

The cardiovascular manifestations of HIV infection

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Cardiovascular illness is common in patients with human immunodeficiency virus (HIV) infection, particularly late in the disease course. As better therapy improves longevity for patients with HIV infection, symptomatic heart failure and related cardiovascular morbidity and mortality are becoming important global health concerns. The incidence of symptomatic heart failure among HIV-infected people followed for 2 to 5 years is 8% to 10%, suggesting that there may be about 3 million prevalent cases of symptomatic HIV-related heart failure. There are many different manifestations of cardiac disease in HIV-infected individuals, including left ventricular systolic dysfunction or cardiomyopathy, pericardial effusion, infective endocarditis, cardiovascular malignancy, vasculitis, atherosclerosis, and autonomic dysfunction. Cardiac disease may result from HIV itself, other infectious etiologies, or may be accelerated by the effects of the antiretroviral agents used to treat HIV infection. In this paper, we will examine the various cardiovascular manifestations of HIV disease and its treatment, review the prevalence, pathogenesis, and treatment options, and discuss preventive measures and monitoring to identify preclinical cardiac disease early on in its course.

Cardiovascular illness is common in patients with HIV infection, particularly late in the disease course.¹⁻³ As better therapy improves longevity for patients with HIV infection, symptomatic heart failure and related cardiovascular morbidity and mortality are becoming important global health concerns. Some 38.6 million adults and children were living with HIV infection at the end of the year 2005.⁴ The incidence of symptomatic heart failure among HIV-infected people followed for 2 to 5 years is 8% to 10%,⁵ suggesting that there may be about 3 million prevalent cases of symptomatic HIV-related heart failure.

The introduction of highly active antiretroviral therapy (HAART) has greatly modified the course of HIV disease, prolonging survival and improving quality of life. However, studies from before the era of HAART therapy remain globally applicable, as HAART is only available to, and tolerated by, a minority of HIV-infected individuals worldwide. In addition, early data have raised concerns that HAART itself is associated with an increased incidence of both peripheral and coronary artery diseases. In this review, we discuss the principal HIV-associated cardiovascular manifestations (*Table I, pages 2 and 3*)⁶ and focus on current concepts of prevalence, pathogenesis, and treatment.

SELECTED ABBREVIATIONS

AIDS	acquired immune deficiency syndrome
CMV	cytomegalovirus
HAART	highly active antiretroviral therapy
HIV	human immunodeficiency virus
P²C² HIV	Pediatric Pulmonary and Cardiovascular Complications of vertically transmitted HIV infection (study)
TNF-α	tumor necrosis factor- α

Keywords: HIV; AIDS; cardiomyopathy; cardiovascular disease; atherosclerosis; highly active antiretroviral therapy

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Dialogues Cardiovasc Med. 2007;12:5-23

Type of disease	Possible causes	Incidence/prevalence	Diagnosis	Treatment
Dilated cardiomyopathy	<p>Drug related Cocaine, AZT, IL-2, doxorubicin, interferon</p> <p>Infectious HIV, toxoplasma, coxsackievirus group B, EBV, CMV, adenovirus</p> <p>Metabolic or endocrine Selenium or carnitine deficiency, anemia, hypocalcemia, hypophosphatemia, hyponatremia, hypokalemia, hypoalbuminemia, hypothyroidism, growth-hormone deficiency, adrenal insufficiency, hyperinsulinemia, hemochromatosis, hemochromocytoma, sarcoidosis, amyloidosis</p> <p>Cytokines TNF-α, nitric oxide, TGFβ, endothelin-I, interleukins</p> <p>Immunodeficiency CD4-100</p> <p>Autoimmune</p>	<p>Up to 8% of asymptomatic patients</p> <p>Up to 25% of autopsy cases</p>	<p>Chest radiograph findings</p> <p>Nonspecific conduction abnormalities PVCs, PACs</p> <p>Echocardiogram findings Low-normal LV wall thickness, increased LV mass, dilated LV, systolic, LV dysfunction</p> <p>Possible laboratory studies Troponin T, brain natriuretic peptide level, CD4 count, viral load, viral PCR, toxoplasma serology, TSH, cortisol, carnitine, selenium, serum ACE, vanillyl-mandelic acid, amyloid, urinalysis, stress testing, myocardial biopsy, cardiac catheterization</p>	<p>Diuretics, digoxin, ACE inhibitors, β-blockers</p> <p>Adjunctive treatment in HIV+ patients Treatment of infection, nutritional replacement, IV Ig, intensify antiretroviral therapy</p> <p>Follow-up Serial echocardiograms</p>
Pericardial effusion	<p>Bacteria <i>Staphylococcus</i>, <i>Streptococcus</i>, <i>Proteus</i>, <i>Klebsiella</i>, <i>Enterococcus</i>, <i>Listeria</i>, <i>Nocardia</i>, <i>Mycobacterium</i></p> <p>Viral pathogens HIV, HSV, CMV, adenovirus, echovirus</p> <p>Other pathogens <i>Cryptococcus</i>, <i>Toxoplasma</i>, <i>Histoplasma</i></p> <p>Malignancy Kaposi's sarcoma, lymphoma, capillary leak, wasting, malnutrition</p> <p>Hypothyroidism</p> <p>Immunodeficiency, uremia</p>	<p>11%/year</p> <p>Spontaneous resolution in 42% of affected patients</p> <p>Approximately 30% increase in 6-month mortality</p>	<p>Pericardial rub on examination</p> <p>Echocardiogram</p> <p>Fluid analysis for Gram stain and culture, malignant cells</p> <p>Associated pleural and peritoneal fluid analysis</p> <p>Pericardial biopsy</p>	<p>Treatment of underlying cause the cause</p> <p>Pericardiocentesis</p> <p>Pericardial window</p> <p>Follow-up Serial echocardiograms Intensify antiretroviral therapy</p>
Infective endocarditis	<p>Autoimmune</p> <p>Bacteria <i>Staphylococcus aureus</i>, <i>Staphylococcus Epidermidis</i>, <i>Salmonella</i>, <i>Streptococcus</i>, <i>Hemophilus parainfluenzae</i>, <i>Pseudallescheria boydii</i>, HASEK</p> <p>Fungi <i>Aspergillus fumigatus</i>, <i>Candida</i>, <i>Cryptococcus neoformans</i></p>	<p>6% increased incidence in IVDA, regardless of HIV status</p>	<p>Blood cultures</p> <p>Echocardiogram</p>	<p>IV antibiotics</p> <p>Valve replacements</p>





Type of disease	Possible causes	Incidence/prevalence	Diagnosis	Treatment
Nonbacterial thrombotic endocarditis	Valvular damage Vitamin C deficiency Malnutrition, wasting DIC Hypercoagulable state Prolonged acquired immunodeficiency	Rare, but clinically relevant emboli in 42% of cases	Echocardiogram	Anticoagulation Treat vasculitis or underlying illness
Malignancy	Kaposi's sarcoma Non-Hodgkin lymphoma Leiomyosarcoma Low CD4 count Prolonged immunodeficiency HHV-8 EBV	Approximately 1% incidence Usually metastatic in HIV+ patients	Echocardiogram biopsy	Chemotherapy possible
Right ventricle and pulmonary disease	Recurrent pulmonary infections Pulmonary arteritis Microvascular pulmonary emboli		ECG Echocardiogram Right heart catheterization	Diuretics Treat underlying lung infection or disease ± anticoagulation
Primary pulmonary hypertension	Plexogenic pulmonary arteriopathy	0.5%	ECG Echocardiogram Right heart catheterization	Anticoagulation Vasodilators Prostacyclin analogs
Vasculitis	Drug therapy with antibiotics and antivirals	Increasing incidence	Clinical diagnosis	Systemic corticosteroids Withdrawal of causative drug
Accelerated atherosclerosis	Protease inhibitors Atherogenesis with virus-infected macrophages Chronic inflammation Glucose intolerance Dyslipidemia	Up to 8% prevalence	Stress testing Echocardiogram Lipid profile	Minimize risk factors
Autonomic dysfunction	CNS disease Drug therapy Prolonged immunodeficiency Malnutrition	Increased in patients, with CNS disease	Tilt-table test Holter monitoring	Procedural precautions
Arrhythmias	Drug therapy (pentamidine) Autonomic dysfunction Acidosis Electrolyte abnormalities		ECG—long QT Holter monitoring	Discontinue drug Procedural precautions
Lipodystrophy	Drug therapy (protease inhibitors)		Echocardiogram Lipid profile Cardiac catheterization Coronary calcium score	Lipid therapy (beware of drug interactions) Aerobic exercise Altered antiretroviral therapy Cosmetic surgery/fat implantation

Table 1. Summary of HIV-associated cardiovascular diseases.

