HIV & Cardiovascular Disease

Invited Editorial

N. A. Boon

Lead Article

The cardiovascular manifestations of HIV infection - S. E. Lipshultz, S. D. Fisher, T. L. Miller, T. S. Sharma, A. N. Milton

Expert Answers to Three Key Questions

How does HIV/AIDS cause cardiomyopathy? - W. Lewis

How can excess cardiovascular morbidity be minimized in HIV-infected individuals? D. J. Betteridge

What can be done about effusive tuberculous pericarditis in HIV-seropositive patients? A. S. Malin, J. G. Hakim

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Bibliography of One Hundred Key Papers
Invited Editorial

Nicholas A. Boon, MA, MD, FRCP(Ed)
Consultant Cardiologist - Royal Infirmary of Edinburgh Honorary Reader in Cardiology
University of Edinburgh - President Elect of the British Cardiovascular Society

HIV AND THE HEART

What can’t be cured must be endured

Proverb

This edition of Dialogues in Cardiovascular Medicine is devoted to the protean and increasingly important cardiovascular manifestations of human immunodeficiency virus (HIV) infection. The human carnage caused by the HIV pandemic that began about 25 years ago is difficult to comprehend. More than 40 million people had been infected by the end of 2005 and there are now approximately 5 million new infections (including 600,000 babies born with HIV) and 3 million deaths every year. Mortality has been particularly high in sub-Saharan Africa, where over 13 million children have been orphaned, and is still rising rapidly in many parts of the world, most notably Asia and Eastern Europe. HIV/AIDS (acquired immunodeficiency syndrome) is now the second leading cause of disease in the world and can produce a sometimes bewildering and quite staggering array of clinical syndromes and illnesses. The mucocutaneous, gastrointestinal, respiratory, and neurological manifestations can be dramatic and have attracted a lot of attention. Although HIV-related heart disease is common, it is frequently overlooked because it is either subclinical or produces nonspecific symptoms such as breathlessness and fatigue that are mistakenly attributed to other problems such as anemia. Some form of heart disease is demonstrable at autopsy in approximately 40% of patients, and by echocardiography in around 25% of patients with AIDS (category C disease). Many of these lesions are mild, and HIV-related heart disease probably causes symptoms in fewer than 10%, and death in fewer than 2% of all patients with HIV infection. Nevertheless, the sheer scale of the pandemic means that there are around 3 million people in the world living with HIV-related heart failure. Delivering effective health care to these patients will be a huge challenge, but also provides an unrivalled opportunity to research the pathophysiology of a wide range of cardiovascular diseases. Moreover, there is a real and tantalizing prospect that studying these diseases will ultimately provide valuable insight into other forms of heart disease, particularly idiopathic dilated cardiomyopathy, primary pulmonary hypertension, and even atherosclerosis.

Dr Nicholas A. Boon, Department of Cardiology, Royal Infirmary of Edinburgh, 49 Little France Crescent, Edinburgh EH16 4SB, UK (e-mail: boons@lineone.net)
The Lead article in this series has been written by Professor **Steven Lipshultz and colleagues**. Lipshultz was among the first to draw attention to HIV-related heart muscle disease, and provides a comprehensive account of the features, epidemiology, pathogenesis, and treatment of the numerous cardiovascular manifestations of HIV disease.

In the first of three Expert Answer articles, Professor **William Lewis**—an eminent pathologist with a long-standing interest in HIV-related heart disease—discusses the complex question of how HIV causes heart muscle disease, the dominant cardiac complication of HIV infection at the beginning of the epidemic. The hypotheses that he describes are fascinating and are clearly relevant to other forms of heart muscle disease.

The advent of highly active antiretroviral therapy (HAART) has had a major impact on HIV morbidity and mortality in many parts of the world. Long-term survival is no longer unusual and in many health care systems, HIV infection has become just another chronic illness that requires careful surveillance and disease management. In this sort of setting, premature coronary artery disease is now much more common than heart muscle disease and the other manifestations of profound immunosuppression. In the second Expert Answer article Professor **John Betteridge**, an international authority on metabolic disease and lipidology, reviews the compelling reports of premature arterial disease in HIV infection and the extent to which this may be due to a particularly severe form of the metabolic syndrome induced by HAART. His observations provide an intriguing perspective on the pathogenesis of atherosclerosis and will be of great help to clinicians wrestling with the extraordinarily difficult problem of how to manage severe hyperlipidemia in patients receiving HAART.

Cardiovascular problems associated with advanced immunodeficiency, such as heart muscle disease, pericardial effusion, and pulmonary hypertension, continue to predominate in resource-poor countries where fewer than 5% of patients are able to access antiretroviral drugs. Coinfection is also more common in such settings. The third Expert Answer addresses the issue of concurrent infection with HIV and tuberculosis. Approximately one third of the 40 million people with HIV are coinfected with **Mycobacterium tuberculosis**, and in some countries up to 30% of patients with tuberculosis are coinfected with HIV. Around 75% of these people reside in sub-Saharan Africa where tuberculous pericardial effusion has been a very prominent problem and one of the most common AIDS-defining illnesses. Drs **Adam Malin** and **James Hakim** are among the very few clinicians to have conducted high-quality research, including therapeutic clinical trials, in these patients. Their excellent article on the management of tuberculous pericarditis in AIDS, like all the others in this series, highlights the need for more research and contains many important wider messages.
The cardiovascular manifestations of HIV infection

Steven E. Lipshultz,* MD; Stacy D. Fisher,† MD; Tracie L. Miller,* MD; Tanvi S. Sharma,* MD; Angela N. Milton,* BS

* Department of Pediatrics - University of Miami Miller School of Medicine and Holtz Children’s Hospital of the University of Miami-Jackson Memorial Medical Center - Miami, Fla - USA
† Mid-Atlantic Cardiovascular Associates - Baltimore, Md - USA

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.

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

**Address for correspondence:** Steven E. Lipshultz, MD, Department of Pediatrics, University of Miami Miller School of Medicine, Medical Campus-MCCD-D820, 1601 NW 12th Avenue, 9th Floor, Miami, FLA 33136 (e-mail: slipshultz@med.miami.edu)

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**SELECTED ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS</td>
<td>acquired immune deficiency syndrome</td>
</tr>
<tr>
<td>CMV</td>
<td>cytomegalovirus</td>
</tr>
<tr>
<td>HAART</td>
<td>highly active antiretroviral therapy</td>
</tr>
<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
</tr>
<tr>
<td>P2C2 HIV</td>
<td>Pediatric Pulmonary and Cardiovascular Complications of vertically transmitted HIV infection (study)</td>
</tr>
<tr>
<td>TNF-α</td>
<td>tumor necrosis factor-α</td>
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</tbody>
</table>
**Possible causes**

**Drug related**
- Cocaine, AZT, IL-2, doxorubicin, interferon

**Infectious**
- HIV, toxoplasma, coxsackievirus group B, EBV, CMV, adenovirus

**Metabolic or endocrine**
- Selenium or carnitine deficiency, anemia, hypocalcemia, hypophosphatemia, hypokalemia, hypoalbuminemia, hyperinsulinemia, hypomagnesemia, hypothyroidism, growth-hormone deficiency, adrenal insufficiency, hypercalcemia, hemochromatosis, sarcoidosis, amyloidosis

**Cytokines**
- TNF-α, nitric oxide, TGFβ, endothelin-1, interleukins

**Immunodeficiency**
- CD4-100

**Autoimmune**
- Bacteria
  - Staphylococcus, Streptococcus, Proteus, Klebsiella, Enterococcus, Listeria, Nocardia, Mycobacterium
- Viral pathogens
  - HIV, HSV, CMV, adenovirus, echovirus
- Other pathogens
  - Cryptococcus, Toxoplasma, Histoplasma
- Malignancy
  - Kapo's sarcoma, lymphoma, capillary leak, wasting, malnutrition
- Hypothyroidism
- Immunodeficiency, uremia

**Incidence/prevalence**

**Dilated cardiomyopathy**
- Up to 8% of asymptomatic patients
- Up to 25% of autopsy cases

**Pericardial effusion**
- 11%/year
- Spontaneous resolution in 42% of affected patients
- Approximately 30% increase in 6-month mortality

**Infective endocarditis**
- 6% increased incidence in IVDA, regardless of HIV status

**Diagnosis**

**Chest radiograph findings**

**Non-specific conduction abnormalities**

**Echocardiogram findings**

**Possible laboratory studies**

- Troponin T, brain natriuretic peptide level, CD4 count, viral load, viral PCR, toxoplasma serology, TSH, cortisol, corticosterone, selenium, serum ACE, vanillylmandelic acid, amyloid, urinalysis, stress testing, myocardial biopsy, cardiac catheterization

**Treatment**

**Diuretics, digoxin, ACE inhibitors, β-blockers**

**Adjunctive treatment in HIV+ patients**

- Treatment of infection, nutritional replacement, IV Ig, intensify antiretroviral therapy

**Follow-up**

- Serial echocardiograms
Table 1. Summary of HIV-associated cardiovascular diseases.

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

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.

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.6 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, antmyocyte 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 borderzone 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, 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 (eg, infection with CMV, Epstein-Barr virus, or adenovirus) who are at risk for myocarditis.6,8,22

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 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. Several studies have shown that effusion may be transient. 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.

Monitoring and therapy

Screening echocardiography is recommended in HIV-infected individuals, regardless of the stage of disease (Figure 2). All HIV-infected patients with evidence of heart failure, Kaposi's sarcoma, tuberculosis, or other pulmonary infections should undergo baseline echocardiography and ECG testing. 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.

jugular venous pressure, dyspnea, hypotension, persistent tachycardia, and pulsus paradoxus, or (ii) echocardiographic signs of tamponade, such as valvular inflow respiratory variation evident on continuous-wave Doppler echocardiography, septal bounce, right ventricular diastolic collapse, and a significant effusion. 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). Infections with Aspergillus species, and Pseudallescheria boydii.

**Infected 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. 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. 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. 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. Fulminant courses of infective endocarditis with high mortality can be seen in late-stage AIDS, but several cases have been successfully treated with antibiotics. 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.

**Nonbacterial thrombotic endocarditis**

Nonbacterial thrombotic endocarditis, otherwise known as marantic endocarditis, is the growth of large friable, sterile vegetations on the cardiac valves. These lesions have been associated with disseminated intravascular coagulation and systemic embolization. Lesions are rarely diagnosed ante-mortem. When they are, they cause clinically relevant emboli in an estimated 42% of cases. 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. 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. 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. 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. 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. 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%). 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. 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.

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. 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. 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. 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.

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. 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. The multinational Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study Group found an incidence of 3.5/1000 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. The multinational Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study Group found an incidence of 3.5/1000 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. 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).

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

**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.

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 empha-
sized. 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 chole-
sterol, insulin resistance, and diabetes. The “metabolic
syndrome” is as strong a contributor to early heart dis-
ease as cigarette smoking. It should be treated with
intensive lifestyle changes, including weight control,
physical activity, and medication. The Guidelines de-
fine 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 unreli-
able 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 con-
comitant initial therapy. If HIV-associated wasting is
also present, it should be treated before dyslipidemia
is treated.

In asymptomatic members of the general public, reduc-
ing cholesterol concentration lowers the rate of car-
diovascular events. The combination of a cholesterol-low-
ering 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-methyl-
glutaryl coenzyme A (HMG-CoA) reductase inhibitors
because it is less likely to cause drug interactions.
However, cholestyramine and colestipol may be asso-
ciated with increased triglyceride levels, and their ef-
effect on antiviral drug absorption has not been studied.
Colestevam 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 dyslipi-
demia in patients with HIV infection have been de-
vised by the US-based Adult AIDS Clinical Trial Group
Cardiovascular Disease Focus Group. For protease in-
hibitor–treated HIV-infected patients with hypercholes-
terolemia, treatment with low-dose pravastatin (ini-
tial dosage, 20 mg/day), atorvastatin (10 mg/day), or
rosuvastatin (5 mg/day) is recommended. Careful mon-
itoring of virologic status and creatine kinase values is
recommended for patients on these therapies. Lova-
statin or simvastatin therapy should be avoided because
of interactions with protease inhibitors or non–nucle-
oside reverse transcriptase inhibitors and risk of rhab-
domyolysis. 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 rea-
sonable 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 lipodystro-
phy (fat wasting of the face, limbs, and buttocks) and
relative conservation or enhancement of central adi-
posity (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-pep-
tide, and lower HDL levels.38 In patients with elevated
lipoprotein(a) levels, protease inhibitor therapy in-
creased 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 dis-
tribution 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 inhibi-
tors.49 Ritonovir 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-
**Cardiac drug interactions**

- Zidovudine and dipyridamole
- 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
- 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
- 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
- Amphotericin B
  - Dose toxicity
  - Ketoconazole or itraconazole
  - Cytochrome P450 metabolism and drug interactions—increases levels of sildenafil, warfarin, HMG-CoA reductase inhibitors, nifedipine, digoxin
- Foscarnet
  - Reversible cardiac failure, electrolyte abnormalities
- Ganciclovir
  - Zidovudine
- Pentamidine
  - Hypotension, QT prolongation, arrhythmias (torsades de pointes), ventricular tachycardia, hyperglycemia, hypoglycemia, sudden death. These effects are enhanced by hypomagnesemia and hypokalemia
- Vincristine, doxorubicin
  - Decrease digoxin level

**Cardiac side effects**

- Rare: lactic acidosis, hypotension
- Accelerated risk with cardiopulmonary bypass
- Zidovudine: skeletal muscle myopathy, myocarditis
- Implicated in premature atherosclerosis, dyslipidemia, insulin resistance, diabetes mellitus, fat wasting, and redistribution
- Erythromycin
  - Orthostatic hypotension, ventricular tachycardia, bradyarrhythmia, 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
- Pentamidine
  - Hypotension, QT prolongation, arrhythmias (torsades de pointes), ventricular tachycardia, hyperglycemia, hypoglycemia, sudden death. These effects are enhanced by hypomagnesemia and hypokalemia
- 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
patients 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).8 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, mibebradil, 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, foscarin, 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-
reported 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. 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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HIV & Cardiovascular Disease

Expert Answers to Three Key Questions

1. How does HIV/AIDS cause cardiomyopathy?
   W. Lewis

2. How can excess cardiovascular morbidity be minimized in HIV-infected individuals?
   D. J. Betteridge

3. What can be done about effusive tuberculous pericarditis in HIV-seropositive patients?
   A. S. Malin, J. G. Hakim
How does HIV/AIDS cause cardiomyopathy?

William Lewis, MD
Professor of Pathology - Emory University School of Medicine - Department of Pathology - Atlanta, Ga - USA

**HIV/AIDS-related cardiomyopathy is a relatively recent concern. Only in the last decade, thanks to antiretroviral therapy, have human immunodeficiency virus type 1 (HIV 1) infection and acquired immunodeficiency syndrome (AIDS) become chronic, at least in the developed world. For this reason, and because of confounding factors (comorbidity, the iatrogenic impact of nucleoside reverse transcriptase inhibitors) and widely differing study populations, some major issues remain unresolved: the prevalence of cardiomyopathy in HIV infection (figures range from zero to 10%), the cellular target of HIV (cardiomyocytes lack CD4 receptors), and the specific impact, if any, of cardiac HIV infection. However, there is now strong evidence, found in around half of autopsy cases, that underlying the cardiomyopathy is a myocarditis resulting from interaction between cytokines and HIV structural proteins.**

Acquired immunodeficiency syndrome (AIDS) was first described in 1981, but its etiological agent was not identified as the human immunodeficiency virus type 1 (HIV-1) until 1983-1984. At that point, the virus that came to be known commonly as HIV was characterized and a deeper appreciation of key elements of the syndrome of AIDS became available. Infection with HIV, the primary retrovirus responsible for AIDS, occurs as a result of exposure to infected body fluids through sexual, perinatal (blood, blood products, illicit injection drugs, occupational injury), or vertical transmission (mother to fetus).

**WHAT IS THE SCOPE OF HIV/AIDS HEART DISEASE?**

To put the AIDS epidemic in perspective, more than 40 million people worldwide were infected with HIV as of 2005, and more than 20 million have died since the epidemic began. Most deaths occurred in sub-Saharan Africa, where over 13 million children have been orphaned. In the United States, over 1 million people are now “HIV positive” (infected with HIV based on virological testing), although not all have AIDS. In the developed world, the HIV infection rate is rising in eastern Europe.

