin A/C and nucleoside-induced mitochondrial dysfunction[49], although no mutations or polymorphisms in the gene encoding lamin A/C associated with aberrant adipocyte tissue distribution or metabolic abnormalities have been detected in HIV-infected patients with lipodystrophy. However, this could explain many of the side effects seen in people taking nucleosides, including peripheral neuropathy, pancreatitis, leukopenia, and possibly lipodystrophy[50,51]. It has been suggested that lipodystrophy might also be related to an imbalance in the immune system that remains after triple-drug therapy is started; even though triple-drug therapy prevents HIV from attacking immune system cells, it may not halt the negative effects of HIV on other cells in the body[50,51]. However, the temporal and causal relationship between the three major components of the HAART-related metabolic syndrome, i.e. dyslipidemia, visceral adiposity and insulin resistance remains to be elucidated.

Antiretroviral therapy and cardiovascular risk

Risk stratification and pharmacological therapy. Evaluation of traditional cardiovascular risk factors according to the Framingham score with intervention for those that can be modified is important for patients on HAART. These risk factors may be added to nonreversible risk factors, such as male sex, age greater than 40 years, and family history of premature coronary heart disease. Patients may also be smokers and may have a sedentary lifestyle, both of which predispose to coronary heart disease and stroke. Existing guidelines for the management of dyslipidemias in the general population, such as those of the National Cholesterol Education Program, also currently represent the basis for therapeutic recommendations in HIV-infected individuals[52]. Dietary modification and exercise are general health measures likely to be beneficial in HIV infected patients with a HAART-related metabolic syndrome[52].

Fibrate derivatives and statins can lower PI-associated cholesterol and triglyceride levels, although further data are needed on interactions between statins and PI. Since most statins are metabolized through the CYP3A4 pathway, the inhibition of CYP3A4 by PIs could potentially increase the concentration of statins by several-fold, thus increasing the risk of skeletal muscle or hepatictoxicities. Fibrates are unlikely to have significant interactions with PIs, since their principal metabolic pathway is CYP4A.

In patients with very high levels of triglycerides, dietary supplementation with fish oils (omega-3 fatty acid supplements) can be given, despite lack of testing in this subset of patients. In patients with dyslipidemia who do not respond to diet and exercise and eventually to drug treatment with statins or with fibrates, a combined therapy can be tried. However, the concomitant use of statins and fibrates increases the risk of skeletal muscle toxicity and should be carefully monitored. Hypoglycemic agents may have some role in managing glucose abnormalities, but troglitazone cannot be recommended for fat abnormalities alone and metformin may cause lactic acidosis[53].

Switching from PIs. Patients with PI-related dyslipidemia can be switched to PI-Sparing 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 start a PI-sparing regimen including nevirapine show a significant increase in HDL-cholesterol[54]. If further confirmed, these findings might influence the initial choice of therapy for HIV-1 infection and lead to novel approaches targeted at raising HDL-cholesterol for coronary heart disease (CHD) prevention in patients on HAART.

HAART and CHD. Acute coronary syndromes (unstable angina, myocardial infarction) may be observed among HIV-infected patients receiving PIs. Patients with additional pre-existing risk factors (e.g., hypertension, diabetes, smoking and increased plasma-homocysteine levels) may have a higher risk for acute coronary syndromes or stroke because of accelerated atherosclerosis[55]. However, data on occurrence of CHD among HIV-infected subjects receiving HAART are largely limited to case reports[56-59] and controlled prospective studies are lacking.

A large multinational joint venture with participation by 11 national HIV cohorts is now addressing this major issue. Approximately 22,000 subjects are being followed at 180 sites across Europe, Australia and the US. The data presently available indicate that treated subjects with preserved immunity, better viral suppression, lipodystrophy and older age are at risk for cardiovascular disease based on lipid profiles. To what extent this will lead to accelerated atherosclerosis is presently unknown, but data on the incidence of cardiovascular events will become available by the end of 2002. In a retrospective analysis of the Frankfurt HIV-Cohort Study, Rickerts, et al. reported a four-fold increase in the annual incidence of myocardial infarction among HIV-infected patients after introduction of HAART regimens including PIs compared to a pre-HAART period. In this study, previous HAART therapy that included PIs was significantly associated with a higher incidence of myocardial infarction both in univariate analysis and in a multiple regression model[60].

Anabolic-androgenic steroids may be taken by patients with wasting diseases such as AIDS to improve physical appearance and strength as well as athletes seeking to increase muscle mass and improve performance. Unfortunately, these agents are associated with an increased risk of acute myocardial infarction. Varriale, et al. reported an otherwise unexpected acute myocardial infarction in a 39-year-old man with HIV infection that was apparently linked to androgen use. It is important for clinicians to be aware of the association and to counsel patients carefully about adverse effects of anabolic steroids[61].