Abbreviations: ACE, angiotensin-converting enzyme; AZT, azidothymidine; CMV, cytomegalovirus; CNS, central nervous system; DIC, disseminated intravascular coagulation; EBV, Epstein-Barr virus; ECG, electrocardiogram; HHV, human herpesvirus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; HTN, hypertension; IL-2, interleukin 2; IVDA, intravenous drug abuse; IV Ig, intravenous immunoglobulin; LV, left ventricular; PAC, premature atrial complex; PCR, polymerase chain reaction; PVC, premature ventricular complex; TGF β , transforming growth factor- β ; TNF- α , tumor necrosis factor- α ; TSH, thyroid-stimulating hormone.

Reproduced from reference 6: Fisher SD, Lipshultz SE. Cardiovascular abnormalities in HIV-infected individuals. In: Zipes DP, Libby P, Bonow RO, Braunwald E, eds. Heart Disease: A Textbook of Cardiovascular Medicine. 7th ed. Philadelphia, Pa: Elsevier/Saunders Co; 2005(chap 61):1719-1729. Copyright © 2005, Elsevier/Saunders.

MANIFESTATIONS

Left ventricular dysfunction

Left ventricular dysfunction is a common consequence of HIV infection in both adults and children. Cardiomyopathy carries a worse prognosis when it is HIV-related.⁷

Clinical presentation

Cardiovascular abnormalities are common in HIV-infected individuals, but often go unrecognized or untreated, resulting in increased cardiovascular-related morbidity and mortality and reduced quality of life. Clinicians may mistakenly attribute signs of cardiovascular abnormalities to pulmonary or infectious causes, an error that delays appropriate treatment.⁸

Signs and symptoms of heart failure in these patients may be atypical or masked by concurrent illness, dehydration, or malnutrition. Electrocardiography (ECG) may reveal nonspecific conduction defects or repolarization changes. Up to 57% of asymptomatic HIV-infected patients have baseline ECG abnormalities, including supraventricular and ventricular ectopic beats.⁶ Cardiomegaly or pulmonary congestion may be evident or absent on chest radiographs. Brain natriuretic peptide levels may facilitate cardiomyopathy diagnosis.⁹ Echocardiography is the only specific validated noninvasive test for detecting left ventricular systolic dysfunction in this population; it often reveals increased left ventricular mass with low-normal or increased wall thickness and a dilated left ventricle.¹⁰

Dilated cardiomyopathy is strongly associated with a CD4 count of less than 100 cells/mL.⁸ In children, cardiovascular abnormalities, a history of wasting, or a positive cytomegalovirus (CMV) test predict serious cardiac events.¹⁰

Clinical and echocardiographic findings suggest that diastolic dysfunction is relatively common in long-term survivors of HIV infection. Left ventricular diastolic dysfunction may precede systolic dysfunction.⁸

Incidence

Left ventricular dysfunction was reported in 8% of asymptomatic HIV-infected adults after 5 years of follow-up.⁶ When cardiomyopathy was diagnosed, CD4 counts were generally less than 400 cells/mL. The mean annual incidence was estimated at 15.9 cases/1000 asymptomatic patients. Cardiomyopathy was diagnosed an average (standard deviation) of 28 (10) months after enrollment in asymptomatic patients.⁶

Pathogenesis

Myocarditis may be important in HIV-related cardiomyopathy, but autopsy and biopsy studies have revealed only scant and patchy inflammatory cell infiltrates in the myocardium.¹¹ In tissue from patients with HIV-related cardiomyopathy, only inflammatory cells had HIV-1 RNA and DNA, but several cell types exhibited virus envelope protein gp120.¹² Perivascular macrophage infiltration was linked with adjacent cardiomyocyte apoptosis.¹² Right ventricular biopsy performed within 1 month of the diagnosis of cardiomyopathy revealed myocarditis in 63 of 76 patients.⁶

Possible HIV-related causes of cardiomyopathy include myocardial infection with HIV itself, antimyocyte antibodies associated with HIV infection, opportunistic infections, viral infections (coxsackievirus B3, CMV, and Epstein-Barr virus), autoimmune response to viral infection, cardiotoxicity from illicit drugs such as cocaine, nutritional deficiencies, hypothyroidism, and possibly drug toxicity.^{6,13,14} Myocardial biopsy may be clinically helpful by revealing a treatable opportunistic infection.

Opportunistic infections do not sufficiently explain the development of dilated cardiomyopathy, because up to 40% of dilated cardiomyopathy patients have never experienced an opportunistic infection.¹⁴ In non-HIV infected patients who have undergone heart transplantation, viral infection in endomyocardial biopsy tissue predicts acute cardiac events¹⁵; a similar relationship may hold for viral infection and HIV-related heart disease. Other common factors in HIV infection that are related to the development of cardiomyopathy include nutritional deficiencies and wasting, various growth factors, cytokine overexpression, alteration of the renal angiotensin system, hypothermia, hyperthermia, abnormalities of thyroid or adrenal gland function, autonomic dysfunction, secondary effects of encephalopathy, dyslipidemia, and hyperinsulinemia.⁶

Pathogenesis in children

In children with vertically transmitted HIV infection, two mechanisms of pathogenesis have been described. One is dilation of the left ventricle with relative thinning of the LV walls. The other is concentric hypertrophy of the muscle where the ratio of wall thickness to end-systolic dimension remains normal or is increased.¹⁶

Course of disease

Asymptomatic left ventricular dysfunction may be transient. In one small study, abnormal fractional shortening detected on serial echocardiography resolved in 3 of 6 patients after 9 months.¹⁷ The 3 patients with

persistently depressed left ventricular function died within 1 year of the baseline study. In HIV-infected patients, cardiomyopathy is associated with increased mortality independent of CD4 count, age, sex, or risk group. The median survival to acquired immune deficiency syndrome (AIDS)-related death was 101 days in patients with left ventricular dysfunction and 472 days in patients at similar infection stage with a normal heart (*Figure 1*).¹⁸ Patients with isolated right ventricular dysfunction or borderline left ventricular dysfunction did not necessarily have a lower CD4 count and did not have an altered prognosis.¹⁸

In the Pediatric Pulmonary and Cardiovascular Complications of vertically transmitted HIV infection (P²C² HIV) study (median age of children, 2.1 years), 5-year cumulative survival was 64%.¹⁷ Mortality was higher in children with baseline depressed left ventricular fractional shortening or with increased left ventricular dimension, thickness, mass, wall stress, heart rate, or blood pressure. Decreased left ventricular fractional shortening and increased wall thickness also predicted survival after adjustment for age, height, CD4 count, HIV RNA copy number, clinical center, and encephalopathy.¹⁶ Fractional shortening was abnormal for up to 3 years before death, whereas wall thickness identified a population at risk only 18 to 24 months before death. Thus, in children, fractional shortening may be a useful long-term predictor and wall thickness a useful short-term predictor of mortality.¹⁶ Postmortem cardiomegaly was associated with echocardiographic evidence of increased left ventricular mass and documented chronically increased heart rate shortly before death, but not with anemia, encephalopathy, or HIV viral load.¹⁶ In HIV-infected children, mild persistent depression of left ventricular function and elevated left ventricular mass were associated with higher all-cause mortality.¹⁶

Rapid-onset congestive heart failure has a grim prognosis in HIV-infected adults and children, with more than half of patients dying from primary cardiac failure within 12 months of presentation.¹⁹ Mild, progressive heart failure may better respond to medical therapy in these patients.^{6,19}

Therapy

No studies have investigated the effect of specific cardiac therapeutic regimens (other than intravenous immunoglobulin) on outcome in these patients.²⁰⁻²² Therefore, therapy for dilated cardiomyopathy associated with HIV infection is generally similar to therapy for nonischemic cardiomyopathy. It includes diuretics,