Because of the severe effects of immunodeficiency in AIDS, the course of untreated illness was rapidly fatal in the early days of epidemic. This resulted in part from unfamiliarity with the condition and lack of effective therapy to treat HIV infection. Unfortunately, today many of those same problems persist in resource-poor areas where the diagnosis of HIV/AIDS may be made late in the disease and where antiretroviral therapy is not yet available.

Justifiably, in the early days of the epidemic, heart disease in the setting of HIV/AIDS was not considered a critical clinical consideration. More urgent clinical problems were abundant and eclipsed all others. The advent of widespread use of antiretroviral therapy for HIV/AIDS in the developed world, coupled with guidelines for antiretroviral treatment from the Center for Disease Control (CDC), has contributed...
greatly to prolongation of productive life and has led to initiating similar approaches in parts of the developing world. As a consequence of more effective treatment and care for patients with HIV/AIDS, longevity with HIV/AIDS has added to the clinical spectrum of diseases referable to the various organ systems. Thus, in the last decade of the epidemic (at least in the developed world) HIV/AIDS has taken on the behavior of a chronic illness that requires continuous monitoring and therapy (analogous to diabetes mellitus).

The role of heart disease (specifically cardiomyopathy [CM]) in HIV/AIDS patients in the developing world may be somewhat different and has only recently been addressed more extensively. Because a variety of cardiovascular illnesses may be intersecting in that population, heart disease from HIV/AIDS may not be as pressing as other more common cardiovascular illnesses. This review primarily addresses HIV/AIDS in the developed world. It should be understood that improvements in therapy and survival occurring in patients with HIV/AIDS throughout the world may make points discussed here applicable to other geographic locales.

**HAS AIDS CARDIOMYOPATHY EVOLVED WITH HIV/AIDS?**

As alluded to above, early in the HIV/AIDS epidemic, the heart was recognized as an authentic target of disease, but significant clinical cardiac involvement was unusual (or not reported) based on the profound effects of opportunistic infection, respiratory failure, wasting, and Kaposi’s sarcoma, which were more prevalent and life-threatening, and which more accurately characterized this relatively new clinical entity. Although HIV is etiologically linked to AIDS per se, controversy persists regarding the prevalence of myocardial infection with HIV (or related pathogens), the cellular target for HIV infection within the heart, and the clinical impact, if any, of HIV infection in that target organ. All of these important points led to attempts at identifying the pathogenetic role (if any) of HIV infection of the myocardium in HIV/AIDS CM.

Autopsy findings from studies performed early in the epidemic defined many pathological features, but focused predominantly on other organs. Cardiac effects, where demonstrated, appeared frequently as accompanying findings. A series of papers examined postmortem findings in HIV/AIDS that particularly focused on the cardiovascular system. Incidence of cardiac involvement at autopsy varied, appeared dependent on the pathological and clinical definitions and criteria applied to the cases. Findings varied somewhat based on epidemiological features among the different populations of HIV/AIDS patients in different settings within the developed world. Although it was understood that most autopsy studies from the United States came from urban, academic medical centers, the demographics followed closely the patient populations of the particular geographic location, which were somewhat unique. For example, some of the autopsy studies included a significant number of patients who were intravenous drug abusers; others included a predominantly homosexual male population, and so on. Female patients were relatively few in most of the earlier studies.

This simple, but important, demographic factor created some gaps in understanding the global concept of HIV/AIDS CM. Frequently, distinct patterns of illnesses could be found in some populations. Ultimately, that demographic artifact could skew the interpretation of those data when applied to other populations. Moreover, it may be reasonable to suggest comorbid conditions impact the cardiovascular health of patients with AIDS and may thus impact cardiac performance and development of HIV/AIDS CM, and these also could impact results. This latter point becomes increasingly reasonable with the advent of antiretroviral therapy, and the role of comorbid conditions must be ascertained in HIV/AIDS CM cases and must be considered in all studies that are population-based in a given locale.

When CM in HIV/AIDS was reported in 1986, the index patient received no antiretroviral therapy. Additional CM cases in HIV/AIDS were reported subsequently. The prevalence of CM in HIV/AIDS appeared to be increasing, but ranged ≈10% or less based on autopsy findings in the developed world and unpublished data. A 1-year consecutive enrollment study of patients admitted to the intensive care unit in an urban center revealed 6% of admissions with either HIV-1 infection or HIV/AIDS had echocardiographically-documented CM. Mortality was 25%. Persistent echocardiographic abnormalities in HIV/AIDS were considered ominous predictors of CM, but other changes were reversible and thus considered less serious. In Britain, 13 of 173 HIV/AIDS patients had CM as a correlate of advanced HIV-1 disease. Data indicated no correlation between HIV/AIDS CM and other potential causes of CM, myocarditis, zidovudine (= azidothymidine, AZT) treatment, or infection with cytomegalovirus or *T. gondii.* In hemophiliacs, 2 of 27 patients...
with HIV-1 infection had echocardiographically documented CM.27 Recent data from intensive care settings in the United States point to increased admissions with cardiovascular disease and HIV/AIDS and declining admissions with respiratory failure in that setting.28,29

Contrasting data come from other European centers. The direct effect of HIV/AIDS on the development of “heart disease” was evaluated in a report from Scandinavia in a population of HIV/AIDS patients without opportunistic infections.30 According to echocardiography, no patient had significant pericardial effusions, cardiac tumors, endocarditis, or CM. In a subgroup that died of AIDS, HIV was not a myocardial pathogen. Other studies suggested that myocardial filling and relaxation abnormalities are important in HIV infection.31 From these points, it may be inferred that the pathogenetic or etiological ties between HIV and CM in HIV/AIDS were not strong.

**DOES HIV INFECTION THE MYOCARDIUM, AND IF SO HOW?**

One reasonable hypothesis to explain CM in HIV/AIDS is to consider HIV itself a cardiac pathogen. HIV gains entry into cells through binding between its envelope glycoprotein group 120 (gp120) and CD4 receptors found on specific lymphocytes, including helper T cells, and macrophages and dendritic cells. Unfortunately, the fact that cardiac myocytes lack CD4 receptors creates a conundrum for understanding of the pathogenetic mechanisms of CM in HIV/AIDS. Evidence proving that HIV enters human cardiac myocytes is less compelling and more circumstantial. This weakens a pathogenetic link between HIV/AIDS and the development of CM and myocarditis in patients.

Pathological studies from our group32 and others33 addressed the question of whether HIV served as an infectious agent in the human myocardium. They documented HIV infection in pathological sections of myocardium in patients with HIV/AIDS. The in situ hybridization techniques offered the relatively unique advantage of preserved histologic architecture and precise localization of HIV sequences within particular tissue (eg, heart).

The major technical shortcoming was that in situ hybridization as performed in those studies could not unambiguously identify cell type (ie, myocyte vs nonmyocyte). Nonetheless, data from our study32 indicated over 20% autopsy heart samples exhibited HIV infection. The abundance of signal was small and HIV infection in the heart neither correlated with clinical evidence of CM, nor was cytological identity of the infected cell ascertained based on the limitations alluded to above.

Convincing experimental data from simian immunodeficiency virus (SIV) studies in nonhuman primates clarified some of the ambiguities. Although in vivo models of HIV/AIDS are generally limited in many ways,34 SIV is an authentic model of HIV/AIDS, and thus may serve as a model of CM and myocarditis in HIV/AIDS. Unfortunately, primate studies are limited in number because of logistic difficulties, ethical considerations, and so on. Despite this, data from Shannon’s group and others suggest SIV (and thus HIV) is harbored in the nonmyocyte pool of myocardial cells, instead of the cardiomyocytes.35-38 The studies further point out that CM in the simian model of HIV/AIDS is a chronic condition, that infection with retrovirus is targeted to the nonmyocyte pool, and that clinical events correlate with severity of infection and injury.

Taken together, these important experimental issues tie inflammation of the heart to CM in HIV/AIDS.

**WHAT IS THE ROLE OF MYOCARDITIS IN HIV/AIDS CM?**

Myocarditis in HIV/AIDS has varying prevalence in the reports over the decades. However, myocarditis could provide a rational explanation for the development of CM in HIV/AIDS. Variability was apparent. A Scandinavian study of 60 consecutive autopsies revealed 42% prevalence,30 while in Southern California, a 74% prevalence was described,39 and in 100 autopsies from Puerto Rico, changes in the heart occurred in 32% of cases. In Reilly’s postmortem review,40 26 of 58 samples satisfied the Dallas criteria for myocarditis with clinical correlation, and lymphocytic infiltrates were found more commonly early in the HIV/AIDS epidemic.20,41

As mentioned, the prevalence of inflammatory infiltrates in the heart of patients with HIV/AIDS varied substantially in early studies and the relationship of the identified infiltrates to either cardiac dysfunction or HIV infection in the heart were similarly tenuous. Findings at UCLA indicated less than 10% prevalence of bona fide myocarditis from autopsy samples of myocardium. Other investigators in the United States and elsewhere found significantly higher prevalence of inflammatory infiltrates in the heart. Data from large studies performed in Italy putatively corroborated high prevalence of AIDS CM and significant cardiac infection with HIV in HIV/AIDS patients.42-44 However, those papers were retracted editorially44,45. This unfortunate series of events further obfuscated the diagnosis and treatment of myocarditis and of CM in HIV/AIDS.
WHAT IS THE ROLE OF CYTOKINES IN CM IN HIV/AIDS?

Because cytokines play key roles in AIDS, and in cardiac dysfunction and congestive heart failure (CHF) in the broader sense, it is reasonable to consider that circulating or locally acting cytokines may be involved pathogenetically or pathophysiologically in CM in HIV/AIDS. Cytokines that are reasonable candidates for impacting cardiac function in HIV/AIDS include endothelin (particularly ET-1) and tumor necrosis factor-α (TNF-α). Left ventricle expression of atrial natriuretic factor (ANF), a marker of left ventricle hypertrophy, cardiac dysfunction and remodeling, and reversion to an embryologically earlier genetic program, may also be important diagnostically and prognostically. Based on information from the numerous studies of CHF unrelated to HIV/AIDS and from studies of HIV/AIDS in absence of cardiovascular disease, substantial information has been obtained regarding the role of cytokines and the potential interaction of cytokines with HIV structural proteins in the pathogenesis of AIDS CM. Finkel’s group demonstrated that HIV envelope gp120 induces nitric oxide production through inducible nitric oxide synthase in vitro and that p38 MAP kinase is mechanistically involved in cardiac dysfunction. Other investigators suggested that reactive nitrogen species may be critical pathophysiologically. Some evidence links gp120 to HIV/AIDS and CM both in human samples and those from primates, and may serve as the link between primate findings in vivo and clinical data. Taken together, these points may offer a plausible relationship between the pathogenesis of CM in patients with HIV/AIDS and in patients who are not infected.

DOES ANTIRETROVIRAL THERAPY IMPACT CM IN HIV/AIDS?

Despite new antiretroviral agents being developed and some promise from HIV vaccine studies, HIV/AIDS remains a major clinical threat. Treatment approaches were developed as early as the mid-1980s and focused on stopping viral replication. The earliest successful group of antiretroviral drugs came from a class called nucleoside reverse transcriptase inhibitors (NRTIs), which are pharmacological analogs that mimic native nucleosides used for DNA replication. Today, in combinations of highly active antiretroviral therapy (HAART), NRTIs are cornerstones of AIDS therapy in the developed world. Moreover, HAART containing NRTIs is being brought to some areas in the developing world in heroic efforts.

Shortly after NRTIs became efficacious in the developed world, NRTI side effects were noted in patients. In particular, HIV/AIDS patients that received relatively high-dose therapy, particularly AZT, experienced a disabling skeletal muscle myopathy that resembled some relatively rare mitochondrial genetic diseases. Although earlier data existed from studies in vitro that suggested the possibility of toxicity from NRTIs, data from those studies were not extrapolated to clinical situations.

A series of seminal clinical observations, a group of related experimental studies, tragic results in a clinical trial with a NRTI for hepatitis B infection, and related in vitro and in vivo studies shed light on mechanisms of NRTI toxicity. It was demonstrated that AZT toxicity in humans was related mechanistically to mitochondrial dysfunction, particularly inhibition of mitochondrial (mt) DNA replication in vitro by active AZT triphosphate. Those data were correlated with data from studies in vivo of NRTI toxicity to heart muscle in rats, mice, woodchucks, and other species. A “DNA polymerase α hypothesis” was generated and evolved into the “mitochondrial dysfunction hypothesis” that expands its original scope. At present, NRTI toxicity encompasses defective mtDNA replication, alteration of intramitochondrial and intracellular processing of NRTIs, related defects from oxidative stress, and genetic defects of the mitochondrial genome.

The cornerstones of the concept of acquired mitochondrial dysfunction are energy deprivation secondary to mtDNA depletion, mitochondrial oxidative stress from ineffective utilization of electron transport, and mtDNA mutations that may result from oxidative mtDNA damage or from mutagenic changes from NRTIs per se. The current prevailing theory suggests that it is eminently reasonable to consider AZT-induced mitochondrial toxicity to involve defective mtDNA replication (reviewed in 74,82-84), but it should be noted that the hypothesis is neither proven clinically nor accepted universally. Importantly, the cellular locus at which the pathophysiological defect occurs may require further investigation.

In the earlier experimental studies, decreased mtDNA, mtRNA, mitochondrial polypeptides, and defective mitochondrial ultrastructure, correlate with micromolar, mixed Ks for dideoxy-NRTI triphosphates with pol γ. Intriguing recent data from patients suggest that genetic differences in either the mtDNA “template,” in the enzymatic and structural machinery of the mitochondrial DNA replicon, or in en-
zymes and transporters that maintain nucleotide precursor pools88 each may impact mitochondrial dysfunction.

WHERE DOES OPPORTUNISTIC INFECTION FIT IN HIV/AIDS CM?

Immune-compromised patients are vulnerable to a variety of infections. Opportunistic infections of the heart in patients with AIDS have been documented anatomically in the pericardium, myocardium, and endocardium, but again the prevalence has changed as the epidemic is into the 3rd decade. Among the documented cardiac infections include: *T. gondii*,90-92 *Cryptococcus* species,93 CMV,94-96 *Candida*,97,98 disseminated *P. carinii*,99,100 atypical mycobacteria,101 *Aspergillus*,102 *T. cruzi*,103,104 and *Microsporidium*.100 Irrespective of the infectious agent, it is clear today that in the developed world the effects of metabolic syndrome and mitochondrial dysfunction from HAART outweigh any of the risks described earlier in the epidemic.

WHAT ROLE DO ILLICIT DRUGS PLAY IN CM IN HIV/AIDS?

Because risk behaviors for HIV/AIDS infection may be associated with other risk behaviors, illicit drugs may be associated with HIV/AIDS. In the developed world, intravenous drug abuse is a significant risk behavior associated with HIV/AIDS. It is possible that such behavioral risk factors could also confound a pathogenetic relationship between AIDS and myocarditis. It may be reasonable to consider the relative contributions of both HIV/AIDS and conditions related to its attendant risk behaviors (such as infectious endocarditis and intravenous drug abuse) in consideration of HIV/AIDS CM. Abuse of known cardiotoxins (eg, cocaine105 or alcohol106) can contribute to the development of heart failure in HIV/AIDS and to the development of CM, since CM from those toxins can occur independent of HIV/AIDS exposure. Importantly, cocaine has been documented as a cause of CM, which occasionally has been reported to be reversible.107 The role of other nonprescription drugs and home remedies in the development of CM in HIV/AIDS may become more important in the future.

Figure 1 gives an overview of the above etiologies for CM in HIV/AIDS.

WHERE DOES CM IN HIV/AIDS GO FROM HERE?

It is abundantly clear that CM in HIV/AIDS, like the disease itself, has undergone some remarkable...
How does HIV/AIDS cause cardiomyopathy? - Lewis

changes over the 20 years since the first case was documented. Clearly, the nature and role of inflammatory heart disease, cytokines acting locally and systemically, nutritional status, illicit drugs, and therapeutic side effects have played a role in this period. As we approach the next, and hopefully the last decade of HIV/AIDS epidemic, host genetics at the pharmacological and toxicological levels likely will have greater impact on both clinical decision-making and on the course of disease for individuals and populations infected with HIV and with CM in HIV/AIDS.108-111

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How does HIV/AIDS cause cardiomyopathy? - Lewis


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How can excess cardiovascular morbidity be minimized in HIV-infected individuals?