HAART and peripheral vascular disease. Also the issue of surrogate markers of subclinical atherosclerosis has been addressed. A study was performed on a cohort of 168 HIV-infected patients to measure the intima-media thickness and indirectly assess the cardiovascular risk. In this population a high prevalence of atherosclerotic plaques within the femoral or carotid arteries was observed, but their presence was not associated with the use of PIs[62]. Different results were reported in another study, in which a higher than expected prevalence of premature carotid lesions in PI-treated patients when compared to PI-*naïve* patients was observed[63].

HAART, hypertension and coagulation disorders. PI-induced insulin resistance may cause increased sympathetic activity and sodium retention, potentially leading to hypertension[64,65]. Recent reports indicate that elevated blood pressure may be related to PI-induced lipodystrophy and metabolic disorders, especially to fasting triglyceride levels[66]. Moreover, 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 deficiency of protein S[67,68]. These abnormalities have been associated with documented thromboses involving both veins and arteries and seem to be related to PI-containing HAART[65,67].

In a large multicentre epidemiological survey, Sullivan, et al. reported an incidence of clinically recognized thrombosis of 2.6/1000 person/years in a sample of 42,935 HIV-infected adults[69]. Thrombosis was more common in patients who were 45 years of age or older, had opportunistic infections, were hospitalized, or were prescribed megestrol or indinavir[69]. 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 persons.

Table 2. *Cardiovascular actions/interactions of common HIV therapies*[24]

Class	Drugs	Cardiac drug interactions	Cardiac side effects
Antiretroviral	i) Abacavir (Ziagen)		Rare: Lactic acidosis
A) Nucleoside reverse Transcriptase inhibitors	ii) Zidovudine (AZT, Retrovir)	ii) Dipyridamole	i) Hypotension ii) Skeletal muscle myopathy, (mitochondrial dysfunction hypothesized, but not seen clinically)
B) Non-nucleoside reverse transcriptase inhibitors	i) Delavirdine (Rescriptor) ii) Efavirenz (Sustiva) iii) Nevirapine (Viramune)	Warfarin (class interaction) i) Calcium channel blockers iii) Beta blockers, nifedipine, quinidine, steroids, theophylline.	
C) Protease inhibitors	i) Amprenavir (Agenerase) ii) Indinavir (Crixivan) iii) Nelfinavir (Viracept) iv) Ritonavir (Norvir) v) Saquinavir (Invirase, Fortovase)	All are metabolized by cytochrome p-450 and interact with: sildenafil, amiodarone, lidocaine, quinadine, warfarin, "statins" iv) Calcium channel blockers, prednisone, quinine, increases beta blocker levels 1.5-3x	Implicated in premature atherosclerosis, dyslipidemia, insulin resistance, fat wasting and redistribution (lipodystrophy)
Anti-infective			
A) Antibiotics	i) Erythromycin	i) Cytochrome p-450 metabolism and drug interactions	Orthostatic hypotension, ventricular tachycardia, bradycardia, torsades (drug interactions)
	ii) Trimethoprim/ sulfamethoxazole (Bactrim)	ii) Increases warfarin effects	Orthostatic hypotension, anaphylaxis, QT prolongation
B) Antifungal agents	i) Amphotericin B ii) Ketoconazole iii) Itraconazole (Sporanox)	Digoxin toxicity ii) & iii) Cytochrome p-450 metabolism and drug interactions- increases levels of sildenafil, warfarin, "statins", nifedipine, digoxin	i) Hypertension, arrhythmia, renal failure, hypokalemia, thrombophlebitis, bradycardia, angioedema, dilated cardiomyopathy
C) Antiviral drugs	i) Foscarnet ii) Ganciclovir	ii) Zidovudine	i) Reversible cardiac failure, electrolyte abnormalities ii) Ventricular tachycardia, hypotension
D) Anti-parasitic	i) Pentamidine (IV)*		Hypotension, arrhythmias (torsade de pointes, VT), hyperglycemia, hypoglycemia, sudden death
Chemotherapy agents	i) Vincristine	i) Decreases digoxin level	i) arrhythmia, myocardial infarction, cardiomyopathy
	ii) Interferon-α		ii) Orthostatic hypotension, myocardial infarction, cardiomyopathy, ventricular and supraventricular arrhythmias, sudden death, atrioventricular block
	iii) IL-2		iii) Hypotension, arrhythmia, sudden death, myocardial infarction, cardiac failure, capillary leak, thyroid alterations iv) Myocarditis, cardiomyopathy, cardiac failure
	iv) Doxorubicin (Adriamycin)	iv) Decreases digoxin level	