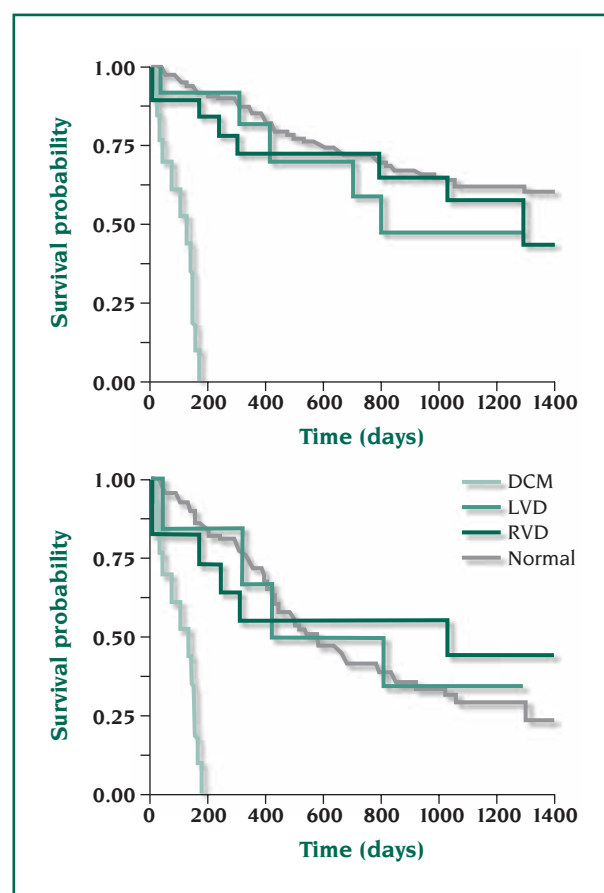


Figure 1. *Top*, Survival curves for 296 human immunodeficiency virus (HIV)-infected patients with structurally normal hearts, dilated cardiomyopathy (DCM), left ventricular dysfunction (LVD), or right ventricular dysfunction (RVD). *Bottom*, Time to death related to acquired immunodeficiency syndrome (AIDS) in 81 patients with CD4⁺ cell counts less than 20×10⁶ cells/L.

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digoxin, β -blockers, and angiotensin-converting enzyme (ACE) inhibitors, as tolerated. However, because HIV-infected patients are likely to have decreased systemic vascular resistance and may be at risk for multiple drug interactions, they are less likely to tolerate standard therapy than are more typical heart failure groups.

Opportunistic or other infections should be aggressively sought and treated because cure may improve or resolve the cardiomyopathy.⁶ In HIV-infected patients with clinical heart failure and persistent or worsening left ventricular dysfunction despite treatment with standard anticongestive therapy, an endomyocardial biopsy should be considered. Serum troponin level should be checked at the time of cardiomyopathy diagnosis and may help to differentiate between a coronary syn-

drome and ongoing myocarditis. A persistent low, positive serum troponin supports a diagnosis of myocarditis and suggests endomyocardial biopsy and perhaps therapy with intravenous immunoglobulin.^{8,20,21}

Once left ventricular dysfunction is identified, serial echocardiographic studies should be performed as recommended by a cardiologist. In this population, routine examinations, chest radiographs, and ECGs have been nonspecific in the diagnosis of left ventricular function. On the basis of data from before the HAART era, we recommend a baseline echocardiographic evaluation at the time of diagnosis of HIV. Asymptomatic patients should then have a follow-up echocardiogram every 1 to 2 years. Patients with symptomatic HIV infection without cardiovascular abnormalities should have an annual echocardiogram.⁸ When echocardiography identifies cardiovascular abnormalities, the follow-up should be guided by a cardiologist. Echocardiography should also be considered in patients with unexplained or persistent pulmonary symptoms and in those with viral coinfection (eg, infection with CMV, Epstein-Barr virus, or adenovirus) who are at risk for myocarditis.^{6,8,22}

We suggest a baseline echocardiographic study, repeated every 1 to 2 years, for asymptomatic HIV-infected patients. In patients with left ventricular dysfunction, echocardiography should be repeated after 2 to 4 weeks of therapy. Patients who improve should continue therapy and undergo echocardiography after 1 year. Echocardiography and possibly a brain natriuretic peptide level should also be considered in patients with unexplained or persistent pulmonary symptoms or viral coinfection.^{6,8,9} If left ventricular function is worsening, troponin levels are positive, or the clinical course deteriorates despite aggressive medical therapy, an endomyocardial biopsy should again be considered. Early detection of left ventricular dysfunction may allow intervention in time to affect outcome. Outcomes studies are needed to support this recommendation.

In HIV-positive children, monthly immunoglobulin infusions have been associated with minimized left ventricular dysfunction, as indicated on serial echocardiograms by an increase in left ventricular wall thickness and a reduction in peak left ventricular wall stress.²¹ The effectiveness of immunoglobulin therapy may be the result of removing cardiac autoantibodies or of dampening the secretion or effects of excessive cytokines and cellular growth factors. Similar studies in adults have not been published.

Nutritional status should be evaluated. Patients with low serum levels of selenium or carnitine, especially those with anorexia, wasting, or diarrhea syndromes, should receive nutritional supplementation with these nutrients or with a multivitamin. Thyroid hormone levels should also be evaluated and any deficiencies treated.⁸

Nutritional deficiencies are common in HIV infection, particularly in late-stage disease. Poor absorption and diarrhea both lead to electrolyte imbalances and deficiencies in elemental nutrients. Deficiencies of trace elements have been associated with cardiomyopathy.⁸

For example, selenium deficiency increases the virulence of coxsackievirus to cardiac tissue. Selenium replacement may reverse cardiomyopathy and restore left ventricular function in nutritionally depleted patients. Levels of vitamin B₁₂, carnitine, and growth and thyroid hormone can also be altered in HIV disease; all have been associated with left ventricular dysfunction.^{6,8}

Pericardial effusion

Clinical presentation

HIV-infected patients with pericardial effusions generally have lower CD4 counts than do those without effusions.²³ Effusions are generally asymptomatic. Useful serial echocardiographic data were collected in the Prospective Evaluation of Cardiac Involvement in AIDS Study, which followed 231 patients over 5 years.²⁴ In this group, 3 patients had effusions at entry into the study, and 13 developed effusions during follow-up. Pericardial effusions were generally small and asymptomatic. The incidence of pericardial effusion among adult patients with AIDS was 11% per year.²³ Conversely, HIV infection should be suspected whenever young patients have pericardial effusion or tamponade. In children with vertically transmitted HIV infection, pericardial effusions occur less frequently and tend to be small and nonprogressive.¹⁶

Pathogenesis

Pericardial effusion may be related to an opportunistic infection or to malignancy, but most often the cause is not clear. The effusion is often part of a generalized serous effusive process ("capillary leak") also involving pleural and peritoneal surfaces. Other causes include uremia (HIV-associated nephropathy, drug nephrotoxicity). Fibrinous pericarditis with or without effusion is also relatively common, comprising 9% of cardiac lesions found in AIDS patients in one autopsy series.²²⁻²⁴



Course of disease and prognosis

Among subjects with AIDS, 36% of those with pericardial effusion were alive after 6 months of follow-up, compared with 93% of those without effusion.²³ Several studies have shown that effusion may be transient.^{6,24} However, in patients who have developed an effusion, mortality is markedly higher than in those at a similar stage of infection who have never developed effusion.²⁴

Monitoring and therapy

Screening echocardiography is recommended in HIV-infected individuals, regardless of the stage of disease (Figure 2).²⁵ All HIV-infected patients with evidence of heart failure, Kaposi's sarcoma, tuberculosis, or other pulmonary infections should undergo baseline echocardiography and ECG testing.⁸ Patients should undergo pericardiocentesis if they have: (i) pericardial effusion and clinical signs of tamponade, such as elevated