D. John Betteridge, BSc, MB BS, PhD, MD, FRCP, FAHA
Department of Medicine - University College London Medical School - London - UK

In the general population, considerable interest has focused on defining a set of cardiovascular (CVD) risk factors that have long been known to cluster together more commonly than by chance in an effort to identify individuals at risk for CVD. For example, the National Heart Lung and Blood Institute (NHLBI) together with the American Heart Association1 and the International Diabetes Federation2 have provided simple, clinically based approaches to identifying the cluster of CVD risk factors often referred to as the metabolic syndrome.

An attractive hypothesis to explain the clustering of risk factors is insulin resistance. Risk factors included in both definitions are hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol, raised blood pressure, raised fasting glucose or type 2 diabetes, and central obesity. Given recent evidence pointing to central obesity (measured as waist circumference) reflecting visceral obesity as a better determinant of CVD risk, the IDF has proposed that this should be the central feature together with any two of the other factors. There is no doubt that the prevalence of metabolic syndrome is increasing dramatically throughout the developed and developing world due to a combination of genetic factors and increasing overweight and decreased physical activity. What has this to do with human immunodeficiency virus (HIV) and the heart? The introduction of effective combinations of antiretroviral drugs (often referred to as highly active antiretroviral therapy, HAART) has transformed the management of HIV/acquired immunodeficiency syndrome (AIDS), resulting in major reductions in morbidity and mortality. However, many individuals treated with HAART develop metabolic abnormalities, together with altered fat distribution, very similar to those described in definitions of the metabolic syndrome in the general population. In fact, in the author’s opinion, it is reasonable to conclude that HAART-treated HIV patients have a rapidly developing and often severe form of metabolic syndrome, which is likely to bring with it an increased CVD risk. This looks to be the case. These observations prompt the question, can CVD risk in HAART-treated HIV/AIDs patients be reduced through effective management of this, in part, iatrogenically induced metabolic syndrome?

In this chapter, the metabolic abnormalities and the risk of CVD will be described together with approaches to management. Although morbidity and mortality outcome trials are not available and indeed are unlikely to be performed, it is probable, by extrapolation from what has been learned from the general population, that effective management of the metabolic abnormalities in HIV/AIDs will translate into CVD risk reduction.
CARDIOVASCULAR DISEASE IN HIV/AIDS

Widespread use of HAART (usually two nucleoside reverse transcriptase inhibitors [NRTIs] in combination with one or two protease inhibitors [PIs]) has led to a dramatic and sustained reduction in morbidity and mortality associated with HIV/AIDS. Along with this, the nature of CVD in these patients has changed markedly. Prior to the introduction of HAART therapy and still relevant to much of the world where HAART therapy is not available, dilated cardiomyopathy, pericardial effusion, endocarditis, HIV-associated pulmonary hypertension, and vasculitis were the major cardiovascular manifestations. Where HAART therapy is available, it is now the development of atherosclerosis-related disease that is the major problem.

Several early reports pointed to an increased risk of CVD in HIV/AIDS patients observed in different countries. Out of 700 patients on HAART therapy for 18 months, 9 patients developed coronary events. In the French Hospital Database observed between 1996 and 1999, the relative hazard for myocardial infarction (MI) was 2.56 in those who had received PIs compared with those who had not. In a cohort of 5672 patients (mean age 43 y), those taking PIs were at significantly increased risk after adjustment for other risk factors. In the Frankfurt HIV-cohort study involving 4993 patients treated between 1983 and 1998, previous HAART therapy was associated with risk of MI, and the relationship persisted after multiple regression analysis.

The large prospective observational cohort study Data collection on Adverse events of anti-HIV Drugs (DAD) has helped clarify the magnitude of the risk. In the DAD report, which involved 23,468 patients from 11 previously established cohorts followed from December 1999 to April 2001, there were 126 MIs from a total of 36,199 person-years of follow-up. Importantly, risk of MI increased with longer exposure to HAART. The adjusted rate of MI per year of exposure was reported as 1.26 (95% confidence interval [CI], 1.21 to 1.41, \( P<0.001 \)).

SURROGATE MEASURES OF ATHEROSCLEROSIS

Endothelial dysfunction, carotid artery intima-medial thickening, and coronary artery calcification are important surrogate markers of atherosclerosis in HIV/AIDS patients. Endothelial dysfunction is considered to be an important early event in atherosclerosis and can be measured using surrogate markers such as endothelial dysfunction, carotid intima-media thickness, and coronary artery calcification.

SELECTED ABBREVIATIONS AND ACRONYMS

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<tr>
<th>ABBREVIATION</th>
<th>ACRONYM</th>
<th>EXPLANATION</th>
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<tr>
<td>AIDS</td>
<td>acquired immunodeficiency syndrome</td>
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<tr>
<td>ALIVE</td>
<td>AIDS Link to IntraVenous Experience [study]</td>
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<td>BIP</td>
<td>Bezafibrate Infarction Prevention [trial]</td>
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<td>BMI</td>
<td>body mass index</td>
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<td>CHICAGO</td>
<td>Carotid intima-media thICkness in Atherosclerosis using pioglitazOne [trial]</td>
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<td>CPK</td>
<td>creatine phosphokinase</td>
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<td>CTT</td>
<td>Cholesterol Treatment Trialists</td>
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<tr>
<td>CVD</td>
<td>cardiovascular disease</td>
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<td>DAD</td>
<td>Data collection on Adverse events of anti-HIV Drugs</td>
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<td>FFA</td>
<td>free fatty acid</td>
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<td>FIELD</td>
<td>Fenofibrate IntErvention and Lowering in Diabetes [trial]</td>
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<td>FMD</td>
<td>flow-mediated vasodilation</td>
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<td>HAART</td>
<td>highly active antiretroviral therapy</td>
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<td>HIV</td>
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<td>IGT</td>
<td>impaired glucose tolerance</td>
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<td>IMT</td>
<td>intima-media thickness</td>
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<td>JBS 2</td>
<td>Joint British Societies–2 [guidelines on CVD prevention]</td>
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<tr>
<td>MI</td>
<td>myocardial infarction</td>
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<td>NCEP ATP III</td>
<td>National Cholesterol Education Program—Adult Treatment Panel III</td>
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<td>NRTI</td>
<td>nucleoside reverse transcriptase inhibitor</td>
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<td>PI</td>
<td>protease inhibitor</td>
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<tr>
<td>PPARα; PPARγ</td>
<td>peroxisome proliferator-activated receptor–alpha (–gamma)</td>
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<tr>
<td>PROACTIVE</td>
<td>PROspective pioglitAzone Clinical Trial In macroVascular Events</td>
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<tr>
<td>RCT</td>
<td>randomized controlled trial</td>
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<tr>
<td>SREBP</td>
<td>sterol regulatory element binding protein</td>
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<td>TZD</td>
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<tr>
<td>UKPDS</td>
<td>United Kingdom Prospective Diabetes Study</td>
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<tr>
<td>VA-HIT</td>
<td>Veterans Affairs High-density lipoprotein Intervention Trial</td>
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Normal carotid intima-media thickness (IMT), assessed noninvasively in the brachial artery. The usual technique is to measure flow-mediated brachial artery dilatation by high-resolution ultrasound after arterial occlusion. This process is mediated by endothelial nitric oxide release. Nitroglycerin is administered as control, being a direct stimulus for smooth muscle relaxation. Thirty-seven patients on antiretroviral therapy, 22 of whom were receiving PIs, mainly indinavir and nelfinavir, were studied. Patients on PIs were found to have higher levels of plasma cholesterol (5.7 vs 4.4 mmol/L) and triglycerides (4.4 vs 2.5 mmol/L) and to have impaired flow-mediated vasodilation (FMD) compared with those on other medications (2.6%±4.6% vs 8.1%±6.7%; P=0.005). No differences were observed in vasodilatation induced by nitroglycerin. In this study, the reduction in FMD appeared to be partly explained by lipid and lipoprotein abnormalities.11

There is no doubt that carotid intima-media thickness (IMT), assessed by high-resolution B-mode ultrasound, is among the best validated surrogate end points and has been shown to correlate strongly with risk of future cardiovascular events.12 Fifty-nine HIV patients were studied with carotid ultrasound.13 Of these patients, 28 had been on PIs for greater than 18 months. Drug-naïve patients matched for age, HIV risk factors, CD4 count, and smoking, together with 16 HIV-negative individuals, were also studied. Patients receiving PIs had higher concentrations of plasma apoprotein B and triglyceride concentrations, and IMT was significantly increased compared with patients not on PIs and normal controls. Significant correlations were described between total cholesterol, HDL cholesterol (negative correlation), apoprotein B, and triglyceride with IMT, pointing to the likely role of the dyslipidemia in explaining the increased IMT.13 These findings support earlier reports of increased carotid IMT abnormalities in patients receiving PIs compared with those naïve to PIs and age- and body mass index (BMI)-matched HIV negative individuals. These cross-sectional analyses have been extended by a prospective study of the progression of IMT over 12 months in HIV patients. In HIV-positive patients (n=121), progression of IMT was significantly greater compared with a control group of 27 age- and sex-matched HIV negative controls.

Coronary artery calcification score has been assessed by spiral CT in 98 black HIV patients, 55 of whom were receiving PIs. Recruited from the AIDS Link to IntraVenous Experience (ALIVE) cohort, an ongoing prospective study of the natural history of HIV infection among injection drug users in Baltimore.16 Patients on PIs had higher total and low-density lipoprotein (LDL) cholesterol, which correlated with the duration of PI usage and higher coronary calcium scores.

**METABOLIC CHANGES IN PATIENTS WITH HIV/AIDS**

HIV/AIDS patients develop metabolic abnormalities that are similar in many ways to those seen in the metabolic syndrome. The metabolic syndrome (synonyms: syndrome X, syndrome of impaired insulin sensitivity, insulin resistance syndrome, Reaven’s syndrome) is a constellation of CVD risk factors in an individual, secondary to genetic and environmental factors such as obesity, particularly central obesity. A major abnormality is thought to be resistance of target tissues to insulin-mediated glucose uptake. Indeed, as has been pointed out, insulin resistance represents a major underlying abnormality driving CVD. The “gold standard” measurement of insulin sensitivity is the glucose clamp technique. Exogenous insulin is infused and plasma glucose is clamped at a fixed concentration by glucose infusion. At steady state, the glucose infusion rate equals glucose disposal, a measure of overall insulin sensitivity.18

In the metabolic syndrome, originally defined by the World Health Organization (WHO), an important criterion was that the individual should be in the highest quartile of the population for insulin resistance.19 Although there are simpler measures of insulin resistance, other than the glucose clamp, derived from fasting glucose and insulin, these assessments are not generally available. More recently, the NHLBI in the USA1 and the IDF2 have developed more simple clinical definitions. The cluster of cardiometabolic risk factors, hypertriglyceridemia, low HDL cholesterol, hypertension, raised fasting glucose or frank diabetes, and increased waist circumference was defined by the NHLBI to help the physician identify the metabolic syndrome without the need for measures of insulin and insulin sensitivity. An individual having three or more factors has the syndrome. The identification of such individuals enables effective targeting for risk factor management in primary prevention of CVD.1

In a meta-analysis based on seven populations using the Adult Treatment Panel III of the National Cholesterol Education Program (NCEP ATP III) definition, the estimated relative risk for CVD was 1.65. The metabolic syndrome is also associated with increased risk of diabetes, the hazard ratio being 2.99 in the same meta-analysis. Important analyses of data from...
studies such as INTERHEART? (not an acronym) show that central obesity measured by waist circumference is a better predictor of CVD risk than obesity as measured by the BMI. Taking these developments into account, the IDF has proposed that central obesity should be a prerequisite for the clinical diagnosis together with any two of the other factors.2

**INSULIN RESISTANCE IN HIV/AIDS PATIENTS**

HIV/AIDS patients receiving HAART medication containing PIs develop insulin resistance. In a 5-year cohort study of the effects of PIs, up to 60% of patients developed impaired glucose tolerance (IGT) or more rarely frank diabetes.22 In the DAD study, the overall prevalence of diabetes was 2.5%23 and in a univariate model, all treatment regimens were associated with an increased risk of diabetes when compared with drug-naive patients.

Detailed studies of glucose metabolism in HIV patients before and after therapy with PIs and also a group of normal subjects have been reported.24 Before PI therapy, fasting glucose in patients was similar to controls, 4.69 mmol/L vs 4.96 mmol/L. After treatment, fasting glucose rose significantly to 5.49 mmol/L (P<0.001). There was also a significant increase in fasting insulin (111 vs 90 pmol/L, P<0.001), indicating the development of insulin resistance. Further analyses showed a decrease in insulin sensitivity of approximately 50% and of pancreatic β-cell function of approximately 50%. First-phase insulin response decreased by 25%. Of interest, plasma turnover of nonesterified fatty acids was increased, which may have contributed to the insulin resistance. The authors concluded that instigation of the treatment with PI-containing regimens was associated with the development of peripheral insulin resistance in skeletal muscle and adipose tissue and in addition there was impairment of β-cell function, which led to failure to fully compensate by increasing insulin production.24

Hyperinsulinemia, insulin resistance, and type 2 diabetes are commonly seen in patients with lipodystrophy associated with HIV/AIDS, as is the case in other forms of lipodystrophy. Type 2 diabetes was found in 7% of patients with lipodystrophy compared with 0.5% in controls matched for age and BMI.25 In the same report, IGT was present in approximately 35% compared with 5% in matched controls.

The mechanisms of these changes in insulin and glucose metabolism remain to be fully explained. Altered flux of other fuel substrates, particularly free fatty acids (FFA), are likely to be important. Increased FFA lead to increased FFA oxidation in the liver and increased gluconeogenesis.26 Increased FFA flux to muscle leads to increased FFA oxidation and decreased glucose utilization. Both of these effects will lead to increase in insulin production and hyperinsulinemia. Increased hepatic and skeletal fat are commonly seen in this situation of insulin resistance and hyperinsulinemia.27,28

Increased FFA flux was described in a small group of patients after starting HAART therapy.24 Increased rates of lipolysis leading to increased FFA turnover have also been described by another group.29 These effects may be, in part, explained by reduction in the important adipokine, adiponectin, which normally would suppress adipose tissue lipolysis.30 Another important regulator of FFA metabolism, insulin resistance, and glucose metabolism is peroxisome proliferator-activated receptor–gamma (PPARγ). PPARγ expression has been shown to be reduced in subcutaneous adipose tissues in HIV/AIDS patients with lipodystrophy due to altered expression of the adipogenic factor sterol regulatory element binding protein (SREBP)-1.31

Protease inhibitors (eg, amprenavir, indinavir, nelfinavir, and ritonavir) have been shown to have important direct effects on glucose and insulin metabolism. In in vitro studies, insulin-mediated glucose uptake was reduced in skeletal muscle and adipocytes by nelfinavir.32 The mechanism of these effects is likely to be reduced glucose transport by glucose transporter 4 (GLUT-4).33 In vivo studies in normal volunteers, indinavir reduced glucose disposal during euglycemic hyperinsulinemic clamp studies.34

To what extent increased insulin resistance in HIV patients will lead to frank diabetes awaits long-term follow-up. There does seem to be an increased prevalence, but much less than the prevalence of IGT. For diabetes to develop β-cell failure, it is necessary to reach a stage such that hyperinsulinemia can no longer compensate for the insulin resistance.

**DYSLIPIDEMIA IN HIV/AIDS**

Dyslipidemia is common in HAART-treated patients, but the mechanisms are complex and multifactorial, involving, among other factors, the stage of HIV infection, nutritional status, the type of pharmacological therapy, the presence of insulin resistance and lipodystrophy, and genetic factors, eg, apoprotein E genotype or the presence of familial dyslipidemias (reviewed in references 35 to 37). In asymptomatic
individuals with HIV, HDL cholesterol falls. This could relate to a reduction in the major protein of HDL, apoprotein A1. In symptomatic individuals, HDL cholesterol falls further together with an increase in triglycerides. At this stage, plasma cholesterol concentrations may fall, but there is a shift in LDL density distribution toward smaller, denser particles. The mechanisms for these changes are not fully understood, but correlations have been described between triglycerides and B subunit microglobulin, a marker of immune activation, and also with the cytokines, tumor necrosis factor--alpha (TNFα), and interferon gamma.

