The cardiological complications associated with HIV infection and acquired immune deficiency syndrome (AIDS)

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Abstract

Our increased understanding of the human immunodeficiency virus (HIV), including elucidation of the processes of transmission and replication, has led to the development of relatively effective therapies to minimise and manage the clinical consequences of HIV infection. These therapeutic developments have undoubtedly improved rates of morbidity and mortality in infected patients. The improvements in quality of life and life expectancy have been accompanied by an increase in the number of patients demonstrating cardiac complications, occurring either as a result of the infection itself or the drugs used to control the virus.

Cardiac involvement occurs frequently in HIV/AIDS patients and it seems likely that the myocardium, pericardium and/or endocardium are involved. Myocarditis, one of the most common types of cardiac involvement observed in HIV patients, the cause of which can be difficult to identify, may be responsible for myocardial dysfunction. Opportunistic infections, including HIV itself, have been suggested as the cause of myocarditis. Dilated cardiomyopathy is usually found in the late stage of HIV infection and myocarditis may be the triggering causative factor. The mechanism behind pericardial effusion remains unclear but it too may be related to infections or neoplasms.
Non-bacterial thrombotic endocarditis and infective endocarditis have been described in AIDS patients, both of which cause significant morbidity. Human immunodeficiency virus-related pulmonary hypertension is a diagnosis of exclusion, and symptoms and signs may mimic other pulmonary conditions in AIDS patients. Cardiac Kaposi's sarcoma and cardiac lymphoma are the frequently encountered malignant neoplasms in AIDS patients – the prognosis is grave in patients with these conditions.

Key words: AIDS, HIV, cardiological complications.

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Introduction

At the outset of the acquired immune deficiency syndrome (AIDS) pandemic, physicians were restricted to treating symptoms associated with opportunistic infections resulting from autoimmune destruction mediated by the human immunodeficiency virus (HIV). Lack of any effective antiretroviral therapy meant that the primary concern was the management of opportunistic infections; this necessitated the use of an expansive and exhaustive range of medical treatments including antifungals, antibiotics, analgesics, oncology therapies and antiparasitic compounds as well as treatments for diarrhoea and ulcers. The development of compounds with specific antiretroviral activity against HIV proliferation had the effect of reducing the onset of opportunistic infections – this brought about significant improvements in the quality of life, while delaying the rate of progression to AIDS and death.[1,2] Clinicians previously faced with treating a 'fatal' disease subsequently faced a new challenge, that of managing life-long therapy. In doing so, clinicians had to focus on the long-term consequences of the disease *per se* and the toxicities of the drugs used to treat it.

The possibility of cardiac involvement in the pathology of AIDS was first raised in the early 1980s with the reporting of myocardial Kaposi sarcoma at autopsy.[3] Cardiac involvement has since been reported to occur in as many as 28–73% of AIDS patients.[4] Ventricular dysfunction, pericardial effusions, dilated cardiomyopathy and rhythm disturbances (including high-grade atrial and ventricular ectopy and sudden death) provide evidence that HIV infection is likely to have multiple direct and indirect effects on the heart. The increased incidence of cardiac complications with HIV infection is not restricted to adults; in infants and children the cardiac complications of AIDS range from incidental microscopic inflammatory findings at necropsy to clinically significant, extensive and chronic cardiac dysfunction.

Patients tend to be receiving varied medications to treat conditions associated with HIV infection in addition to their antiretroviral therapies. Many of these have cardiovascular effects

Table 1. Cardiotoxicity, metabolic disturbances and cardiological events associated with drugs frequently used in HIV patients

Drug	Clinical and metabolic disturbances
Antiretroviral therapy	
Non-nucleoside analogues	↑ total cholesterol; ↑ HDL cholesterol*
Nucleoside analogues	myocarditis; dilated cardiomyopathy; rhabdomyolysis; myopathy; ↑ total cholesterol; ↑ triglyceride; lipoatrophy; diabetes
Protease inhibitors	lipodystrophy; atherosclerosis; ↑ total cholesterol; ↑ triglyceride; ↑ insulin; ↑ HDL cholesterol; ↑ LDL cholesterol
Adjuvant therapy	
Amphotericin B (antifungal)	dilated cardiomyopathy; hypertension; bradycardia
Doxorubicin (Kaposi's sarcoma)	cardiomyopathy
Foscarnet (CMV)	cardiomyopathy
Ganciclovir (CMV)	ventricular tachycardia
Interferon-α (antineoplastic; antiviral; immunomodulator)	arrhythmia; myocardial infarction/ischaemia
Pyrimethamine (toxoplasmosis)	cardiomyopathy; sudden death; heart failure
Pentamidine (*pneumocystis carnii*)	QT prolongation; *Torsades de pointes*
Trimethoprim-sulphamethoxazole (*pneumocystis carnii)*	QT prolongation; *Torsades de pointes*

Key: CMV = cytomegalovirus; HDL = high density lipoprotein; LDL = low density lipoprotein
*Some evidence has been presented for improvements in HDL:total cholesterol ratios indicating an improvement in atherogenic profile

and toxicities (table 1). It is not yet completely clear whether all these conditions are directly related to the disease or to its treatment. We discuss here the cardiac complications most frequently observed and associated with HIV infection itself rather than its associated pharmacology (table 2).