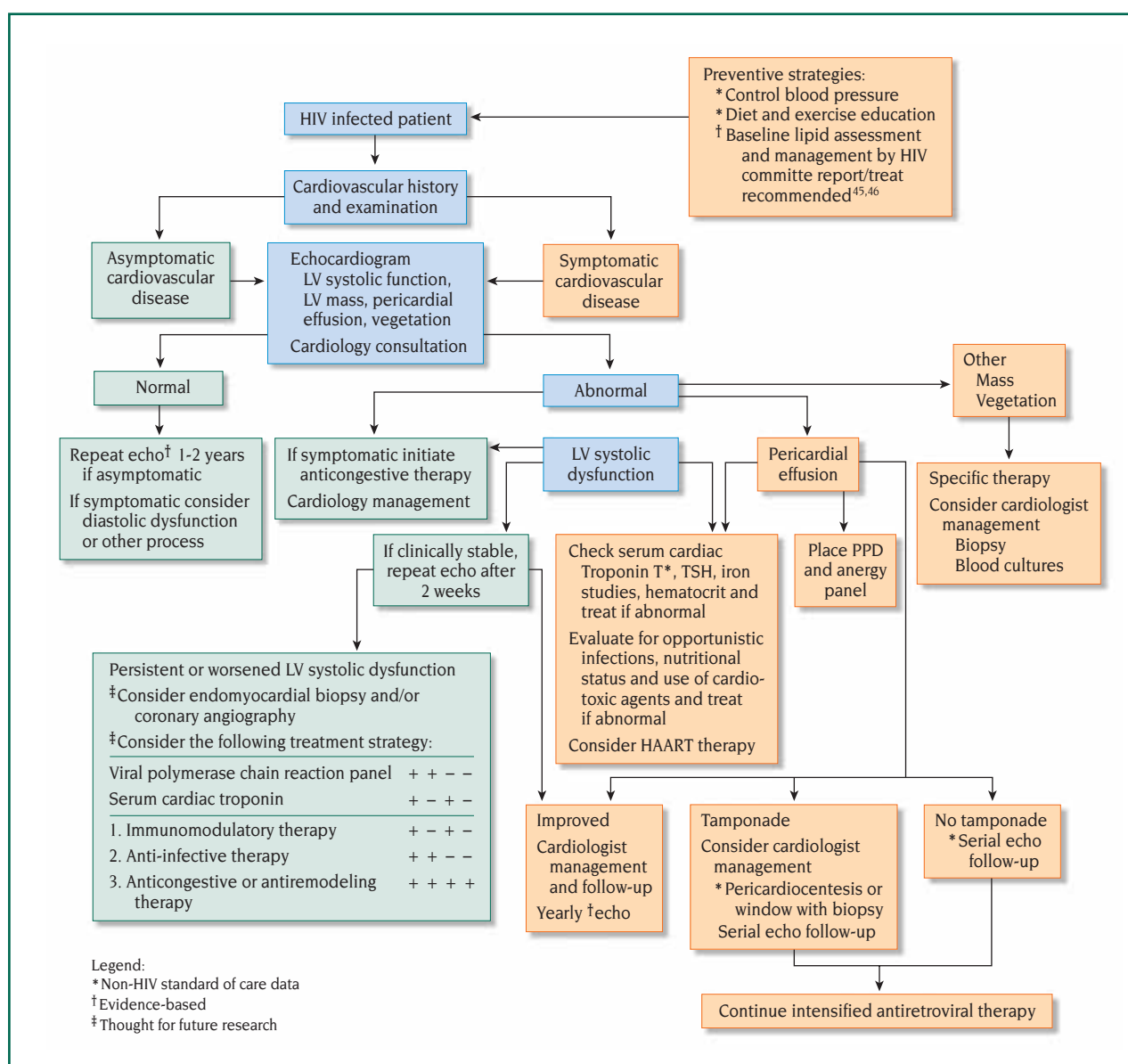


Figure 2. Cardiac dysfunction in human immunodeficiency virus (HIV)-infected patients.

Abbreviations: HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; LV, left ventricular; PPD, purified protein derivative; TSH, thyroid-stimulating hormone.

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jugular venous pressure, dyspnea, hypotension, persistent tachycardia, and pulsus paradoxus; or (ii) echocardiographic signs of tamponade, such as valvular in-flow respiratory variation evident on continuous-wave Doppler echocardiography, septal bounce, right ventricular diastolic collapse, and a significant effusion.⁸ Patients with pericardial effusion and clinical or echocardiographic signs of tamponade should undergo pericardiocentesis for both diagnostic and therapeutic purposes. If the effusion is not large enough for safe pericardiocentesis and clinical signs of tamponade are present, a pericardial window may be necessary. Patients with evidence of pericardial effusion without tamponade should be evaluated for treatable opportunistic infections and malignancy. Signs of hemodynamic compromise are more important than the size of the effusion in the decision to proceed with pericardiocentesis or pericardial window.

HAART should be considered if it has not already been instituted at the discovery of pericardial effusion. Repeat echocardiography is recommended after 1 month, unless clinical symptoms of tamponade develop in the interim (Figure 2).^{8,24,25}

Infective endocarditis

Injection drug users are at greater risk than the general population for infective endocarditis, chiefly of right-sided heart valves. Surprisingly, HIV-infected patients have not clearly been documented to have a higher incidence of endocarditis than cohorts of similar behavior risk groups.^{22,26}

As valvular destruction is often immune-mediated, the immune impairment induced by HIV and AIDS may actually be protective, at least in valvular salmonella infections.⁶ The autoimmune response to bacterial endocarditis is often largely responsible for the valvular destruction associated with endocarditis, therefore, the course of the disease in HIV-infected patients may be variable. For example, HIV-infected patients have a higher risk of developing salmonella endocarditis than do immunocompetent patients, because they are more likely to develop salmonella bacteremia during salmonella infection.

Organisms associated with endocarditis in HIV-infected patients include *Staphylococcus aureus* (>75% of cases), *Salmonella species*, *Streptococcus species*, *Enterococcus*, *Haemophilus parainfluenzae*, *Staphylococcus epidermidis*, and *Pseudallescheria boydii*.^{8,24} Infections with *Aspergillus fumigatus*, *Candida species*, and *Cryptococcus neoformans*

have also been reported. Fungal endocarditis is more common in HIV-infected intravenous drug users than in those without HIV infection and may be responsive to therapy.²⁴ Fulminant courses of infective endocarditis with high mortality can be seen in late-stage AIDS, but several cases have been successfully treated with antibiotics.²⁴ Indications for surgery include hemodynamic instability and severe valvular destruction in patients with a reasonable life expectancy after recovery from surgery. Patients who do not have sterile cultures at the time of surgery have increased mortality.²⁷

Nonbacterial thrombotic endocarditis

Nonbacterial thrombotic endocarditis, otherwise known as marantic endocarditis, is the growth of large friable, sterile vegetations on the cardiac valves.²⁸ These lesions have been associated with disseminated intravascular coagulation and systemic embolization. Lesions are rarely diagnosed antemortem. When they are, they cause clinically relevant emboli in an estimated 42% of cases.²⁸ Marantic endocarditis should be considered in patients with systemic embolization, yet should still be considered rare in AIDS patients. Treatment should be directed to the underlying disease state that causes coagulation abnormalities, to the valvular endothelial damage, or to both. Anticoagulation risk-benefit assessment must be made on an individual basis.

Cardiovascular malignancy

Malignancy affects a large number of AIDS patients, generally in the later stages of disease. Cardiac malignancy is usually a manifestation of metastatic disease. Kaposi's sarcoma (angiosarcoma) is associated with human herpesvirus 8 and affects up to 40% of male homosexual AIDS patients and 11% of other AIDS patients. A 50% decline in incidence has been reported in patients on HAART.^{6,22,29} Cardiac involvement has been found in 28% of HIV-infected patients with widespread Kaposi's sarcoma at autopsy, but it is rarely described as a primary cardiac tumor.²⁹ Symptoms are rare, although some may develop if the tumor is epicardial and leads to pericardial effusion. Kaposi's sarcoma has not been found to invade the coronary arteries, but is often an endothelial cell neoplasm with a predilection in the heart for the subpericardial fat around the coronary arteries.⁶

Kaposi's sarcoma involving the heart is generally an incidental finding at autopsy, rarely causing cardiac symptoms. Specific symptoms can be related to pericardial effusion associated with the epicardial location of the



tumor. Pericardial fluid in patients with cardiac Kaposi's sarcoma is typically serosanguineous, without malignant cells or infection.⁶ Kaposi's sarcoma is difficult to treat. Most affected patients die from opportunistic infections related to the advanced stage of immunodeficiency rather than from the malignancy.