Dyslipidemia associated with HAART therapy was first reported with the PI ritonavir when added to NRTIs. As early as 1 week after starting therapy, cholesterol concentrations increased by 30% to 40% and triglycerides by 200%. These changes rapidly reversed after stopping the medication. Similar changes have been described in HIV-negative volunteers given the drug. Other PIs produce similar, but less pronounced, lipid changes. For instance, the risk of hypercholesterolemia in patients treated with ritonavir increased 20-fold with ritonavir compared with 9-fold with nelfinavir and 4-fold with indinavir (reviewed in references 35-37).

Detailed lipid and lipoprotein analyses have been reported in patients receiving PIs compared with those not taking these preparations, showing not only quantitative, but also qualitative changes in lipoproteins. Total cholesterol (5.68 vs 4.43 mmol/L, \( P=0.007 \)) and triglycerides (4.42 mmol/L vs 1.98 mmol/L; \( P=0.009 \)) were significantly increased in patients on PIs. In addition, total and large very-low-density lipoprotein (VLDL) concentrations were increased, as were IDL. In this situation, potentially atherogenic cholesterol is carried on lipoproteins other than LDL and a good measure of this is non-HDL cholesterol, which was 4.65 mmol/L vs 3.34 mmol/L (\( P=0.017 \)).

The effects of HAART therapy on lipid and lipoprotein concentrations have been confirmed in large, prospective studies such as the DAD study. Patients receiving NRTIs alone had similar cholesterol concentrations to those who were drug-naive, while patients receiving combination therapy with all three drug classes had the highest cholesterol concentrations after controlling for other risk factors. The risk of developing hypercholesterolemia was related to cumulative antiretroviral therapy exposure time. Similar findings were found for plasma triglycerides. Increases in lipoprotein (a) and decreases in HDL cholesterol have also been described. Efavirenz, a non-NRTI, also increases plasma cholesterol concentrations. No lipid effects have been observed with NRTIs and nevirapine.

The mechanisms of dyslipidemia remain to be fully documented. Insulin resistance is an important factor leading to increased hepatic VLDL production. PIs have direct effects on the production of triglyceride-rich lipoproteins in cultured cells. Furthermore, ritonavir has been shown to activate lipogenic genes under the control of SREBP-1c, possibly through retarding the degradation of the active, cleaved form of SREBP-1c. PIs may also inhibit hepatic degradation of apoprotein B, which would favor increased VLDL synthesis. Indeed, increased apoprotein B concentration has been described in patients on combination therapy. As there is one molecule of apoprotein B per lipoprotein particle, this indicates an increased number of potentially atherogenic particles. Furthermore, there is a shift in LDL density toward smaller, denser particles, which are thought to be more atherogenic.

**LIPODYSTROPHY IN HIV/AIDS PATIENTS**

As many as 50% of patients develop abnormalities of body composition characterized by subcutaneous lipodystrophy mainly affecting the face and limbs, together with the accumulation of abdominal fat. Increased visceral fat is an important part of the metabolic syndrome and contributes to the metabolic effects of insulin resistance and dyslipidemia. An important determinant of lipodystrophy is the type and duration of HAART therapy, however, a minority of patients have been described with body fat composition-al changes who were naïve to antiretroviral therapy. The regimen most strongly related to the development of lipodystrophy is combination therapy with NRTIs (particularly stavudine) and PIs.

The mechanisms underlying these abnormalities that are associated with more marked metabolic abnormalities of dyslipidemia and insulin resistance as well as cosmetic concerns remain to be fully elucidated. In vitro studies point to effects of PIs on adipocyte differentiation and lipogenesis and increased lipolysis, possibly through blocking PPARγ activation, which is important in adipogenesis. NRTIs in vitro studies have been shown to affect adipocyte differentiation and adipogenesis and lipolysis as seen with the PIs, but the effects appear to be synergistic with PIs. There is some evidence that the effects of NRTIs on adipose tissue may be due to depletion of mitochondrial DNA and inhibition of mitochondrial DNA polymerase gamma in adipose tissue.
LIPID-MODIFYING DRUG THERAPY IN HIV/AIDS

The addition of therapeutic agents is always on top of best endeavors with diet and lifestyle. These are well described elsewhere. Hypertension, an important component of HAART-therapy–induced CVD risk factors, should be treated along current guidelines. Important considerations to take into account when deciding on lipid-lowering therapy are: the absolute CVD risk, the nature of the dyslipidemia, comorbidities such as significantly impaired hepatic or renal function, the nature of HAART therapy (does it contain a PI?), the lipid-modifying capacity, and the evidence base from outcome trials behind a particular drug.

Various ways of determining absolute CVD risk are available based on the major risk factors, hypertension, smoking, cholesterol, and age. These risk assessments are largely based on data derived from the prospective Framingham study. A risk chart that forms part of the Joint British Societies (JBS 2) guidelines defines a 20% 10-year CVD risk as meriting drug therapy.

It is important to note that these charts are used in the assessment for primary prevention only. In patients with established clinical vascular disease, drugs are considered in most individuals. Whether these risk charts are applicable to HIV/AIDS patients is unknown. It is likely that they will underestimate risk; the author, for his part, has a low threshold for instigating drug therapy given the nature of the dyslipidemia and the evidence presented above in relation to surrogate measures of atherosclerosis together with the emerging data from the DAD study.

STATINS

These drugs are specific competitive inhibitors of β-hydroxy-β-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-determining enzyme in cholesterol synthesis. As a result, hepatic cholesterol is reduced, with consequent increased synthesis of LDL receptors and increasing removal of plasma LDL. These effects are well-understood at the molecular level, and it is reassuring that the drugs act at a major regulatory step in cholesterol metabolism. Statins can reduce LDL cholesterol concentrations by up to 60% and are the most effective drugs available. They have also been proved to be safe and well-tolerated in long term, randomized controlled trials (RCTs). Their introduction enabled definitive CVD outcome trials to be performed, which demonstrated conclusively that LDL-lowering is associated with highly significant reductions in all-cause mortality and important CVD outcomes including MI and stroke. RCTs of statins have been performed in patients with established CVD where risk of subsequent events is high, and also in asymptomatic patients (eg, hypercholesterolemia and hypertensive patients, and patients with type 2 diabetes) for the prevention of first events (reviewed in 41).

Fourteen trials involving 90 056 participants were combined in a meta-analysis by the Cholesterol Treatment Trialists’ (CTT) Collaborative Group. In this important analysis, the reduction in events was proportional to the absolute reduction in LDL cholesterol: a 1-mmol/L reduction resulted in a 19% reduction in coronary mortality, a 17% reduction in fatal or nonfatal MI, and a 12% reduction in overall mortality. Importantly, the relative risk reduction was independent of baseline LDL cholesterol concentrations. These findings have contributed to a relatively new concept in clinical management, that it is the absolute CVD risk of the individual that is the prime determinant for lipid-lowering therapy rather than the lipid profile, although clearly the latter is important in determining drug dosage.

Although RCTs have shown enormous benefits with statins, a significant residual risk remains. The question arose whether more intensive LDL-lowering would result in further benefit. A meta-analysis has examined data from four recent trials of intensive versus conventional statin therapy in patients with acute coronary syndromes or with stable coronary disease involving 27 584 patients. More intensive statin therapy (higher dose or more potent drug) was associated with a further 16% reduction in coronary death and MI (hazard ratio [HR], 0.84; 95% CI, 0.77-0.91; P<0.0001). In addition, there was an 18% further reduction in stroke (HR, 0.82; 95% CI, 0.71-0.96; P=0.012). On the basis of these trials, the NCEP ATP III provided further guidance on goals of therapy for those at highest risk of CVD: statin therapy may be started regardless of baseline LDL cholesterol with an LDL cholesterol goal <1.8 mmol/L.

The atherogenic lipoprotein profile typical of insulin resistance is characterized by moderate hypertriglyceridemia, low HDL cholesterol, and a shift in the density of LDL toward smaller, denser particles. In this situation, the calculation of LDL cholesterol underestimates not only the number of LDL particles, but also cholesterol carried on other potentially atherogenic particles, such as remnant lipoprotein particles. A useful measurement in this situation is non-HDL cholesterol (total cholesterol minus HDL cholesterol), which reflects the cholesterol carried on...
The primary effect of statins is to lower the plasma concentration of apoprotein B–containing lipoproteins and these drugs are first-line therapy even in the situation of mixed dyslipidemia with increased triglyceride as well as cholesterol. In general terms, higher doses of statins are required to achieve goals of therapy when plasma triglycerides are also raised. When the LDL goal is achieved, but triglycerides remain raised (>2.3 mmol/L, 200 mg/dL) a useful secondary goal is non-HDL cholesterol <3 mmol/L. In this situation, the dose of statin should be increased. When the maximum dose of statin (or maximum tolerated dose) is not sufficient to achieve the appropriate goal of therapy, combination therapy may be indicated. A very useful approach is to add ezetimibe, a specific inhibitor of intestinal cholesterol absorption. When added to a statin, further LDL cholesterol reductions of approximately 20% can be achieved. To put this into context, each doubling of statin dosage is associated with an average further 6% LDL reduction, so it is clear that the addition of ezetimibe is roughly equal to three dose titrations of the statin. This effect is very useful when only low doses of statin are tolerated or when low doses are used for safety reasons.

The choice of statin is important when coadministered with PIs. PIs inhibit cytochrome (cyp) 450 3A4, which metabolizes several commonly used statins, atorvastatin, simvastatin, and lovastatin, plasma levels increase and therefore also the risk of important side effects such as myositis. However, in practice, in the author’s experience, atorvastatin is generally well tolerated if the dose is kept low. In theory, fluvastatin and pravastatin are the statins of choice as they are not metabolized through cyp 450 3A4. Fluvastatin is metabolized through cyp 2C9, while pravastatin is not metabolized through the cytochrome system. However, these drugs are relatively less powerful and will not achieve goals of therapy in many patients. Rosuvastatin, the newest addition to the statin class, may have important advantages as it is highly effective and is not metabolized through cyp 3A4, but cyp 2C9 cyp 2C19.

The IBS 2 guidelines suggest a total cholesterol goal <4 mmol/L and an LDL cholesterol goal <2 mmol/L. Importantly, these guidelines also emphasize the importance of the percentage reduction in LDL, which should be at least 30%, or the achievement of goal, whichever is greater. There is no reason to suppose that HIV/AIDS patients will respond differently to statins compared with the general population, and the small studies that have been performed confirm this.

**FIBRATES**

The fibrates, which are agonists for peroxisome proliferator-activated receptor–alpha (PPARα), have only modest effects in reducing total and LDL cholesterol. Their main effects are to reduce triglycerides and increase HDL cholesterol. The evidence-based from RCTs to support fibrate therapy is not consistent. Gemfibrozil has been used in a CVD primary prevention trial and a secondary prevention trial. These studies showed significant positive benefit for the drug. However, the populations studied in these trials also respond well to statin therapy. However, in the Bezafibrate Infarction Prevention (BIP) trial, a CVD secondary prevention trial, there was a trend toward reduction in the primary end point, but this did not reach statistical significance. In a post hoc analysis, it was found that hypertriglyceridemic subjects appeared to benefit. In a more recent analysis, patients fulfilling the criteria for metabolic syndrome showed benefit.

A recent study assessed the effect of fenofibrate in a specific diabetic population. In this combined primary and secondary CVD outcomes study, the primary end point (coronary heart disease [CHD] death and nonfatal MI) did not reach statistical significance. Nonfatal MI was reduced significantly, but coronary mortality showed a nonsignificant increase. Total cardiovascular events, (cardiac death, MI, stroke, and coronary and carotid revascularization) were significantly reduced, but total mortality was nonsignificantly increased with fenofibrate. The conflicting results of the Fenofibrate Interventtion and Lowering in Diabetes (FIELD) trial are puzzling.Baseline HDL cholesterol in FIELD was 1.1 mmol/L, whereas in the Veterans Affairs High-density lipoprotein Intervention Trial (VA-HIT), which showed a positive outcome, it was lower, at 0.8 mmol/L. Perhaps this lipid phenotype was better suited for intervention with the fibrate. In FIELD, fenofibrate had a disappointing long-term effect on HDL, with a barely 2% increase by the end of the study. Furthermore, the reduction in LDL was only modest.

Other confounders may be the adverse effect of fenofibrate in increasing homocysteine levels and higher...
How can excess cardiovascular morbidity be minimized in HIV-infected individuals? - Betteridge

THE STATIN-INTOLERANT PATIENT

Although among the best tolerated of all drugs, some patients are intolerant of statins.45 The most common reason for discontinuation, in the author's experience, is muscle aches, generally without elevation of creatine phosphokinase (CPK). Full-blown myositis with muscle pain/tenderness and a CPK greater than 10-fold elevated is becoming increasingly rare if appropriate care is taken, particularly in relation to drug interactions. It is important to emphasize the importance of the statin therapy to the patient and that the statin is unlikely to be at fault. However, sometimes it is necessary to reduce the dose, and in some cases the patient will not take the drug at all. If a small dose of statin is tolerated (in these circumstances, I prefer the water-soluble statin pravastatin) and LDL cholesterol is not to goal, then the addition of ezetimibe is useful, providing a further 20% LDL-lowering.41 On the other hand, ezetimibe on its own is less useful, producing a 15% LDL reduction, although response will vary depending on the individuals ability to absorb cholesterol.

As described above, outcome data with fibrates are mixed. Gemfibrozil is the fibrate with the best outcome data, but should not be combined with a statin. If the major abnormality is a high LDL cholesterol, gemfibrozil will have little impact. Bezafibrate has a better impact on LDL, as well as increasing HDL-cholesterol and decreasing triglyceride, but the clinical benefits from RCTs relate only to post hoc analyses.

The bile acid sequestrants cholestyramine and colestipol reduce LDL cholesterol by up to 30% and their use is supported by RCTs,41 but they are not well tolerated. In addition, in patients already on multiple-drug therapies, timing of administration of the resin is difficult as they can interfere with the absorption of other drugs. They need to be given at least 1 hour before or at least 4 hours after other medications.41

Nicotinic acid, theoretically the best lipid-modifying agent, is not commonly used because of poor tolerability.41 There is no definitive RCT data to guide therapy, but there are studies showing benefit on surrogate end points. Nicotinic acid is currently the best drug for increasing HDL cholesterol, it is better tolerated as an extended release preparation, particularly in terms of flushing. Furthermore, a compound that significantly blocks the flush is in clinical trial. It remains to be seen whether this will improve tolerability in the long term. At the present time, most physicians use extended-release nicotinic acid at doses of 1 to 1.5 g/day to lower triglycerides and increase HDL, usually in combination with a statin. On its own, higher doses are required to reduce LDL effectively. There is a report of the use of nicotinic acid in HIV/AIDS patients receiving potent antiretroviral therapy where the drug was apparently well-tolerated.51

TREATMENT OF SEVERE HYPERTRIGLYCERIDEMIA

Patients with HIV/AIDS may develop severe hypertriglyceridemia with fasting serum triglyceride concentrations over 10 mmol/L and sometimes in the 20 to 30 mmol/L range or higher. Triglyceride concentrations of this order result from a combination of exogenous and endogenous particles, namely chylomicrons and VLDL. Increased hepatic output from the liver, together with postprandial absorption of chylomicrons, swamps the clearance pathway through the enzyme lipoprotein lipase. Other secondary causes, for example, diabetes, hypothyroidism, high alcohol intake, and renal disease, should be excluded.41

Severe hypertriglyceridemia may be associated with recurrent attacks of abdominal pain and sometimes pancreatitis. This lipid abnormality may interfere with the assay for amylase in some laboratories. Hepatosplenomegaly due to accumulation of lipid-laden macrophages may occur. Rarely, there may be memory disturbances and lack of concentration. Some patients develop spectacular skin eruptions, eruptive xanthomata, which appear as crops of raised pinkish, yellow spots over elbows, knees, and buttocks.41 Hypertriglyceridemia may interfere with the measurement of other analytes such as hemoglobin, bilirubin, and liver transaminases, and, by decreasing water volume in plasma, can lead to artificially low sodium measurement.