*Note: Contraindicated if baseline QTc > 0.48

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 alpha[24]. Doxorubicin (adriamycin) 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 used to treat cytomegalovirus diseases[24]. Cardiac arrhythmias have been described with the administration of amphotericin B[70], ganciclovir[71], trimethoprim-sul-

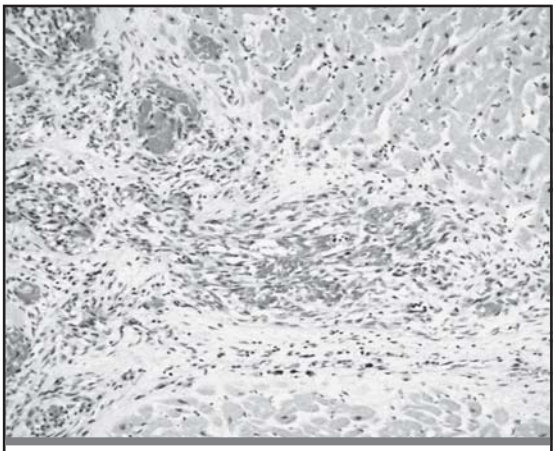

Figure 3. *Kaposi's sarcoma extends from the epicardium into the myocardium as masses of irregular vascular channels (100x).*

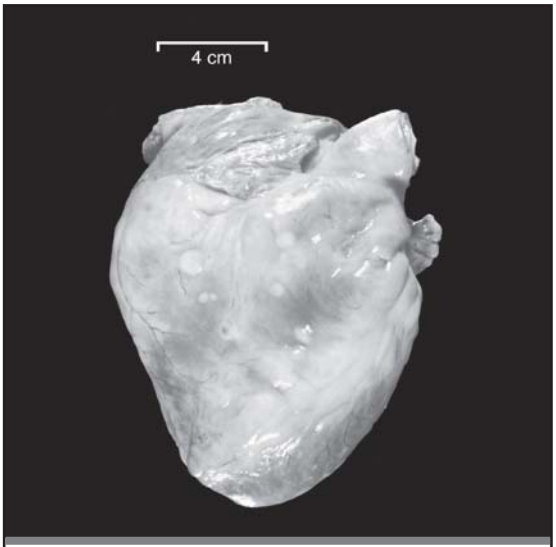

Figure 4. *Non-Hodgkin's lymphoma appears grossly as discreet epicardial nodules.*

famethoxazole[72], and pentamidine[73]. The principal cardiovascular actions/interactions of common HIV therapies are reported in table 2.

Cardiac involvement with AIDS-related neoplasms

The prevalence of cardiac Kaposi's sarcoma (KS) in AIDS patients ranges from 12 to 28% in retrospective autopsy studies in the pre-HAART period[8]. Cardiac involvement with KS usually occurs when widespread visceral organ involvement is present. The lesions are typically less than 1 cm in size and may be pericardial or, less frequently, myocardial, and are only rarely associated with obstruction, dysfunction, morbidity, or mortality[8]. Microscopically, there are atypical spindle cells lining slit-like vascular spaces (Fig. 3).

Non-Hodgkin lymphoma (NHL) involving the heart is infrequent in AIDS[7]. Most are high-grade B-cell (small non-cleaved) Burkitt-like lymphomas, with the rest classified as diffuse large B cell lymphomas (in the REAL classification). Lymphomatous lesions may appear grossly as either discreet localized or more diffuse nodular to polypoid masses[74,75]. Most involve the pericardium, with variable myocardial infiltration[74,75] (Fig. 4). There is little or no accompanying inflammation and necrosis. The prognosis of patients with HIV-associated cardiac lymphoma is generally poor because of widespread organ involvement, although some patients treated with combination chemotherapy have experienced clinical remission[76].

The introduction of HAART has reduced the incidence of cardiac involvement by KS and NHL, perhaps attributable to the patients' improved immunologic state and to suppression of opportunistic infections with HHV-8 and Epstein-Barr virus, that are known to play an etiologic role in these neoplasms[76].

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. However, a careful cardiac screening 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 PI-including HAART may synergistically promote the acceleration of coronary and cerebrovascular disease and increase the risk of death from myocardial infarction and stroke. A close collaboration between cardiologists and infectious disease specialists may be useful for decisions regarding use of antiretrovirals and other therapies for a careful stratification of cardiovascular risk and cardiovascular monitoring.

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