Most primary cardiac malignancies associated with HIV infection are lymphomas.²⁹ The prevalence of non-Hodgkin's lymphoma is increased by a factor of 25 to 60 in HIV-infected individuals; it is the first manifestation of AIDS in up to 3% to 4% of new cases. A review of 21 cases of primary cardiac lymphoma in the literature revealed that dyspnea was the most frequent presenting symptom (67%), followed by right-sided heart failure (19%), biventricular failure (14%), chest pain (19%), and arrhythmias (14%).³⁰ Cardiac lymphoma is associated with rapid progression to cardiac tamponade, symptoms of congestive heart failure, myocardial infarction, tachyarrhythmias, conduction abnormalities, and superior vena cava syndrome.^{29,30} Pericardial fluid in cardiac lymphomas usually, but not always, reveals malignant cells. Systemic multiagent chemotherapy with and without concomitant radiation or surgery has been beneficial in some patients with cardiac lymphoma, but the overall prognosis is poor.^{29,30}

Leiomyosarcoma, associated with Epstein-Barr virus, is a rare, malignant tumor of smooth muscle origin with an increased incidence in children with AIDS. Leiomyosarcomas are largely noncardiac and often involve the arterial wall.⁶ An intracardiac mass in late-stage HIV infection is associated with a uniformly poor prognosis.

Isolated right ventricular disease and pulmonary disease

Isolated right ventricular hypertrophy and right ventricular dilation are relatively uncommon in HIV-infected individuals and are generally related to pulmonary disease.³¹ Primary pulmonary hypertension is rare in the general public, but has been described in a disproportionate number of HIV-infected individuals. Primary pulmonary hypertension was estimated to occur in 0.5% of hospitalized AIDS patients and is estimated to be 200 times more common in HIV-infected individuals.^{6,32} HAART may further increase the risk of pulmonary arterial hypertension.

Pulmonary hypertension diagnosed from screening echocardiography or from right heart catheterization warrants further evaluation for treatable pulmonary infections. Right ventricular hypertrophy on ECG is

common in the presence of pulmonary hypertension. Therapy includes diuretics, anticoagulation (based on individual risk-benefit analysis), endothelium antagonist, and vasodilator agents, as tolerated.^{6,32}

Vasculitis

Reports of vasculitis in HIV-infected patients are increasingly frequent. Vasculitis should be suspected in the setting of fever of unknown origin, unexplained multisystem disease, unexplained arthritis or myositis, glomerulonephritis, peripheral neuropathy (especially mononeuritis multiplex), or unexplained gastrointestinal, cardiac, or central nervous system ischemia. Many types of vasculitis have been described in HIV-infected patients, including systemic necrotizing vasculitis, hypersensitivity vasculitis, Henoch-Schoenlein purpura, lymphomatoid granulomatosis, and primary angiitis of the central nervous system.³³ Immunomodulatory therapy, chiefly with systemic corticosteroid therapy, has sometimes been successful.

Accelerated atherosclerosis

People with HIV infection are at a significantly greater risk for coronary heart disease and myocardial infarction than are uninfected people of the same age. For example, Vittecoq et al found that the incidence of coronary heart disease was between 5 and 5.5/1000 person-years in two cohorts of HIV-infected French patients, most less than 50 years of age. This incidence was at least three times the incidence in the general French male population.³⁴ The multinational Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study Group found an incidence of 3.5/1000 person-years in a prospective database covering 36 199 person-years; 11% of all recorded patient deaths during the 17-month follow-up were caused by myocardial infarction, stroke, or other cardiovascular events.³⁵ Furthermore, Klein et al found that HIV-positive members of the Northern California Kaiser Permanente Medical Care Program, a large health maintenance organization, had a significantly higher rate of hospitalization for coronary heart disease than did HIV-negative members (6.5 vs 3.8 events per 1000 person years, $P=0.03$), and that the rate of myocardial infarction was also greater (4.3 vs 2.9 events per 1000 person years, $P=0.07$).³⁶

Accelerated atherosclerosis has been observed in young HIV-infected individuals without traditional coronary risk factors.^{1,22} Protease-inhibitor therapy markedly alters lipid metabolism and can be associated with premature atherosclerotic disease. Chronic inflammatory

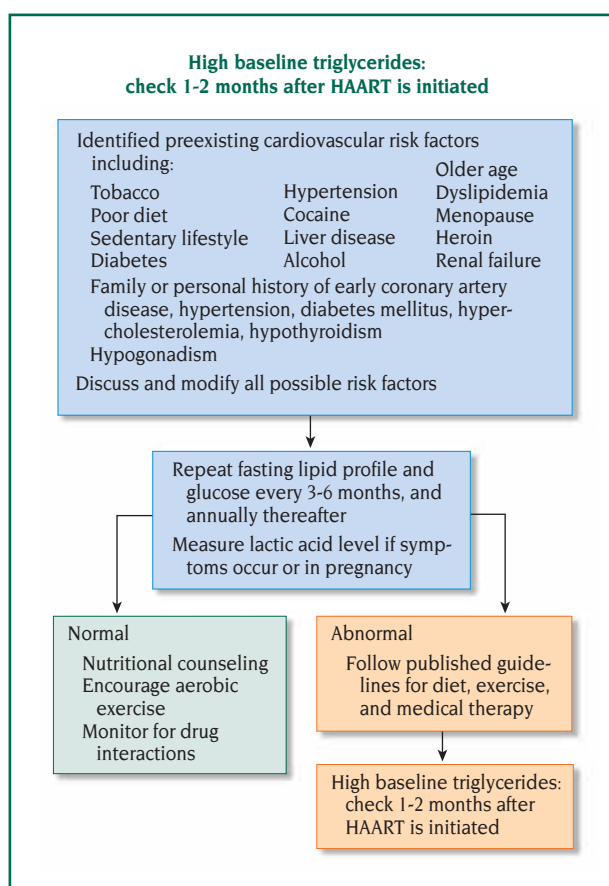


Figure 3. Cardiovascular considerations when initiating highly active antiretroviral therapy (HAART).

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states have also been associated with premature atherosclerotic vascular disease. Vascular inflammation is now known to be an important early step in the development of the fatty streak, the precursor of the atherosclerotic plaque. Inflammation is also important in the progression of the atheroma and in the rupture of the plaque's fibrous cap, which is the key event leading to infarction.²²

Infection with HIV is associated with the activation of inflammatory pathways in the vascular wall. For example, de Larrañaga et al found that HIV-infected patients had significantly higher plasma levels of tumor necrosis factor- α (TNF- α) and interleukin-6 than uninfected controls. These levels correlated with viral load, as did those of von Willebrand factor (which is produced by the vascular endothelium in response to activation or injury).³⁷

Clear morbidity and mortality benefits of protease inhibitor therapy, and specifically HAART, have been shown, with no short-term evidence of increased cardiovascular mortality.^{1,38} Lipodystrophy, including fat redistribution with increased truncal obesity, increased triglycerides and elevated small, dense low-density lipoprotein, and glucose intolerance should still be recognized and treated because of an elevated 10-year cardiovascular risk.^{8,38} Risk stratification based on traditional risk factors plus diet, alcohol intake, physical exercise, hypertriglyceridemia, cocaine use, heroin use, thyroid disease, renal disease, and hypogonadism should be considered for long-term cardiac preventive care (Figure 3).^{6,8}

Long-term risk of accelerated atherosclerosis may be particularly important in HIV-infected children who receive HAART at a very young age and who will likely receive these medications lifelong. Early myocardial infarction may cause substantial morbidity and mortality for these children, although their HIV may be well controlled.³⁹

Autonomic dysfunction

Early clinical signs of autonomic dysfunction in HIV-infected patients include syncope and presyncope, diminished sweating, diarrhea, bladder dysfunction, and impotence. Patients with HIV-associated nervous system disease had the highest risk of abnormalities in autonomic function.⁴⁰ HIV infected individuals with no clinical evidence of autonomic dysfunction and a mean CD4 count of 426 had reduced heart rate variability, suggesting preclinical disease early in infection.⁴⁰ Symptoms warrant evaluation with a baseline ECG for arrhythmia and QT interval duration, Holter or event monitoring for syncope or near syncope, and tilt-table testing in selected patients. Symptomatic patients may benefit from β -blockers, fludrocortisone acetate (Florinef), salt tablets, or dietary salt loading. Possible drug interactions should be evaluated and considered, especially in the setting of a prolonged QT interval. The website www.torsades.org regularly updates a list of these drug interactions.