Treatment of massive hypertriglyceridemia is of some urgency given the risk of pancreatitis. It is important that the patient is counseled to follow a low total fat diet together with reductions in alcohol and refined carbohydrate. In addition, high doses of omega-3 fatty acids...
(fish oil) are useful together with a fibrate or nicotinic acid derivative. As diet and lifestyle measures progress it is often possible to stop the fibrate. If significant mixed lipemia persists, a statin is indicated.

**TREATMENT OF INSULIN RESISTANCE AND TYPE 2 DIABETES**

Insulin-resistant patients are at increased risk of developing frank diabetes. In RCTs in the non-HIV population, lifestyle measures of increased physical activity and weight reduction have been shown to reduce progression to diabetes. In addition, drugs used for the treatment of type 2 diabetes (metformin, acarbose, and thiazolidinediones [TZDs]) have been shown to reduce progression to diabetes. Metformin has been reported to reduce insulin resistance and visceral adiposity in HIV patients with central obesity and hyperinsulinemia. The TZD rosiglitazone has been studied in HIV patients, and improvements in insulin sensitivity were observed probably through its effect in increasing the adipocytokine adiponectin, but conflicting findings were reported on lipoatrophy. Rosiglitazone therapy was associated with increases in total and LDL cholesterol, adverse effects also seen in the non-HIV population. Whether progression to diabetes in HIV patients can be prevented with such interventions is not known and these drugs are not currently licensed for this indication.

Metformin is first-line treatment for established diabetes, but should not be used when there is significant hepatic or renal disease; it improves glycemic control, but is weight-neutral. In a small subgroup of obese patients in the United Kingdom Prospective Diabetes Study (UKPDS), metformin therapy was associated with a reduction in CVD events. TZDs are also very useful agents either alone in patients intolerant of metformin or where it is contraindicated. They are effective in improving glycemic control and insulin sensitivity through activation of the transcription factor PPARγ. Unlike metformin, weight increase is associated with TZD therapy. TZDs can lead to fluid retention and should be avoided in patients with heart failure. In the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROACTIVE), pioglitazone was associated with a reduction in major CVD events in diabetic patients with symptomatic CVD although the primary end point (major CVD events plus revascularizations) did not reach significance. In the Carotid intima-media thickness in Atherosclerosis using pioglitazOne (CHICAGO) trial, pioglitazone was shown to reduce progression of carotid IMT compared with a sulfonylurea. TZDs can be combined effectively with metformin.

Sulfonylureas, which increase insulin secretion, are effective in improving glycemia. However they are used less as first-line agents because of earlier primary failure compared with agents that improve insulin sensitivity. If glycemic control cannot be maintained with oral agents, insulin therapy is required. An effective way of introducing insulin therapy is to use a single injection of long-acting insulin at bedtime titrated to achieve normal fasting glucose concentrations with continuation of metformin therapy during the day. TZDs can be used similarly, but although licensed for use in combination with insulin in the USA, they are not currently licensed in Europe. The goal of therapy for glycemic control is the best achievable for the individual, and JBS 2 guidelines suggest a hemoglobin A1c <6.5%.

**CONCLUSIONS**

HIV/AIDS patients on HAART therapy develop important metabolic abnormalities that resemble the metabolic syndrome, which in the general population is associated with increased risk of CVD and diabetes. Surrogate measures of atherosclerosis and prospective epidemiology studies point to increased CVD risk. Given the chronic nature of HIV/AIDS in developed economies, effective management of these metabolic abnormalities is likely to reduce morbidity and mortality from CVD.

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What can be done about effusive tuberculous pericarditis in HIV-seropositive patients?

Adam S. Malin*, PhD, FRCP; James G. Hakim†, FRCP

*Respiratory Unit - Royal United Hospital - Bath - UK
† Department of Medicine - University of Zimbabwe - Avondale - Harare - ZIMBABWE

The early effusive stage of tuberculous pericarditis (TBP) is life-threatening despite early intervention with antituberculous treatment (ATT). Data from interventional studies in Africa support the use of adjunctive corticosteroids in human immunodeficiency virus (HIV) and non-HIV populations; their use, however, remains controversial. Rapid identification and treatment of TBP is needed in order to minimize the impact of tamponade in the early effusive stage and subsequent constriction. Where resources are available, diagnosis requires echocardiographic confirmation of the effusion, pericardiocentesis for microbiological confirmation, and trimodal treatment including ATT, antiretroviral therapy (ART), and adjunctive corticosteroids. There is no evidence for prolonging the course of ATT beyond the standard 6 months. ART should start early for those with advanced HIV, but be deferred for those with CD4 T cell counts >200 cells/mm³.

Keywords: tuberculosis; tuberculous pericarditis; HIV infection; acquired immunodeficiency syndrome; antiretroviral therapy; prednisolone; Africa

Address for correspondence:
Dr Adam S. Malin, Respiratory Unit, Royal United Hospital, Bath BA2 2BX, UK
e-mail: adam.malin@rub-bath.swest.nhs.uk

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Tuberculosis (TB) is a disease of superlatives. It is the foremost cause of death from curable infection with an estimated 8.9 million new cases and 1.7 million deaths¹,² (malaria, the second commonest cause of death from infection, accounts for just over 1 million). Someone in the world is infected with Mycobacterium tuberculosis (MTB) every second and over 1/3 of the world’s population is infected with MTB.³ There has been a steady global increase in TB since 1990. Africa only accounts for 29% of global TB, but the estimated 0.6% annual global increase is due almost entirely to the rise of TB in Africa (Figure 1).¹

Africa has the highest TB incidence rate in the world (356 cases per 100 000 population per year) and this epidemic is in part due to the spread of the human immunodeficiency virus (HIV). Africa also has the highest proportion of TB cases coinfected with HIV (34% in Africa versus 13% globally)² and TB is the commonest opportunistic infection complicating HIV. This TB/HIV “cruel duel” is particularly invidious as each infection, in turn, accelerates the progression of the other.¹,²,⁴ As a result of HIV, all forms of extrapulmonary TB have increased, including tuberculous pericarditis (TBP). Of those with TBP, the majority are HIV seropositive (67%-92%) and survival is worse in those who are coinfected with HIV.⁵

So what can be done about HIV-seropositive patients with effusive TBP? This article reviews current understanding concerning diagnosis and treatment of HIV-related TBP. Key issues are discussed, including duration of antituberculous therapy (ATT), when to start antiretroviral therapy (ART), and the controversies
surrounding the use of adjunctive corticosteroids. The case favoring corticosteroids includes a single HIV TBP study from Zimbabwe and also a review of parallel data from non-HIV TBP corticosteroid trials in South Africa.

**DIAGNOSIS OF TBP**

**Definitive diagnosis**

Definitive confirmation requires identification of MTB in the pericardial fluid or pericardium. Diagnostic yield is improved by direct inoculation of pericardial fluid into double-strength Kirchner culture medium. However, pericardial fluid microbiological culture is not always achievable and the diagnosis is likely if pericardial biopsy tissue shows caseating granulomata. An important caveat is that granulomata in sarcoidosis may sometimes be caseating, particularly where there is a strong inflammatory component. The overall clinical picture must be taken into account before dismissing this differential diagnosis. Despite best endeavors, positive MTB culture cannot always be obtained (38% to 60% in those with effusive TBP). Moreover, where there is sufficient clinical suspicion a presumptive diagnosis of TBP must be made and empirical treatment started immediately pending the result of culture.

**Presumptive diagnosis**

The clinical suspicion of TBP rests on a combination of pericardial disease and the general features of TB (fever, night sweats, weight loss, and contact with a patient with open TB). The clinical presentation of TBP is variable and includes: acute pericarditis with or without effusion; cardiac tamponade; acute constrictive pericarditis; subacute constriction; effusive-constrictive or chronic constrictive pericarditis, and pericardial calcification. The confirmation of the presence of pericardial effusion depends on clinical, ECG, chest x-ray, and echocardiographic findings. Other imaging modalities such as computed tomography scanning and magnetic resonance imaging of the thorax may give more detailed information regarding the distribution of effusion, loculation, the presence of fibrin, adhesions and masses, calcification of the pericardium, and the presence of additional lung pathology. Where this range of investigations is available and there is a clinical suspicion of pericarditis, the demonstration of pericardial disease is relatively straightforward. In resource-limited countries, diagnosis relies upon clinical presentation, ECG, and chest x-ray findings. Echocardiography is available in some centers, adding greatly to diagnostic accuracy and permitting distinction between degrees of fibrinous deposition.

Circumstantial evidence in favor of TBP includes the presence of pericarditis and evidence of MTB at...
another site. Useful investigations include: three sputum samples in those with a productive cough; bronchial washings if there is evidence of a pulmonary infiltrate; the enzyme-linked immunosorbent spot (assay) (ELISPOT) test\(^{10}\) (an immunological whole-blood assay looking for TB-specific lymphocyte responses); and polymerase chain reaction (PCR) for MTB. Early detection of MTB complex (\(M\) tuberculosis, \(M\) bovis, and \(M\) africanum—all species that cause TB) can be expedited with a combination of rapid liquid culture using radiometric growth detection and DNA probes. Molecular techniques can also be used to detect rifampicin resistance, the key marker of multidrug-resistant TB. Additional supportive evidence includes direct pericardial fluid analysis of elevated adenosine deaminase levels (ADA). This is in contrast to malignant effusions where ADA is low and carcinoembryonic antigen is high. Interferon gamma concentration and pericardial lysozyme have also been used as diagnostic indicators.\(^8\)

Mantoux testing is rarely helpful as it may be negative in the immunocompromised. Moreover, those already vaccinated with BCG (bacille Calmette-Guérin vaccine) or who have had previous TB can react strongly. It is most useful in BCG-naive populations where there is a low incidence of TB or the individual has a previous known negative tuberculin skin test. The ELISPOT is more helpful in this respect as the assay only measures a response to proteins from the MTB complex and not BCG or opportunistic mycobacteria such as \(Mycobacterium avium intracellulare\) (MAI). Thus, a positive result indicates either active or previous infection with MTB complex with no false positives in BCG vaccines. This is very useful in countries with a low incidence of TB, but a high BCG vaccination rate.\(^{10}\)

**TRIMODAL TREATMENT**

**Duration of ATT for HIV-related TBP**

ATT was introduced in the 1940s. Prior to this TBP was invariably fatal. ATT proved to be effective for most cases, with a steady decline in the case-fatality rate to about one third with the introduction of rifampicin in 1968\(^{11}\) and more recent estimates put the case-fatality rate at 8\% to 17\%.\(^{12}\) There is no evidence regarding an optimum duration of treatment for TBP or other forms of extrapulmonary TB in those coinfected with HIV. Indeed, it would seem that HIV-infected patients respond similarly to non-HIV TB cases. Therefore, the World Health Organization (WHO) and others recommend 6 months treatment duration using standard short-course regimens containing rifampicin and isoniazid.\(^{13-15}\) This is in contrast to central nervous system disease where 12 months is recommended.\(^{15}\)
Pericardiocentesis and pericardiectomy

As in non-HIV TBP, pericardial tamponade requires pericardiocentesis, repeated as necessary. In non-HIV TBP, early open surgical drainage showed a reduction in the need for repeat pericardiocentesis, but this has not been examined in HIV-related TBP. Those with severe symptomatic constriction require pericardiectomy irrespective of HIV serostatus. In non-HIV TBP, operative mortality was 10% in one study. Thus, it would be of great benefit if adjunctive corticosteroids reduced progression to constrictive TBP this was suggested by the non-HIV TBP constrictive study, but the difference was not statistically significant.

Additional treatment interventions: ART and corticosteroids

Because of high mortality, ART should be used in conjunction with ATT (discussed below). ART should be initiated early for those with advanced HIV, but deferred in those with less advanced HIV disease. Delayed introduction of ART reduces the risk of drug toxicity and immune reconstitution inflammatory syndrome (IRIS). The role of adjunctive steroids is more controversial. Figure 3 shows the survival results from the only randomized controlled trial (RCT) in HIV-related TBP. This was carried out in Harare, Zimbabwe, and included 58 subjects randomized evenly to either adjunctive prednisolone (60 mg daily tapering over 6 weeks) or placebo. There was a survival benefit with 10 deaths in the placebo group and 5 in the prednisolone group. The study population was relatively small, leading some to debate the author’s conclusion in favor of adjunctive corticosteroids. The HIV TBP results are paralleled by two studies using adjunctive corticosteroids in non-HIV TBP. These are discussed below.

Controversies

Corticosteroids in non-HIV TBP

Two RCTs compared corticosteroids with placebo in non-HIV TBP. Both studies were undertaken by Strang and colleagues in Transkei, South Africa. These were carried out between 1980 and 1984 prior to the HIV pandemic affecting that region. The combined data demonstrated a benefit in favor of adjunctive prednisolone in patients with TBP. The first study examined the impact of prednisolone on constrictive TBP in 143 subjects. Although there was a trend in favor of steroids improving survival and reducing the need for pericardiectomy, this was not statistically significant. The second larger study looked at effusive pericardial disease in 240 subjects. All were randomized to adjunctive prednisolone (adult dose of 60 mg daily tapering over 11 weeks) or placebo. There was a 21% reduction in adverse outcomes for subjects receiving steroids (19% versus 40%; \( P=0.003 \)) where adverse outcome was defined as death from pericarditis, pericardiectomy, or subsequent open surgical drainage.

In a Cochrane systematic review, Mayosi and colleagues assessed the three key corticosteroid TBP RCTs—the HIV seropositive study from Zimbabwe and the two non-HIV studies from South Africa. The authors concluded that there was insufficient evidence to recommend adjunctive steroids in the treatment of TBP. Their recommendation has not been generally adopted. The arguments against the use of steroids are as follows.

The role of corticosteroids in HIV-related TBP

In the case of the HIV seropositive study in Zimbabwe, the core argument is based on the selection of relative risk (RR) as the statistical
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analysis at 18 months. This is an analysis of “all-cause death” at a single time point. It does not take into account the preceding data, in particular the relative time to death in the prednisolone and placebo treatment arms. If log-rank chi-square analysis is performed, the difference is highly significant ($\chi^2=8.19$, degrees of freedom $|df|=1$, $P=0.004$). The Kaplan-Meier survival curves also show cause of death (Figure 3). In the first 6 months, deaths were due to MTB infection, either disseminated disease or worsening pericarditis. Deaths beyond 6 months were due to noncardiac, non-TB HIV–related conditions.5

At the time of the study, ART was not available in Zimbabwe. Thus, treatment was limited to ATT with or without prednisolone. Just under half the study population was significantly immunocompromised with CD4 T cell counts <200 cells/mm$^3$. Moreover, by diagnostic definition, all patients had WHO Stage 4 disease (this applies to all forms of extrapulmonary TB). Thus, with the absence of ART, it was not surprising to see subsequent acquired immunodeficiency syndrome (AIDS) deaths unrelated to TBP 1 year after entry into the study. Calculating RR showed no survival benefit between the groups at 18 months. Possible explanations include: (i) there was a survival benefit from prednisolone, but the power of the study was not strong enough to show a difference in RR at 18 months with the study population dying of other HIV-related causes (Type 1 statistical error — rejection of a true hypothesis), (ii) prednisolone simply defers death in those who have a poor prognosis (true benefit, but short-lived), (iii) the survival benefit from prednisolone was present initially, but then lost because of late adverse effects of the prednisolone (as for ii); and (iv) there is no survival benefit from prednisolone (Type 2 statistical error for the log-rank $\chi^2$ test — acceptance of a false hypothesis). Given that many of the deaths occurred early in the study (9 of the 15), a repeat analysis of the survival data looked at the results at 6 months (unpublished data). This showed a survival benefit in the prednisolone group irrespective of the statistical test (Mantel-Cox $\chi^2=6.19$, df=1, $P=0.013$) or RR 0.13 (confidence interval [CI], 0.02-0.94). Similarly, if TB deaths are compared either at 6 months or 18 months, the result is even more significant using both log-rank and RR (data not shown). However, this latter analysis is less robust than “all-cause death” given the uncertainty surrounding cause of death without postmortem data.

The authors favor the first of these explanations. Of the 9 deaths in the first 6 months, all were related to MTB (3 disseminated TB and 6 had active pericardial infection) and 8 of the 9 were in the placebo group. Beyond 6 months, 6 further AIDS-related deaths occurred; 4 in the prednisolone arm and 2 in the placebo arm. None of these were attributed to pericardial constriction or late manifestation of TB. The data at 6 months favor a survival benefit from prednisolone. However, the 18-month data remain moot and this will only be resolved by increasing the power of the study, preferably in a setting where ART is available.

Corticosteroids reduce morbidity

There is strong evidence to show that prednisolone leads to a more rapid reduction of clinical features in HIV-related TBP,5 non-HIV–related TBP,6,7 and HIV-related pleural TB.19 In the Zimbabwe TBP trial, echocardiography suggested a more rapid reduction in pericardial fluid, but the difference was not significant. However, there was an improvement in physical activity ($P=0.02$), a faster resolution of raised jugular venous pressure ($P=0.017$), hepatomegaly ($P=0.007$), and ascites ($P=0.0015$). The 4 cases that developed constrictive pericarditis occurred equally in both groups.5 In the non-HIV–related TBP group, prednisolone reduced the need for repeat pericardiocentesis from 23% to 10% ($P=0.025$).6

A more recent study was carried out in Uganda looking at the role of corticosteroids in HIV-related pleural TB to see if the benefits seen in TBP could be translated to pleural disease. There was a marked improvement in symptoms and signs in the prednisolone group with more rapid resolution of the effusion ($P<0.001$), anorexia ($P<0.001$), cough ($P<0.01$), and weight gain ($P<0.01$). This supports a clear anti-inflammatory benefit in the first weeks of treatment, but did not translate into an overall benefit. There was no survival benefit, but an increase in numbers of Kaposi’s sarcomas in the prednisolone group (4.2 cases/100 person years versus 0 cases/100 person years; $P=0.02$).19

Non-HIV–related TBP

Similar to HIV-related TBP, the Cochrane collaboration systematic review concluded that there was no strong data to support the use of corticosteroids for non-HIV–related TBP. The systematic review calculated relative risk of death for those receiving corticosteroids as being 0.65, but with the 95% CI crossing unity (0.36-1.16), suggesting this difference may have occurred by chance. The review noted that participants on corticosteroids in the effusive study were more likely to be cured at 24 months (alive and symptom-free) than participants on placebo (RR, 0.48; 95% CI, 0.29 to 0.80).18
The original published studies used per-protocol analyses rather than intention-to-treat with exclusion of those who failed to comply with the study protocol (20% and 17.5%, respectively). Groups excluded were those who were incorrectly diagnosed, those who defaulted on treatment, or those who were lost to follow-up. Without an intention-to-treat analysis, this raised the question concerning outcomes of those lost to follow-up. Thus, Mayosi and colleagues conducted a “sensitivity analysis” to explore the potential effect of loss to follow-up always representing a trial death. This worst-case scenario resulted in a nonsignificant result (RR 0.78, 95% CI 0.52 to 1.18).18 Strang and colleagues addressed these issues in a subsequent paper with an additional follow up and outcomes at 10 years. They achieved a very high 10-year follow-up of 96%. The data were reanalyzed on an intention-to-treat basis. All randomized patients were included and factor analysis was performed using a logistic regression model. This allowed pooling of the two studies with stratification of the constrictive and effusive study populations with inclusion of variables associated with survival. Prednisolone conferred an overall survival advantage with a hazard ratio of 0.64 (95% CI, 0.41-0.99, P=0.044). The association was even stronger when only deaths from TBP were assessed (P=0.004).20

Benefits and adverse effects of corticosteroids in the context of HIV

Corticosteroids when given alone will strongly depress the immune response to MTB and may lead to reactivation of latent infection and dissemination. Moreover, corticosteroid-induced immunosuppression in the context of HIV can predispose to opportunistic diseases such as Kaposi’s sarcoma (associated with human herpesvirus-8 infection), herpes zoster, other herpetic infections, Candida and Cryptococcus.19,21 Additional problems include hyperglycemia, hypertension, and dyspepsia. However, corticosteroids are also anti-inflammatory. This property is put to good use where the inflammatory component is particularly damaging. Corticosteroids confer a definite survival benefit in severe HIV-related Pneumocystis pneumonia (PCP).22 There is circumstantial evidence showing benefits in some of the non-HIV–associated forms of extrapulmonary TB including: central nervous system disease,13-15 pericarditis,13-15,20 lymphadenitis compromising the airway, and ocular and ureteric disease.15 Evidence is less strong for pleural TB,15,19 and there is no evidence in favor of corticosteroids for pulmonary disease.

The decision to add corticosteroids to ATT depends on the balance of clinical benefit against risk. There are compelling arguments for the use of corticosteroids in HIV-related TB. They may suppress unwanted inflammation within the MTB-infected organ, but also reduce systemic inflammation. TB is known to cause a high degree of immune activation resulting in increased HIV replication in vitro23 and in vivo.4 Additional laboratory data support a mechanism whereby proinflammatory cytokines such as tumor necrosis factor–alpha (TNF-α) result in increased levels of the transcription factor nuclear factor kappa B (NF-κB). This can bind to the viral genome and promote transcription of proviral DNA. Corticosteroids suppress this pathway by inducing a transcription inhibitor, I-κB.24 A study in asymptomatic HIV subjects showed that prednisolone reduced immune activation and led to a sustained increase in CD4 T cell counts.25 In the TBP study in Zim-
improvement in immune function. Paradoxically, this may result in an apparent worsening of disease giving the impression of treatment failure. However, it may also be due to a wide variety of hypersensitivity reactions as a consequence of IRIS. This is the body’s restored ability to mount an inflammatory response following immune recovery. Typically, IRIS occurs within 2 to 12 weeks of starting ART, but it can occur as early as 5 days. Clinical features include: fever, abscesses, lymph node enlargement, skin rash, arthritis, and worsening pericardial disease. It occurs more frequently when ART is added to patients who have recently started ATT and is less common if ART is deferred by 8 weeks. Another risk factor is a CD4 count below 50 cells/mm³.

Combining TB and ART treatment

There are problems with combining TB and ART regimens. There are no significant difficulties with nucleoside reverse transcriptase inhibitors (NRTIs). However, these are usually recommended in combination with a drug from another class: typically a combination of two NRTIs and a protease inhibitor (PI) or two NRTIs and a non-nucleoside reverse transcriptase inhibitor (NNRTI). Difficulties arise because rifampicin is a strong inducer of the cytochrome P450 enzyme (CYP 3A). This increases the metabolism of the PIs. A variety of options are available including switching rifampicin to rifabutin and using the protease inhibitor indinavir. However, neither of these drugs is readily available in resource-limited countries and the general advice is to avoid PIs when treating for TB. The best combination is probably efavirenz, an NNRTI, in combination with two NRTIs. Rifampicin will decrease the blood level of efavirenz, possibly requiring a dose adjustment. Adequate contraception is essential in women of child-bearing age as this NNRTI is contraindicated in pregnant women during the first trimester. Nevirapine, another NNRTI, is an alternative to efavirenz. Drug levels tend to be very variable between patients, further confounded by rifampicin-induced drug level reduction. There is also a risk of fatal hepatotoxicity and liver enzymes must be monitored. Nevirapine is relatively inexpensive, has a high therapeutic index and studies have shown a benefit at least in short-term outcomes. Triple NRTIs represent a third option. Drug combinations include: zidovudine plus lamivudine with either tenofovir, or abacavir. These drugs are not affected by rifampicin. The aciclovir regimen may be used safely in pregnancy and there is less risk of hepatotoxicity as compared with the nevirapine regimen. However, comparative antiviral potency for these triple NRTI combinations is promising, but not yet proven.

SUMMARY

Current management of HIV-related TBP includes short-course ATT for 6 months. ART should be started early for those with low CD4 T cell counts, but deferred in those less immunocompromised. There is good evidence that use of corticosteroids improves morbidity and mortality, and similar data are seen in non-HIV TBP. Thus, the authors recommend their use. However, the HIV-related TBP evidence is limited to a single, relatively small study. The results are encouraging, with strong evidence for a survival benefit at 6 months, but with conflicting statistical analyses at 18 months. A multicenter study with a large sample size is needed to investigate corticosteroid dose and duration of treatment. A higher prednisolone dose may be more effective since rifampicin leads to an effective halving of the corticosteroid level. Moreover, the adverse effects of corticosteroid-induced immunosuppression need further assessment. A shorter course of prednisolone may be just as effective. Any new multicenter study could also take advantage of better TB diagnostic techniques and the inclusion of ART.

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Research in intermediary metabolism depends on the use of radioisotopes. In cardiology, isotopes have become essential both for research and clinical use. In experimental cardiology, isotopes are used for the determination of coronary blood flow and for the identification of receptors, among others. The measurement of coronary flow and the viability of the heart muscle in man by positron emission tomography (PET) scan also relies on the use of isotopes. Where and when did the use of isotopes in medicine and cardiology commence?

The first use of tracers in a living organism was in plants by Hevesy in 1923, using lead in seedlings and the lead content of plants upon placing them in culture solution containing nonradioactive lead. Later, George de Hevesy became a pioneer in the field of the use of radioisotopes for biology and medicine. A native of Hungary, he worked with Lord Rutherford, later obtaining his PhD in 1908 from the University of Freiburg, Germany. He took refuge in Sweden in 1943 before the invading Germans.

Further advances in the field of the use of isotopes in biology and medicine were not possible until 1932 when physics lent a helping hand by the discovery of artificial radioactivity by Irène Joliot-Curie and her husband, Frédéric Joliot-Curie in 1933. Irène was the daughter of the discoverer of radium, Marie Curie; she became her mother’s assistant at the Radium Institute in Paris. In 1934, the Joliot-Curies succeeded in artificially producing radioactive elements, thereby furnishing proof of the possibility of transforming elements. On Monday, January 15, 1934, a communication was presented to the session of the French Academy of Science entitled A New Type of Radioactivity, with the authors Irène and Frédéric Joliot-Curie. The text of the announcement read, “it has been possible, for the first time, to create...
by means of external causes, radioactivity of certain substances which remain stable for a measurable time."

Another physicist, Enrico Fermi, gave a boost to the biomedical use of isotopes by the use of uranium-produced radioactive isotopes. The first radioiodine was produced by Fermi in 1934, which made possible the study of the function of the thyroid gland. A great step forward was the construction of the cyclotron by Lawrence in Berkeley in 1932. This instrument found immediate use in medicine and led to the discovery of $^{131}\text{I}$ and of $^{32}\text{P}$. Soon isotopes of sodium, potassium, calcium, and strontium became available. Without this work by physicists, the medical use of isotopes in the investigation of metabolism and the development of PET scan for the measurement of cardiac metabolism and coronary blood flow would not be possible.

Hevesy’s work was soon followed by the studies of Schoenheimer at the College of Physicians and Surgeons, Columbia University, who carried out his studies on intermediary metabolism with the use of isotopes. It was H. Urey who discovered heavy hydrogen (deuterium). An argument soon arose what to call this new isotope. Names such as bar-hydrogen and diplogen were proposed by Rutherford, but the name “deuterium” was finally chosen. Later, $^{15}\text{N}$ was concentrated in Urey’s laboratory in the form of heavy ammonia. The advent of the radioimmunoassay technique had made possible to measure the concentration of the unknown unlabeled antigen by comparing its inhibitory effect on the binding of radioactively labeled antigen to specific antibody with the inhibitory effect of known standards.

The application of radioisotopes to cardiology began with G. Liljestrand from Stockholm who in 1939 determined the normal blood volume in the ventricles of the human heart. In 1940, Hevesy used radioactive phosphorus to determine the circulation time. His cardiologist coworker was Nylin, who used isotopes for the determination of residual blood in the cardiac ventricles and in the measurement of the circulation time. In 1947, H. Blumgart, at Harvard, accomplished accurate measurements of the “velocity of blood flow” (circulation time) using intravenous radium and detection time of arrival at certain points of the circulation.

Another step was taken by M. Prinzmetal of Los Angeles in 1949 who used a Geiger counter positioned over the heart to record “radiocardigrams.” He thought this would offer a simple and safe method for the determination of the “pumping qualities of the heart.”
At that time the possible dangers of radioisotopes became a matter of concern, and Prinzmetal affirmed that he had consulted several experts in the field of atomic energy in California and elsewhere on the danger of radioactive material; “their opinion was unanimous that the amount of radioactivity used is completely safe by all methods of estimation.” Efforts in the early 50s were not successful in determining myocardial blood flow with isotopes. Some investigators placed a counter on the chest over the heart to observe the descending slope of the left ventricular component of the radiocardio-gram, while others attempted to estimate myocardial blood flow. However, admixture of blood and overlapping of the individual curves make these determinations difficult.

A decisive step forward was taken with the development of the gamma ray camera for in vivo studies in 1952 by Anger, after having worked on radar during the war, he designed what is now referred to as the Anger camera at the Donner laboratory in Berkeley. In 1958, he constructed his scintillation camera employing an 11-inch crystal. This opened the way for myocardial scanning with single photons still used today in diagnostic cardiology.

The use of positron emitters made scanning of the heart with the PET scan possible. Positron emitters were discovered in 1937 by Carl D. Anderson from the California Institute of Technology in Pasadena. These new particles are positive-charged electrons (positrons). It is interesting that Anderson received the Nobel prize while he was still an assistant professor. Later attempts were made to use positron emission in the measurement of the coronary blood flow. In 1964, this writer used $^{82}$Rb which emits positron 90% of the time for determination of coronary blood flow in man. The advantage of the coincidence method as compared to the single proton emissions is elimination of most accidental counts, arising from natural radioactivity, cosmic radiation and background. The coincidence counting method gives approximately five times the counting rates of single photon emission.

At this point in time, the 1970s, the technique for imaging and metabolic determination of the brain and of the heart by PET scan merged. Studies in
cardiac and cerebral metabolism by PET scanning received a boost through the discovery of Louis Sokoloff, trained in psychiatry and working at the University of Pennsylvania, who devised a novel approach to the exploration of regional cerebral metabolism, later adapted to the heart. Employing 14C-labeled deoxyglucose, he mapped the spatial distribution of regional rates of cerebral and cardiac glucose utilization and their changes in the response to physiologic stimuli in awake animals. 18F-deoxyglucose traces the initial uptake of the hexokinase-mediated phosphorylation of glucose to glucose-6-phosphate as a key metabolic step in the glycolytic flux in heart and brain. This glucose analog is a poor substrate for glycolysis, for the fructose-pentose shunt, and for dephosphorylation. Because the phosphorylated analog is rather impermeable to the cell membrane, it becomes virtually trapped in the brain and heart in proportion to the rates of regional cerebral glucose metabolism. These findings were responsible for the development of the PET scan by Ter-Pogossian and Phelps of Saint Louis who took advantage of short-lived radioisotopes, since their use permitted serial measurements of biological processes. Although the use of PET scan in clinical cardiology has not been universally acknowledged, its importance as a research tool is undisputed. One of the possible uses of PET scan is differentiation between viable and nonviable cardiac tissue. This is based on “mismatch” between regional coronary blood flow and metabolism determined with 18F-deoxyglucose. Normal or elevated rates of glucose utilization together with diminished blood flow in heart muscle of patients with myocardial infarction relative to normal myocardium suggest the presence of myocardial ischemia. This mismatch (diminished blood flow together with normal or increased glucose uptake) reveals a high incidence of residual tissue viability in ventricular segments during the subacute phase of myocardial infarction. Apparently, cardiac muscle devoid of 18F-deoxyglucose uptake is irreversibly damaged while the damage with intact 18F-deoxyglucose uptake may be reversible.