In all patients with symptoms of autonomic dysfunction or with advanced HIV disease, procedural precautions should include electrolyte monitoring and correction, baseline ECG, bedside telemetry, and blood pressure monitoring. A defibrillator with transcutaneous pacing capability, atropine, and epinephrine should be available during procedures that require sedation.



Drug therapy with the potential to prolong the QT interval such as intravenous pentamidine should be initiated cautiously. If the QTc is greater than 0.48 s and cannot be corrected by electrolyte replacement, therapy should not be started.^{6,8}

MONITORING

Routine, systematic cardiac evaluation, including a comprehensive history and thorough cardiac examination, is essential for the care of HIV-infected adults and children. The history should include traditional risk factors, environmental exposures, and therapeutic and illicit drug use. Routine blood pressure monitoring is important because HIV-infected individuals have been reported to develop hypertension at a younger age and more frequently than in the general population.⁴¹

Routine ECG and Holter monitoring is not warranted unless patients have symptoms such as palpitations, syncope, stroke, or dysautonomia. These tests can also be useful in monitoring drug therapies that may prolong the QT interval, such as pentamidine, methadone, or antibiotics.^{8,42}

Asymptomatic cardiac disease related to HIV can be fatal, and cardiac symptoms are often disguised by secondary effects of HIV infection, so that systematic echocardiographic monitoring is warranted. We recommend a baseline echocardiogram at the time of HIV diagnosis and follow-up every 1 to 2 years (*Figure 2*).²⁵ Symptomatic patients with HIV infection without cardiovascular abnormalities should have annual echocardiographic follow-up. Echocardiography should also be considered in patients with unexplained or persistent pulmonary symptoms and in those with viral coinfection at risk for myocarditis.⁷ An international consensus panel recommended slightly less aggressive echocardiographic monitoring with a baseline echocardiogram for any patient at high risk or with any clinical manifestation of cardiovascular disease and serial studies every 1 to 2 years or as clinically indicated thereafter.⁴³ Patients with cardiac symptoms should have a formal cardiac assessment, including baseline echocardiography, ECG, and Holter monitoring and should begin directed therapy.⁸ Brain natriuretic peptide levels may be helpful in diagnosing ventricular dysfunction.⁹

In patients with left ventricular dysfunction, serum troponin assays are indicated. Serum troponin elevations warrant consideration of cardiac catheterization and endomyocardial biopsy. Biopsy-proven myocarditis

should prompt considering therapy with intravenous immunoglobulin.^{20,21} CMV inclusions on the biopsy specimen warrant antiviral therapy, and abnormal mitochondria should encourage consideration of a drug holiday from zidovudine. Echocardiography should be repeated after 2 weeks of therapy to allow a more aggressive approach if left ventricular dysfunction persists or worsens and to encourage continued therapy if improvement has occurred.⁸

TRADITIONAL MODIFIABLE RISK FACTORS

Preventing cardiovascular disease by exercising

The effects of exercise on the immune system vary with its intensity. Moderate activity stimulates the immune system, but strenuous activity suppresses natural killer-cell function, lymphocyte proliferation, immunoglobulin production, and cytokine cascade activation. Prolonged strenuous exercise, such as long-distance running, causes a leukocytosis, which increases neutrophils and depresses lymphocytes for up to 6 hours. In many clinical conditions, the biologic effect of exercise on the immune system is unclear, but it appears to be safe in controlled training situations. Exercise should be intense enough and should last long enough to provide benefits for the heart, lungs, and skeletal muscle, but must not be so strenuous as to induce injury.

Chronic illness, such as HIV, is likely to result in decreased physical activity, poor muscle strength, decreased aerobic capacity, and overall deconditioning. Pulmonary function studies of adults with HIV infection have shown lower workload, lower anaerobic threshold, and decreased oxygen consumption when compared with an age-matched control group. These conditions appear to be reversible; oxygen consumption improves with aerobic training in HIV-infected adults. A retrospective study of self-reported exercise patterns in 415 adults with HIV and controls suggested that exercise three or four times per week significantly slowed HIV disease progression. Studies of progressive resistance and aerobic training in HIV-infected adults have been limited, but data show that exercise helps patients gain lean body mass. Furthermore, controlled training programs in HIV-infected patients have not decreased CD4 lymphocyte counts or increased cytokine activation. Strength-resistance training can decrease truncal adiposity, which is part of the fat redistribution syndrome that develops in many HAART-treated patients. In a small pilot study of 10 men, 16 weeks

of resistance training significantly improved strength and decreased fat mass, particularly in the trunk.

Encouraging lifelong physical activity programs would appear to be even more important as HIV infection becomes a chronic disease. Because HAART may predispose patients to the chronic problems of abnormal lipid metabolism, fat redistribution, insulin resistance, and premature cardiovascular disease, it will be important to determine whether exercise programs that benefit people without HIV infection are practical and effective in patients with HIV.⁸

Encouraging a healthy diet

High consumption of fruits and vegetables is associated with a reduced incidence of ischemic vascular disease. There is no evidence that β -carotene supplements reduce the risk of cardiovascular disease, and in fact they may be harmful. Evidence of a protective effect of antioxidant supplements in healthy people is insufficient to recommend them.

Smoking cessation

Smoking is strongly associated with overall mortality and ischemic vascular disease. The increased risk associated with smoking falls after patients stop smoking, so smoking cessation should always be encouraged.

Managing hypertension

Lifestyle interventions reduce blood pressure, but the evidence that these interventions reduce mortality or morbidity is inconclusive. Lifestyle interventions that may be beneficial include: aerobic exercise; a low-fat, high-fruit and vegetable diet; possibly moderate alcohol consumption; salt restriction, especially in older people; modest weight reduction of 3% to 9% of body weight; a daily potassium supplement of about 60 mmol (2 g, about the amount in five bananas); fish oil supplementation in large doses of 3 g/day; possibly calcium supplementation; and possibly magnesium supplementation.

Drug treatment reduces blood pressure, and it does so more than lifestyle changes. The main benefit of treating hypertension is lowering the risk of cardiovascular disease. The evidence of reduced mortality and morbidity is strongest for diuretics, β -blockers, and ACE inhibitors. In large-scale clinical trials, diuretics alone and together with β -blockers have decreased mortality in patients with hypertension.

The best tolerated drugs for treating hypertension are diuretics (particularly in low doses) and angiotensin II receptor antagonists. β -Blockers, ACE inhibitors, and calcium-channel blockers generally have mild adverse effects. Some authorities recommend that calcium channel blockers be reserved for patients who do not respond to, or cannot tolerate, diuretics, β -blockers, ACE inhibitors, or angiotensin II receptor antagonists. ACE inhibitors may be particularly useful in patients with diabetes, especially those with nephropathy, and for patients with heart failure or left ventricular dysfunction. A β -blocker without intrinsic sympathomimetic activity should be considered for hypertensive patients with angina pectoris, myocardial infarction, or migraine. For patients with hyperlipidemia, an ACE inhibitor, α -blocker, or calcium-channel blocker would be potentially useful. In African-Americans, diuretics and calcium-channel blockers are often more effective than β -blockers, ACE inhibitors, or angiotensin II receptor antagonists. If a drug from one class is ineffective or poorly tolerated, a drug from another class should be tried. If more than one drug is needed, the second drug is usually a diuretic.⁴⁴

In HIV-infected patients with hypertension, standard treatment based on guidelines from the Joint National Commission should be followed because there are currently no specific subpopulation studies.