Radioisotopes have become an important tool handed to cardiology by the basic sciences, physics and chemistry. More and more, clinical and investigative cardiology will depend on the use of sophisticated methods. However, while the techniques may become more complex, the basic simplicity of great discoveries remains.
HIV & Cardiovascular Disease

Summaries of Ten Seminal Papers

Steven E. Lipshultz*, MD; Jorge A. Alvarez*, AB; James D. Wilkinson†, MD, MPH

*Department of Pediatrics - Division of Clinical Research; and †Department of Epidemiology and Public Health - University of Miami Miller School of Medicine - Miami, Fla - USA

(e-mail: slipshultz@med.miami.edu)

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8. Cardiovascular risk and body-fat abnormalities in HIV-infected adults

9. Impact of HIV and highly active antiretroviral therapy on leukocyte adhesion molecules, arterial inflammation, dyslipidemia, and atherosclerosis
S. D. Fisher and others. Atherosclerosis. 2006

10. Class of antiviral drugs and the risk of myocardial infarction

Selection of seminal papers by Steven E. Lipshultz, MD
Department of Pediatrics University of Miami Miller School of Medicine - Miami, Fla - USA

Highlights of the years by Ian Mudway, MD
Cardiovascular Research - The Rayne Institute
St Thomas' Hospital - London SE1 7EH - UK

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Progressive left ventricular (LV) dilation and inadequate left ventricular hypertrophy place human immunodeficiency (HIV)-infected children at increased risk for congestive heart failure (CHF) or cardiac death. HIV-infected children have a 20% incidence of CHF. Cardiac disease is one of the leading causes of mortality in children living with HIV for 5 years or more. Although the causes of progressive HIV cardiovascular diseases are multifactorial, it is likely that infectious and immunological mechanisms are contributory.

Intravenous (IV) immunoglobulins are immunomodulatory agents that have been shown to be beneficial in the treatment of the myocarditis of Kawasaki disease during childhood. Circulating immune complexes are elevated in HIV infection, but fall significantly with IV immunoglobulin treatment. Elevated serum autoantibodies in HIV-infected patients suggest that cardiac involvement may be related to autoimmunity. IV immunoglobulins inhibit the production and downregulate the secretion of tumor necrosis factor-α (TNF-α) and interleukin 1α in HIV-infected patients. IV immunoglobulins are also associated with reduced levels of TNF-α, interleukin 6, and interleukin 8, which are associated with reduced cardiovascular involvement in children with Kawasaki disease. IV immunoglobulins inhibit intracellular viral replication, reverse lymphocyte activation, and when given monthly have been shown to reduce the incidence of bacterial and viral infections and to slow the declining CD4+ counts, suggesting an immunomodulatory benefit.

Because CHF has been observed empirically to improve after treatment with IV immunoglobulins in other conditions and because LV dysfunction in pediatric HIV may be immunologically mediated, we examined the relation between immunoglobulins and LV structure and function in HIV-infected infants and children without CHF. We found that higher endogenous serum immunoglobulin G levels and treatment with IV immunoglobulins were associated with significantly greater LV wall thickness and lower LV peak wall stress. We also found that higher endogenous serum immunoglobulin A levels were associated with more normal LV wall thickness and LV thickness-to-dimension ratios. LV contractility, fractional shortening, end-systolic wall stress, and thickness-to-dimension ratio all showed a trend toward more normal values with higher endogenous immunoglobulin values or during treatment with IV immunoglobulins.

Our study demonstrated more normal LV structure and function in HIV-infected children who received monthly IV immunoglobulins treatments and in those children with higher endogenous serum immunoglobulin G levels. These results suggest that both impaired myocardial growth and the LV dysfunction observed might be immunologically mediated and responsive to immunomodulatory therapy. The results of this study may have implications for the continuum of myocarditis to dilated cardiomyopathy to CHF and its control. Progressive LV dilation is common in HIV-infected patients, is associated with inadequate LV hypertrophy resulting in elevated LV afterload, which reduces left ventricular function and may contribute to the frequent cardiovascular morbidity and mortality seen in pediatric HIV.

The association of therapy with IV immunoglobulins with a more normal hypertrophic response of the myocardium suggests that regular monthly use may be associated with the prevention of heart failure, reduced morbidity, improved quality of life assessments, and lower economic costs.

This is one of the only studies to demonstrate that HIV-associated cardiovascular disease can be reduced by a specific intervention targeted to mechanisms that have been thought linked to the pathophysiology of HIV-associated cardiovascular diseases.

Austria, Finland, and Sweden enter the European Union; Jacques Chirac is elected president of France; and “51 Pegasi b,” the first planet outside our solar system, is discovered.
Abnormalities of left ventricular structure and function are common in human immunodeficiency virus (HIV)-infected children and are often persistent and progressive. The clinical importance of these echocardiographic abnormalities in HIV-infected children was unclear before this study was performed.

Although recommendations for serial echocardiographic monitoring of HIV-infected children had been published prior to this study, they had not become part of the standard of clinical care of these children. This study determined the clinical value of echocardiographic findings as predictors of mortality after adjustment for demographic variables and other risk factors. Longitudinal profiles of the echocardiographic measurements to determine how early the predictors could distinguish between survivors and nonsurvivors were determined in this study as well.

In this study, the 5-year cumulative survival was 64%. In univariate models mortality was significantly higher in children who, at baseline, had depressed left ventricular fractional shortening or contractility; increased left ventricular dimension, thickness, mass, or wall stress; or increased heart rate or blood pressure.

Decreased left ventricular fractional shortening and increased wall thickness were predictive of mortality, after adjustment for immunodeficiency (CD4+ count), HIV viral load, clinical center, and encephalopathy. This showed that echocardiographic measurements of left ventricular structure and function provide noninvasive independent markers of disease and death in HIV-infected children that may be clinically useful.

In multivariable analyses, left ventricular fractional shortening was more predictive of survival than load-independent left ventricular contractility. This may relate to the fact that fractional shortening represents the end products of multiple processes, including preload, afterload, heart rate, and contractility, all of which may be disturbed in these patients.

In addition to replacing left ventricular load-independent contractility with left ventricular fractional shortening as a significant independent marker of mortality in the multivariate models, replacing left ventricular wall thickness with left ventricular mass provided similar significant findings. Left ventricular fractional shortening showed abnormalities for up to 3 years before death, whereas left ventricular wall thickness identified a population at risk on 18 to 24 months before death. Left ventricular fractional shortening may be useful as a long-term independent predictor and wall stress as a short-term predictor of mortality.

The regular use of serial echocardiograms in this population may identify children at risk who may benefit from more careful examinations and potentially effective interventions to alter the course of the disease.

This was the first study to validate that echocardiography in this population useful to identify children at risk for subsequent mortality, independent of other known risk factors. In addition, this work shows that children at risk for subsequent mortality can be identified in advance of death. These two important findings provide one of the first situations where recommendations for serial echocardiographic monitoring of children are validated in an evidence-based way. That is to say that echocardiographic measurements of left ventricular structure and function are validated independent surrogate end points for all-cause mortality in this population. Future studies may determine whether treatment of echocardiographic abnormalities associated with increased mortality is beneficial.

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The 27th Summer Olympic Games open in Sydney, Australia; the Danes vote against joining Europe’s common currency; and the DVD “Digital Video Disc” is introduced as an optical disc storage media format.
Heart muscle disease related to HIV infection: prognostic implications


BMJ. 1994;309:1605-1607

Summary written by: Jorge A. Alvarez (main author), James D. Wilkinson, and Steven E. Lipshultz

By the early 1990s, there had been a few studies published in the medical literature relating human immunodeficiency virus (HIV) infection to its associated cardiac comorbidities (pericardial effusions, arrhythmias, malignancy, endocarditis, and cardiomyopathy). However, there was still a need for a description of the natural history of HIV-associated cardiac dysfunction. Furthermore, anecdotal evidence had existed for poor prognosis in the setting of impaired left ventricular function.

Currie and colleagues were one of the first to study this question using a prospective, well-sized cohort of HIV-infected adults. Their cohort was recruited in Edinburgh, mainly from a single medical center. The cohort represented all major risk groups for HIV, including injection drug users, men who have sex with men, heterosexuals, and recipients of blood products. Over the course of four years of data collection, the subjects were followed with serial echocardiography, chest radiography, and electrocardiography. They found that echocardiographic evidence of cardiac dysfunction was present in 44 subjects: 13 with dilated cardiomyopathy (DCM), 12 with right ventricular dilatation, and 19 with borderline left ventricular dysfunction. Chest radiographs (utilizing a cutoff value of 0.5 cardiothoracic ratio) were found to be less useful, as were electrocardiograms, which showed nonspecific T-wave changes. Among those with cardiac dysfunction, the DCM group had the worse outcomes: 12 of the 13 died within 1 year. Compared with those with normal hearts, survival in the DCM group (using Kaplan-Meier survival estimates) was significantly lower ($P<0.001$), whereas there was no statistical difference in survival among the other two dysfunctional groups compared with those with normal echocardiograms. Similar associations were found with CD4 cell counts, which were significantly lower in the DCM group ($P<0.001$) while no differences were found among the other three groups.

Utilizing Cox’s proportional hazards regression and adjusting for the reduced CD4 cell count, along with age, sex, risk groups, Centers for Disease Control status, and interval of time between echocardiogram and CD4 count, the presence of DCM was independently associated with mortality (hazard ratio [HR], 11.68; 95% confidence interval [CI], 4.32-31.58). Those with isolated right or borderline left ventricular dysfunction showed slightly increased hazard ratios, but neither were statistically significant (HR, 1.17; 95% CI, 0.51-2.70 and HR, 1.48; 95% CI, 0.56-3.95, respectively).

This study found that isolated right and borderline left ventricular dysfunction are not associated with reduced CD4 cell counts and do not carry adverse prognostic implications. More importantly, this study identified the extremely poor outcome for people with HIV and DCM. Compared with those with HIV who either have seemingly normal hearts or other cardiac dysfunctions, the rapid progression toward death was an important trend to notice at the time and make other physicians, including cardiologists and infectious disease specialists, aware of. While DCM is strongly associated with lowered CD4 count, it was also seen to be an independent predictor of mortality, further reinforcing the concept that CD4 count alone should be used to determine prognosis.

This study provided important evidence for the monitoring of HIV-infected individuals using echocardiographic measures, as well as a call for future studies to evaluate the efficacy of treatment specific to heart failure. It would be important to investigate these prognostic associations in a contemporary population who are being treated with highly active antiretroviral therapy (HAART).

1994

Kim Il Sung, President of North Korea dies, aged 82; the Australian government agrees to pay reparations to indigenous Australians who were displaced during the nuclear tests at Maralinga in the 1950s and 1960s; and the Web browser Netscape Navigator 1.0 is released
The use of protease inhibitors (PI) as a component of the human immunodeficiency virus (HIV) treatment regimen in the late 1990s ushered in improved outcomes, but it also brought along derangements in the homeostasis of lipid and glucose metabolism. Clinical researchers had begun recognizing and writing about the redistribution of body fat, dyslipidemia, and glucose intolerance in those treated with PI. Carr and colleagues, having written some of the early descriptions, were one of the first to systematically describe the prevalence and severity of lipodystrophy syndrome associated with PI therapy. In Australia, they had been following a cohort of 113 HIV-positive patients taking PI and compared them with a control group of 45 HIV-naïve patients who were PI-naïve. The treatment group had been on PI therapy for a mean of 13.8 months at baseline and 21 months at time of reassessment for this report. Lipodystrophy was assessed by the subject and physician. Measurements of body fat mass and percentage using dual-energy x-ray absorptiometry (DXA) were made, as well as serum triglycerides, total and high-density lipoprotein (HDL) cholesterol, free fatty acids, glucose, insulin, and C-peptide levels.

Without a standardized definition of lipodystrophy, they implemented a survey tool for the patients to rate the severity for six regions (face, arms, legs, buttocks, abdomen, and neck) and the total score was then partitioned into four groups: none, mild, moderate, and severe. Concurrent physician assessment of lipodystrophy (blinded to the self-report results) revealed a 98% concordance with self-report. 83% of subjects reported some degree of lipodystrophy. 11% severe overall and 25% severe in at least one region. Self-reported severity in peripheral regions was more highly associated with DXA-measured fat mass than central regions ($P=0.005$ vs 0.09, respectively). Self-reported severity was also associated with duration of HIV infection and PI therapy, but not CD4 count or viral load.

Abnormal values of glucose metabolism were found in 23% of subjects on PI: 6% with diabetes and 17% with impaired glucose tolerance. Fasting triglyceride and C-peptide levels were abnormal in a greater percentage in PI recipients as compared with the controls. Also, these two values, when measured during therapy, predicted the severity of lipodystrophy at follow-up. This, in turn, can provide some ability to identify high-risk groups.

The researchers proposed a case-definition for PI-associated lipodystrophy syndrome, which took into account evidence of peripheral fat wasting or central fat accumulation and dysregulation of cholesterol, triglyceride, C-peptide, or glucose. In the absence of acquired immunodeficiency syndrome (AIDS), anabolic steroids, glucocorticosteroids, or immune modulators within the past 3 months of assessment.

In those patients taking PI therapy as part of their regimen, the high prevalence of lipodystrophy and substantial number with abnormal cholesterol, triglyceride, and glucose levels at 21 months, made for a strong case to establish a careful monitoring plan of these values. With the indeterminate nature of therapy duration, longer-term studies were suggested. However, the increased risk of cardiovascular disease secondary to PI therapy, makes the management of other factors, like smoking, sedentary lifestyle, and hypertension, an important component of clinical care.

Apple Computer releases the first iBook; the Islamic Salvation Army abandons armed activities in Algeria following a 21-month cease-fire; and the 200th Anniversary of the birth of Alexander Pushkin is celebrated throughout Russia.
Issues concerned with vertical transmission of human immunodeficiency virus (HIV) had focused mainly on prevention of perinatal infection, but the work of the Pediatric Pulmonary and Cardiovascular Complications of Vertically Transmitted HIV Infection (P^2C^2 HIV) Study Group shifted the focus to a systematic investigation of this vulnerable population. Their early results had shown that subclinical cardiac abnormalities develop early in children infected with HIV-1, and that they are frequent, persistent, and often progressive. Here, they provided an analysis of data compiled from cardiovascular function measured via echocardiogram every 4 to 6 months for up to 5 years in a cohort of 600 infants born to HIV-infected women. The study included 93 infants infected with HIV and 463 uninfected infants (serving as internal controls) from the same cohort. Also included was a comparison group of 195 healthy children born to mothers who were not infected with HIV (serving as external controls). The study group reported that children infected with HIV had a significantly higher heart rate at all ages (mean difference, 10 bpm; 95% confidence interval [CI], 8-13) than internal controls. At birth, both cohort groups of children born to HIV-infected mothers had similar low left ventricular (LV) fractional shortening. At 8 months, fractional shortening was similar in internal and external controls, whereas in children infected with HIV, fractional shortening remained significantly lower than in controls for the first 20 months of life (mean difference from internal controls at 8 months, 3.7%; 95% CI, 2.3-5.1). LV mass was similar at birth in both cohort groups, but became significantly higher in children with HIV from 4 to 30 months (mean difference, 2.4 g at 8 months, 95% CI, 0.9-3.9).

Irrespective of HIV status, infants born to women infected with HIV had significantly worse cardiac function than other infants, as seen by persistently reduced contractility, suggesting that the uterine environment has an important role in postnatal cardiovascular abnormalities. This association was supported by fetal echocardiograms collected by this group, which showed abnormalities irrespective of HIV status measured in the postnatal period. This suggested that children born without HIV infection to HIV-infected mothers should also be monitored long-term and should receive appropriate treatment as needed.

Vertically-transmitted HIV infection was associated with persistent cardiovascular abnormalities, identifiable shortly after birth. Findings of faster heart rate, higher LV mass, and lower LV function are seen to be consistent with an increased risk of heart failure, arrhythmias, and death in prior studies. The indication in this study of the presence of autonomic dysfunction and a hyperadrenergic state suggests that there is a strong association between HIV’s effect on the nervous and cardiovascular systems and mortality. The study of the use of β-adrenergic-receptor blockers in these children for its effect on outcomes was suggested by the group.

The P^2C^2 group provided solid evidence that in HIV-infected mothers the growth of children in utero results in persistent cardiomyopathy postnatally even at 5 years of age. This supports the Barker hypothesis for the fetal origins of adult disease. It did not matter if the children were infected or not—just the fact that they were exposed in utero resulted in sustained problems. This was the first and remains the only example to show that some cardiomyopathies of early childhood have their origin in fetal life with persistence into the postnatal period. Having the knowledge of when this process begins enables preventive strategies to be targeted to that age range. This served as the basis for the CHAART I (Cardiac status of HAART [highly active antiretroviral therapy]-exposed infants of HIV-infected mothers) and the PHACS (Pediatric HIV/AIDS Cohort Study) studies.
Mild dilated cardiomyopathy and increased left ventricular mass predict mortality: the prospective P²C² HIV multicenter study


Am Heart J. 2005;150:439
Summary written by: Jorge A. Alvarez (main author), James D. Wilkinson, and Steven E. Lipshultz

The P²C² HIV (Pediatric Pulmonary and Cardiovascular Complications of Vertically Transmitted Human Immunodeficiency Virus Infection (P²C² HIV) Study Group had published many findings on the plight of children born to HIV-infected mothers. Earlier reports had provided a description of the cardiovascular abnormalities present in this group of children, along with comparisons between infected and noninfected children born to HIV-infected women as well as comparisons with health controls born to noninfected women. Mild echocardiographic abnormalities at baseline had predicted cardiovascular and all-cause mortality. Using the final dataset, this article evaluates the progression of left ventricular (LV) dysfunction and its association with mortality and describes longitudinal changes in LV structure and function and mortality in 185 children vertically infected with HIV, by calculating age- or body surface area–adjusted z scores for 10 echocardiographic parameters.

In this cohort, the median age at first echocardiogram was 2 years (range 0.2-9.4 years) and median follow-up time was 3.6 years (range 0-6.3 years). The 5-year cumulative incidence of congestive heart failure (CHF) was 12.3%. Mean fractional shortening z scores declined from -0.65 at 1 year of age to -1.47 at 3 years of age without further decline between 3 and 10 years of age. Among children with 2 echocardiograms performed in the first year of follow-up, mild LV dysfunction (fractional shortening of <-2 SD on both echocardiograms) was present in 29 (18%) of 158 children. For these 29 children, the 5-year mortality was 55.4%. LV mass z scores were elevated at 1 year (mean z score 0.68, \( P<0.001 \)) and remained elevated throughout follow-up. In the 8 children with LV mass z score of >2 SD on both initial and follow-up echocardiograms, the 5-year mortality was 75%.

In HIV-infected children, LV structure and function progressively deteriorated in the first 3 years of life, resulting in the subsequent persistence of mild LV dysfunction and increased LV mass. The issue of LV hypertrophy was further investigated using measures of LV thickness-dimension ratio and LV wall stress, which were not associated with mortality. This suggested that hypertrophy by itself is a better predictor than its adequacy relative to LV dimension or degree of wall stress. Chronic mild depression of LV function (as measured by fractional shortening) and elevated LV mass were associated with higher all-cause mortality HIV-infected children. The importance of the finding is just how mild the change can be that results in excess mortality at 5 years. The example provided is for a 10-year-old in whom the detection of a 2 SD drop in fractional shortening is equal to a reduction from 34 % to 30%.

The study group recommended for clinicians to perform two serial echocardiograms within the first year of life for children with vertically transmitted HIV infection, as well as research to evaluate how earlier screening leading to detection and therapy potentially improves outcomes.

As the most recent report on the final dataset of longitudinal follow-up, the P²C² HIV group provides a landmark study by clearly defining the longitudinal course of echocardiographic abnormalities in HIV-infected children, but more importantly, since it is likely to transcend HIV, it showed that just a small amount of depressed fractional shortening or just a small amount of increased LV mass were very significant predictors of subsequent mortality. Prior to this study it was known that highly depressed heart function or excessive hypertrophy was a portent of bad outcomes, but no pediatric cardiologist would have blinked an eyelash over the levels of abnormalities found in the children in this study. Small differences from normal in this population had very major effects on risk of subsequent death. What does it mean to be just a little bit off from normal? In this population it is very, very bad.

Cartoons depicting the prophet Muhammad are published in a Danish newspaper; Ireland completes metrification; and Helen Clark, leader of the New Zealand Labor Party, is reelected for a third term.
Previous studies had reported a host of metabolic abnormalities associated with human immunodeficiency virus (HIV) infection and treatment, which included altered regulation of glucose, insulin, cholesterol and triglycerides, are very common. Each of those studies had expressed a concern about the association that HIV infection and treatment may have with the morbidity and mortality of accelerated cardiovascular and cerebrovascular disease.

Bozette and colleagues decided to further investigate this association using a large national database. They conducted a retrospective study of the risk of cardiovascular and cerebrovascular disease among 36,766 patients who received care for HIV infection at the Veterans Affairs facilities, which provide medical services for the US Military, between January 1993 and June 2001. Men made up 98% of the cohort. Their study reported that the use of antiretroviral therapy varied: nucleoside analogs, 70.2%; protease inhibitors, 41.6%; and nonnucleoside reverse-transcriptase inhibitors (NNRTIs), 25.6. The median time of treatment recorded was 17 months, 16 months, and 9 months, respectively. Of those receiving combination therapy, about 2000 included evenly either a protease inhibitor or an NNRTI for at least 24 months. Between 1995 and 2001, the rate of admissions for cardiovascular or cerebrovascular disease decreased (1.7 to 0.9 per 100 patient-years), and the rate of death from any cause decreased (21.3 to 5.0 deaths per 100 patient-years). Regression analyses at the individual level reported that there were no relationships between the use of nucleoside analogs, protease inhibitors, or NNRTIs, and the hazard of cardiovascular or cerebrovascular events. However, the use of antiretroviral drugs (any of them) was associated with a decreased hazard of death from any cause.

The study collected data from a shorter period of time than is usually required for the development of serious vascular disease. Hence, the researchers wished not to imply that the metabolic abnormalities are of no concern. They cited the harmful effect that lipodystrophy has on self-esteem and quality of life, as well as dyslipidemia and hyperglycemia. As a leading risk factor for atherosclerotic disease, it is expected that hyperlipidemia will be harmful to HIV-infected patients over the longer term. The study group cited that patients with a history of treatment for diabetes or hyperlipidemia had a much higher rate of vascular events than those without such a history.

Fear of accelerated vascular disease need not deter patients and providers from using the highest-quality care for HIV, as defined by the use of combination antiretroviral therapy that is compatible with current guidelines. Compromising antiretroviral therapy over the short term may not be necessary. However, prolonged survival among HIV-infected patients means that longer-term observation and analysis are required.

HIV-infected patients are appropriate candidates for all usual methods of risk reduction and health maintenance.

The Space Shuttle Columbia disintegrates upon reentry; more than 10 million people protest against the Iraq war in over 600 cities worldwide; and Dolly, the sheep, the world's first cloned mammal, is euthanized due to a progressive lung disease.
Cardiovascular risk and body-fat abnormalities in HIV-infected adults

S. Grinspoon, A. Carr


Summary written by: Jorge A. Alvarez (main author), James D. Wilkinson, and Steven E. Lipshultz

Grinspoon and Carr provide a masterful review of the current findings in the metabolic derangements in HIV-infected adults as they pertain to lipodystrophy and cardiovascular disease. Beyond the summarization of information known to date, they provide a clear and concise set of figures, tables, as well as synthesized recommendations for screening and intervention.

Lipodystrophy is present in a large percentage of HIV-infected individuals. The interaction between lipodystrophy and treatment medications has been studied, especially with protease inhibitors, in addition to demographic factors like female gender, older age, and lower body weight prior to therapy initiation. The telltale signs, dual-energy x-ray absorptiometry (DXA) and computed tomography (CT) images, as well as time course of the progressive changes, are smartly depicted for the reader. Dyslipidemia has been reported for the following abnormalities in different, but substantial numbers of HIV-infected adults: elevated triglycerides, total and low-density lipoprotein (LDL) cholesterol along with low high-density lipoprotein (HDL) cholesterol. Insulin resistance and subsequent diabetes mellitus are seen in a larger proportion of HIV-infected adults as compared with noninfected, age- and body mass index (BMI)-matched controls (7% vs 0.5%). The authors provide a cohesive figure that attempts to tie together the proposed mechanism for these metabolic alterations.

With all of the aforementioned derangements to normal metabolic functioning, the risk for cardiovascular disease has been thought to be increased in HIV-infected adults. Studies have suggested that the risk may be greater in younger individuals and increases with length of treatment. The absolute risk increase, however, is considered to be low, except for those with multiple risk factors.

The assessment of risk factors for cardiovascular disease is suggested by the authors. They provide a clear table of areas to consider. Modifications to lifestyle, including diet and exercise, as well as therapeutics, like statins, fibrates, metformin, thiazolidinediones, and growth hormone, are all reviewed in sufficient detail. Although the switching of antiretroviral regimens was not compared directly with lifestyle changes or other therapeutics, the authors incorporated both into a matrix of possible interventions and their reported changes to metabolic and anthropometric values. The authors stress that risk-factor modification must balance the risk of progression of HIV disease against the potential risk of progression of cardiovascular disease with long-term maintenance of antiretroviral therapy.

Few studies have been performed to determine whether any specific strategy, including lifestyle modification, medications, or alterations to the timing of antiretroviral therapy might be used to prevent metabolic and body-composition abnormalities in HIV-infected adults.

Overall, the review makes clear that metabolic abnormalities are common in those infected with HIV receiving treatment, especially protease inhibitors. While studies suggest that there is an increased risk of cardiovascular disease, the appropriate management with lifestyle modifications and the use of lipid-lowering and insulin-sensitizing regimens may be helpful. The key message is that clinicians caring for HIV-infected adults should assess cardiovascular risk factors and target risk reduction, though not at the expense of successful treatment of the underlying HIV disease. The authors provide a concise and helpful review of the main issues surrounding the metabolic alterations, its effect on cardiovascular disease, and what we, as clinicians, can do about it with what is known to date.

2005

2005 is designated the World Year of Physics; the prototype of the Airbus A380, the world’s largest passenger plane, debuts in France; and surgeons in France carry out the first human face transplant.
Impact of HIV and highly active antiretroviral therapy on leukocyte adhesion molecules, arterial inflammation, dyslipidemia, and atherosclerosis

S. D. Fisher, T. L. Miller, S. E. Lipshultz

Atherosclerosis. 2006;185:1-11
Summary written by: Jorge A. Alvarez (main author), James D. Wilkinson, and Steven E. Lipshultz

Highlighting the role that highly active antiretroviral therapy (HAART) has played in both extending the lives of human immunodeficiency virus (HIV)-infected adults as well as reducing the risk of early death from opportunistic infections, the authors of this review tackle the issue of cardiovascular comorbidity. Previous studies have shown the relationship between treatment for HIV infection and cardiovascular disease. The authors express concern about the association with myocardial infarction, and in particular focus on the two main sources of cardiovascular disease in this population—vascular inflammation and dyslipidemia. As opposed to other review articles, this one initiates a detailed discussion beginning at the molecular level with results from in vitro and animal studies. The evidence for their hypothesis linking HIV, vascular inflammation, and cardiovascular disease is compelling.

The authors provide several figures to illustrate the activation of nuclear factor kappa B (NF-κB) and the role of inflammatory products to the production and subsequent rupture of atherosclerotic plaques. Next, the link is made to the role that the HIV infection plays in the inflammatory pathway, referencing gene products (tat and nef).

While current treatment guidelines do not recommend the immediate initiation of HAART unless warranted, the authors bring up the next logical issue that potentially allowing long-term, unchecked viral infection can impact the development of atherosclerosis. The ultimate goal of all clinicians treating those with HIV is the mitigation of infection down to "undetectable" levels and the deferment of any acquired immunodeficiency syndrome (AIDS)-defining events. To this end, the proper use of HAART, with the medications available, has to strike a fine balance with the attendant comorbidities, like cardiovascular disease. The authors present evidence that protease inhibitors, traditionally included in HAART regimens, have a relationship to the development of dyslipidemia, whereas other classes of antiretrovirals, such as the nonnucleoside reverse transcriptase inhibitors (NNRTIs), might be a better choice for patients with cardiovascular risks.

Other strategies, such as pharmacologic, nutritional, and physical activity interventions are discussed in detailed. Routine measures, like smoking cessation and restriction of alcohol and fats, are mentioned as strategies to initiation. Exercise training receives a more thorough treatment as it relates to its effects on the immune system and lipodystrophy, as well as its biochemical effects on vascular dysfunction. Finally, the benefits of lipid-lowering drugs are weighed, noting the potential complications by coadministration of protease inhibitors and statins, which both are metabolized by the CYP3A4 pathway. However, the safe usage of pravastatin and the other effects that statins have on vascular endothelial factors make pharmacologic treatment of dyslipidemia possible and effective.

The authors argue that the patients who might benefit the most are those in whom the precursors of vascular plaques, such as fatty streak, smooth muscle cell, macrophage, and T-lymphocyte aggregation are not yet identified by echocardiographic and biopsy findings, but have already developed as a result of unchecked viral inflammation and replication.
Previous findings from the DAD (Data Collection on Adverse Events of Anti-HIV [human immunodeficiency virus] Drugs) Study Group had shown an increased risk of myocardial infarction associated with duration of antiretroviral therapy (ART). In this study, the authors investigated the risk of myocardial infarction with specific ART drug class. For this analysis, there were 150,000 person-years of ART exposure (median 6.9 years) with more patients exposed to protease inhibitors (PI) than nonnucleoside reverse transcriptase inhibitors (NNRTIs). The main outcome, myocardial infarction, was classified as definite (62%), possible (23%), or unclassifiable (15%). Of 345 events, 30% were fatal.

Demographic, cardiovascular risk factors (eg, smoking, family history) including those possibly attributable to ART (eg, diabetes, hypertension, dyslipidemia), and HIV factors (CD4 count nadir, peak viral load) were included in the Poisson regression models.

At the last follow up, more than 90% of the 23,000 study subjects had received ART. There was a 16% increased risk of myocardial infarction for each year of PI exposure after adjustment for demographic and cardiovascular disease risk factors and study design variables. This increased risk decreased to 10% per year PI exposure when the model was additionally adjusted for possible ART-associated risk factors such as diabetes, hypertension, or dyslipidemia. Exposure to NNRTIs was not associated with a significant increase in risk for myocardial infarction.

Although the increased risk per year of PI exposure is relatively small, these findings are very important considering the relatively long duration of PI exposure in this group. As we move into the second decade of widespread use of PI, these findings may gain even more significance. It is also notable that these findings were from a relatively young population (median age at last follow up of 49 years). Although some of the increase risk for myocardial infarction may be attributed to factors such as dyslipidemia and diabetes, an increased risk remained after adjustment for these factors. This suggests another mechanism by which PI increase risk. Animal models have suggested a direct cellular effect of HIV that promotes atherosclerosis.

This study had some limitations. First, it was an observational study, and therapeutic decisions at individual sites might have channeled patients at greatest risk into more cardioprotective therapies. Second, increased risk associated with increased duration of ART may be partly due to the fact that these patients may have had a longer duration of HIV infection. Other confounders not identified in the study may also have an effect. Finally, it is possible that longer follow-up may identify an increased risk of myocardial infarction with exposure to NNRTIs, which was significant in the univariate, but not the multivariate analysis.

Regardless, the findings of increased risk of myocardial infarction with increased duration of PI exposure are compelling in light of the aging of the HIV population who have access to combination ART. Age, as well as PI exposure, are independent risk factors for myocardial infarction, and although not examined in his study, age and other factors may act as effect modifiers for the effect of PI exposure on cardiovascular risk. Control of modifiable cardiovascular risk factors such as smoking cessation, hypertension treatment, and lipid-lowering therapies appear even more important in the context of the increased risk for myocardial infarction associated with combination antiretroviral therapy.

2007

Russian cellist and conductor Mstislav Rostropovich dies, aged 80; inflation rates in Zimbabwe reach a record 1600%; and 52-year-old Nicolas Sarkozy, son of a Hungarian immigrant, is elected president of France, succeeding Jacques Chirac
## Bibliography of One Hundred Key Papers

selected by Steven E. Lipshultz*, MD; Stacy D. Fisher†, MD
Tracy L. Miller*, MD; Tanvi S. Sharma*, MD; Angela N. Milton*, BS

*Department of Pediatrics - University of Miami Miller School of Medicine and Holtz Children's Hospital
of the University of Miami-Jackson Memorial Medical Center - Miami, Fla - USA
†Mid-Atlantic Cardiovascular Associates - Baltimore, Md - USA

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### Bibliography of One Hundred Key Papers

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<td>Viral load and disease progression as responsible for endothelial activation and/or injury in human immunodeficiency virus-1-infected patients. <em>Blood Coagul Fibrinolysis.</em> 2003;14:15-18.</td>
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Langston C, Cooper ER, Goldfarb J, et al.


Lamperth L, Dalakas MC, Dagani F, et al.

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### Bibliography of One Hundred Key Papers

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<tr>
<td>Zareba KM, Miller TL, Lipshultz SE.</td>
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