Lowering cholesterol

Lipid abnormalities in HIV-infected patients predate HAART therapy and have included increases in serum triglyceride and cholesterol levels. HIV infection is associated with low high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, lower triglyceride clearance, increased lipoprotein(a), and higher LDL-B phenotype (small, dense LDL cholesterol). Zidovudine has lowered serum triglyceride levels. Protease inhibitors and non-nucleoside reverse transcriptase inhibitor therapy are both associated with increased serum triglyceride and cholesterol levels. In one study, HAART therapy was associated with 47% of patients having serum cholesterol levels in the elevated but treatable range. The chronic abnormalities in lipids and other cardiovascular risk factors associated with HAART may mean the therapy is linked to premature cardiovascular events, but definitive studies showing a link are lacking.

Because pharmacologic treatment to reduce cholesterol in HIV-infected patients is complicated by drug interactions, nondrug therapies, such as modifying



coronary heart disease risk factors, should be emphasized. The 1994 National Cholesterol Education Program (NCEP) guidelines were recommended as a starting point for HIV-infected patients. More recent NCEP guidelines have been published and should be reviewed (www.nhlbi.nih.gov). The new guidelines increase the emphasis on therapy for “metabolic syndrome”; that is, obesity, physical inactivity, high blood pressure, high triglycerides, high blood sugar, high concentrations of LDL cholesterol, low concentrations of HDL cholesterol, insulin resistance, and diabetes. The “metabolic syndrome” is as strong a contributor to early heart disease as cigarette smoking. It should be treated with intensive lifestyle changes, including weight control, physical activity, and medication. The Guidelines define low HDL cholesterol as less than 40 mg/dL and optimal LDL cholesterol as less than 100 mg/dL.

Because calculated LDL cholesterol values are unreliable in patients with a serum triglyceride level above 400 mg/dL, for patients with serum triglyceride levels above 400 mg/dL, a total cholesterol level above 240 mg/dL or an HDL cholesterol level below 35 mg/dL should prompt dietary interventions. In patients with established coronary heart disease or an LDL above 190 mg/dL, drug therapy should be considered as a concomitant initial therapy. If HIV-associated wasting is also present, it should be treated before dyslipidemia is treated.

In asymptomatic members of the general public, reducing cholesterol concentration lowers the rate of cardiovascular events. The combination of a cholesterol-lowering diet and lipid-lowering drugs reduces cholesterol concentration more than lifestyle interventions alone. In the HIV-infected population, a bile acid sequestrant may have fewer side effects than 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors because it is less likely to cause drug interactions. However, cholestyramine and colestipol may be associated with increased triglyceride levels, and their effect on antiviral drug absorption has not been studied. Colesevelam lowers plasma LDL cholesterol and has an additive effect when taken with a statin. It has fewer gastrointestinal side effects and less interference with intestinal absorption of vitamins and drugs compared with other sequestrants.

Preliminary recommendations for managing dyslipidemia in patients with HIV infection have been devised by the US-based Adult AIDS Clinical Trial Group Cardiovascular Disease Focus Group. For protease inhibitor-treated HIV-infected patients with hypercholes-

terolemia, treatment with low-dose pravastatin (initial dosage, 20 mg/day), atorvastatin (10 mg/day), or rosuvastatin (5 mg/day) is recommended. Careful monitoring of virologic status and creatine kinase values is recommended for patients on these therapies. Lovastatin or simvastatin therapy should be avoided because of interactions with protease inhibitors or non-nucleoside reverse transcriptase inhibitors and risk of rhabdomyolysis. When treatment with HMG-CoA reductase inhibitors (statins) is not appropriate or when patients do not respond to these agents, gemfibrozil (600 mg twice daily) or fenofibrate (200 mg once daily) are reasonable alternatives. Concomitant use of fibrates and statins may increase the risk of skeletal muscle toxicity.

COMPLICATIONS OF THERAPY FOR HIV

Potent antiretroviral medications and HAART, which generally combines three or more agents and usually includes a protease inhibitor, have clearly increased the quality of life and lifespan of HIV-infected patients.¹ However, protease inhibitors have been associated with hyperlipidemia, body fat redistribution, insulin resistance, lactic acidemia, and the development of higher risk atherosclerotic profiles (*Table II, pages 14 and 15, Figure 3*).^{8,22,38,39} HIV-infected patients treated with protease inhibitors have reported substantial decreases in total body fat with peripheral lipodystrophy (fat wasting of the face, limbs, and buttocks) and relative conservation or enhancement of central adiposity (truncal obesity, breast enlargement, and “buffalo hump”) compared with patients who have not received protease inhibitors.³⁸ Lipid alterations associated with protease inhibitors include higher levels of triglycerides, total cholesterol, insulin, lipoprotein(a), and C-peptide, and lower HDL levels.³⁸ In patients with elevated lipoprotein(a) levels, protease inhibitor therapy increased levels by an additional 48%.⁴⁶ In some cases, switching protease inhibitors may reverse elevated triglyceride levels and abnormal fat redistribution. Light aerobic exercise has also helped to treat body fat distribution abnormalities and altered lipid metabolism.⁴⁶ Cardiovascular implications should be considered when initiating HAART therapy (*Figure 3*),⁶ and published guidelines and consensus panel recommendations should be considered for treating abnormalities.^{47,48}

Lipid abnormalities vary with different protease inhibitors.⁴⁹ Ritonavir had the largest adverse effects on lipids, with a mean increase in total cholesterol of 2.0 mmol/L and a mean increase in triglyceride level of 1.83 mmol/L. More modest increases in total cholesterol without large triglyceride increases were found in pa-

Class	Cardiac drug interactions	Cardiac side effects
Antiretrovirals		
Nucleoside reverse transcriptase inhibitors	Zidovudine and dipyridamole	Rare: lactic acidosis, hypotension Accelerated risk with cardiopulmonary bypass Zidovudine: skeletal muscle myopathy, myocarditis
Nonnucleoside reverse transcriptase inhibitors	Calcium channel blockers, warfarin, β -blockers, nifedipine, quinidine, steroids, theophylline Delavirdine can cause serious toxic effects if given with antiarrhythmic drugs and calcium channel blockers	
Protease inhibitors	Metabolized by cytochrome P450 and interact with other drugs metabolized through this pathway, such as selected antimicrobials, antidepressant and antihistamine agents, cisapride, HMG-CoA reductase inhibitors (lovastatin, simvastatin), and sildenafil Potentially dangerous interactions that require close monitoring or dose adjustment can occur with amiodarone, disopyramide, flecainide, lidocaine, mexiletine, propafenone, and quinidine Ritonavir is the most potent cytochrome activator (CYP3A) and P-glycoprotein inhibitor and is most likely to interact. Indinavir, amprenavir, and nelfinavir are moderate. Saquinavir has the lowest probability to interact Calcium channel blockers, prednisone, quinine, β -blockers (1.5- to 3-fold increase) Decreases theophylline concentrations	Implicated in premature atherosclerosis, dyslipidemia, insulin resistance, diabetes mellitus, fat wasting, and redistribution
Anti-infective		
Antibiotics	Rifampin Reduces therapeutic effect of digoxin by inducing intestinal P-glycoprotein, reduces protease inhibitor concentration and effect Erythromycin Cytochrome P450 metabolism and drug interactions Trimethoprim-sulfamethoxazole (Bactrim) increases warfarin effects	Erythromycin Orthostatic hypotension, ventricular tachycardia, bradycardia, torsades de pointes (with drug interactions) Clarithromycin QT prolongation and torsades de pointes Trimethoprim-sulfamethoxazole Orthostatic hypotension, anaphylaxis, QT prolongation, torsades de pointes, hypokalemia Sparfloxacin (fluoroquinolones) QT prolongation
Antifungal agents	Amphotericin B Digoxin toxicity Ketoconazole or itraconazole Cytochrome P450 metabolism and drug interactions—increases levels of sildenafil, warfarin, HMG-CoA reductase inhibitors, nifedipine, digoxin	Amphotericin B Hypertension, arrhythmia, renal failure, hypokalemia, thrombophlebitis, bradycardia, angioedema, dilated cardiomyopathy Liposomal formulations still have the potential for electrolyte imbalance and QT prolongation Ketoconazole, fluconazole, itraconazole QT prolongation and torsades de pointes
Antiviral agents	Ganciclovir Zidovudine	Foscarnet Reversible cardiac failure, electrolyte abnormalities Ganciclovir Ventricular tachycardia, hypotension
Antiparasitics		Pentamidine Hypotension, QT prolongation, arrhythmias (torsades de pointes), ventricular tachycardia, hyperglycemia, hypoglycemia, sudden death. These effects are enhanced by hypomagnesemia and hypokalemia
Chemotherapy agents	Vincristine, doxorubicin Decrease digoxin level	Vincristine Arrhythmia, myocardial infarction, cardiomyopathy, autonomic neuropathy Recombinant human interferon-alpha Hypertension, hypotension, tachycardia, acute coronary events, dilated cardiomyopathy, arrhythmias, sudden death, atrioventricular block, peripheral vasodilation



Class	Cardiac drug interactions	Cardiac side effects
		Contraindicated in patients with unstable angina or recent myocardial infarction Interleukin 2 Hypotension, arrhythmia, sudden death, myocardial infarction, dilated cardiomyopathy, capillary leak, thyroid alterations Anthracyclines <i>(Doxorubicin, daunorubicin, mitoxantrone):</i> myocarditis, cardiomyopathy Liposomal anthracyclines As above for doxorubicin and also vasculitis
Systemic corticosteroids	Corticosteroid Decrease salicylate levels and increase gastric ulceration in combination with salicylates	Corticosteroids Ventricular hypertrophy, cardiomyopathy, hyperglycemia
Pentoxifylline		Pentoxifylline Decreased triglyceride levels, arrhythmias, chest pain Megace Edema, thrombophlebitis, hyperglycemia
Megestrol acetate (Megace)		Epoetin alfa (erythropoietin) Hypertension, ventricular dysfunction
Methadone		Prolonged QT interval
Amphetamines		Increased heart rate and blood pressure

*See Piscitelli and Gallicano,⁴⁹ Table II, for cytochrome P450 isoforms and selected drugs used in the care of HIV-infected patients. HMG-CoA₃-hydroxy-3-methylglutaryl coenzyme A.

Table II. Cardiovascular actions and interactions of drugs commonly used in HIV therapy.*

Reproduced from reference 6: Fisher SD, Lipshultz SE. Cardiovascular abnormalities in HIV-infected individuals. In: Zipes DP, Libby P, Bonow RO, Braunwald E, eds. Heart Disease: A Textbook of Cardiovascular Medicine. 7th ed. Philadelphia, Pa: Elsevier/Saunders Co; 2005(chap 61):1719-1729. Copyright © 2005, Elsevier/Saunders.

tients taking indinavir and nelfinavir. Combination with saquinavir did not further elevate total cholesterol. In some cases, switching protease inhibitors may reverse both elevations in triglyceride levels and abnormal fat deposition. Low-level aerobic exercise has also helped reverse lipid abnormalities.^{8,38,45}

Zidovudine (or azidothymidine, AZT) has been implicated in skeletal muscle myopathies,⁶ and cultured cardiac muscle cells treated with AZT develop mitochondrial abnormalities,⁴⁹ suggesting that AZT-treated patients may experience cardiac muscle myopathies. However, such proposed AZT-associated myopathies have not been found in clinical data, except for rare patients with left ventricular dysfunction who improved when AZT therapy was stopped.⁶

Multiple medication reactions and interactions have occurred during the treatment of HIV infection and are a major cause of cardiac emergencies in HIV-infected patients (*Table II*).⁶ Future therapies may inhibit HIV-1 cell entry and may have less toxic effects.⁵⁰

Cardiovascular complications of therapeutic drugs in HIV-infected patients

More than 50 drugs are associated with the type of ventricular arrhythmia called torsades de pointes. This condition places patients at very high risk for sudden arrhythmic death. It can be caused by drugs that delay cardiac repolarization and lengthen the QT interval, usually by blocking cardiac potassium channels. In the past 3 years, terfenadine, astemizole, cisapride, mibefradil, and grepafloxacin were removed from the market because they were linked to torsades de pointes. Therapies used in HIV-infected patients that have been associated with torsades de pointes include pentamidine, foscarnet, and trimethoprim sulfamethoxazole, among other anti-infective therapies.

Itraconazole, a synthetic antifungal agent used to treat systemic fungal infections, has recently been determined to be at least as effective as amphotericin B and is recommended for fever in neutropenic cancer patients. However, itraconazole has recently been re-

ported to have negative inotropic effects and to be associated with the development of congestive heart failure. Itraconazole should be prescribed with caution for HIV-infected patients.

Nearly 20% of the US population use complementary or alternative medications. Most patients do not disclose the alternative medications they take, in part because health care providers often do not explicitly ask for this information. Understanding the effects of these drugs in HIV-infected patients may help reduce complications that could arise from their use. Direct effects include bleeding from garlic, ginkgo, and ginseng; cardiovascular instability (myocardial ischemia/infarct, stroke, and cardiovascular collapse from catecholamine depletion) from ephedra and hypoglycemia from ginseng. Pharmacodynamic herb-drug interactions include potentiation of the sedative effect of anesthetics by kava and valerian. Pharmacokinetic herb-drug interactions include the increased metabolism of many drugs used in HIV-infected patients by St John's wort, through induction of enzyme cytochrome P450 3A4, which decreases their efficacy.⁸

Perinatal transmission and vertically transmitted HIV infection

Most children with HIV are infected in the perinatal period, but HIV transmission can be minimized if mothers are given antiretroviral therapy before and during parturition, and if infants are given prophylactic zidovudine after birth.²² Rates of congenital cardiovascular malformations in cohorts of HIV-uninfected and HIV-infected children born to HIV-infected mothers ranged from 5.6% to 8.9%. These rates were 5 to 10 times higher than reported in population-based epidemiological studies, but not higher than in normal populations similarly screened.⁵¹ In the same cohorts, serial echocardiograms performed at 4- to 6-month intervals showed subclinical cardiac abnormalities to be common, persistent, and often progressive.⁵¹ Some had dilated cardiomyopathy (left ventricular contractility 2 standard deviations or more below the normal mean and left ventricular end-diastolic dimension 2 standard deviations or more above the mean) and inappropriate left ventricular hypertrophy (elevated left ventricular mass in the setting of decreased height and weight). Depressed left ventricular function correlated with immune dysfunction at baseline, but not longitudinally, suggesting that the CD4 cell count may not be a useful surrogate marker of HIV-associated left ventricular dysfunction. The development of encephalopathy was highly correlated with a decline in fractional shortening.

In children with vertically transmitted HIV-1 infection, disease can progress rapidly or slowly. Rapid progressors have higher heart rates, higher respiratory rates, and lower fractional shortening on serial echocardiographic examinations than nonrapid progressors and HIV-uninfected children who are similarly screened.¹⁹ Rapid progressors have higher 5-year cumulative mortality, higher HIV-1 viral loads, and lower CD8+ (cytotoxic) T-cell counts than nonrapid progressors.¹⁹ Knowing the patterns of disease allows more aggressive therapy to be initiated earlier in rapid progressors.

FUTURE PERSPECTIVES

HIV-related cardiovascular disease is an underrecognized and underappreciated cause of symptomatic illness and a predictor of all-cause mortality in late-stage HIV infection. A high degree of suspicion and early screening may allow appropriate intervention and improve the quality of life in those affected.

Because cardiovascular disease is common in HIV-infected patients, and because physical examination is not reliable for diagnosis, baseline and serial echocardiographic monitoring may be essential in detecting early disease and targeting patients who would benefit from early intervention and aggressive early antiretroviral therapy.

Preventing cardiovascular disease in HIV-infected patients is preferred to treating cardiovascular disease in symptomatic HIV disease. No HIV-specific preventive cardiovascular strategies have been developed, but evidence-based recommendations can be extrapolated from those used for the general population. However, because of medication interactions and side effects, HIV infected patients should receive individualized therapy.

As longevity improves for HIV-infected patients, cardiovascular disease will predominate as a cause of mortality and will surface as a vital area of research. Research may translate to other diseases using HIV as a model of chronic immunosuppression in a large population. Understanding genetic predispositions to QT prolongation may guide therapy. Understanding the causes of cardiomyopathy may require diverse research efforts, such as studying the effects of cytokines, mitochondria, and neurohormonal pathways. Observations, such as the knowledge that mildly increased LV mass and mild LV dysfunction increase mortality, may translate to allow early identification of at risk populations in other cardiomyopathies.



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