Myocarditis

Myocarditis is perhaps the most frequently reported form of cardiovascular involvement in HIV infection. Evidence from autopsy indicates that unspecific myocarditis may occur in as many as 33% of patients with AIDS; with specific causes being found in fewer than 20% of cases.[4,5] Where it has been investigated, myocarditis has been found in all infected patients with congestive heart failure, left ventricular dysfunction and/or ventricular tachycardia.[5]

Pathogens frequently associated with myocarditis in AIDS patients include *Toxoplasma gondii*, *Mycobacterium tuberculos*, and *Cryptococcus neoformans*; the spectrum of associated infections is broad and *Candida albicans*, cytomegalovirus and herpes simplex are also among those considered possible causative organisms.[4,5] Some evidence has been presented to support the involvement of the HIV virus itself; HIV and/or its proteins have been found in heart tissue samples collected from patients with AIDS, both in the presence and absence of overt cardiac disease.[6,7]

A form of lymphocytic myocarditis, having a variety of pathological characteristics, has been described, with lymphocytic infiltrate both with and without necrosis of the myocardial fibres and focal and mild myocarditis with a mononuclear infiltrate.[5,8] Clinical symptoms can include abnormal fractional shortening, globular shape and/or hypokinesis, although the presence of these symptoms may not necessarily involve overt myocardial necrosis that can be proven on autopsy.

Pericardial effusion

Pericardial effusion may occur in as many as 20% of AIDS patients.[9,10] Various clinical manifestations have been reported, including asymptomatic pericardial effusion, pericarditis, cardiac tamponade and constrictive pericarditis. Most patients present with an asymptomatic increase in the cardiac silhouette on chest X-ray,[11] and the symptoms and clinical consequences of pericarditis in AIDS patients tend to be similar to those observed in non-infected patients. Although the pericardial effusion is often small and not associated with haemodynamic consequences, larger effusions may cause cardiac tamponade.[12,13] Despite the presence of effusion being associated with a shortening of life expectancy, the size of the pericardial effusion *per se* does not appear to show any association with prognosis.

Cardiac tamponade demonstrates an annual incidence of approximately 9% in AIDS patients with pericardial effusion, while as many as 1% of the total AIDS population develops cardiac tamponade annually.[13] It is not always possible to identify specific causes but individual case reports imply the involvement of multiple organisms associated with pericardial effusion secondary to HIV infection.[14] As pericardial effusion seems to be associated with a low CD4 cell count and is most often caused by opportunistic infections and/or malignant neoplasms, it may be looked on as an indicator or an associate of end-stage HIV infection. Despite its incidence in advanced stages of HIV infection, it is rarely the eventual cause of death.

Table 2. Frequently observed cardiac complications in patients with HIV/AIDS

Complication	Incidence	Comment
Myocarditis	Up to 30%	It may be responsible for myocardial dysfunction. Difficult to identify the cause. Opportunistic infections (including HIV itself) may be responsible
Pericardial effusions	Up to 20%	The underlying mechanism is unclear but it may be related to infections or neoplasms
Dilated cardiomyopathy	10–30%	Usually found in the later stages of HIV infection. Myocarditis may be the triggering causative factor
Endocarditis	3–5%	Non-bacterial thrombotic endocarditis and infective endocarditis can both cause significant morbidity
Pulmonary hypertension	< 5%	Human immunodeficiency virus-related pulmonary hypertension is a diagnosis of exclusion, and symptoms and signs may mimic other pulmonary conditions
Malignant neoplasma	< 3%	Cardiac Kaposi sarcoma and cardiac lymphoma are the frequently encountered malignant neoplasms and prognosis is poor
Cardiac tamponade	~ 1%	

Dilated cardiomyopathy

Echocardiography and autopsy studies indicate a prevalence of substantial and clinical dilated cardiomyopathy in the AIDS population of 10–30%.[5,15,16] Clinically significant cardiomyopathy is less common (1–3% of patients). The findings of prospective studies suggest that a proportion of HIV-infected patients may be predisposed to developing a progressive and clinically significant form of heart disease.[17] Although left ventricular diastolic impairment can occur in the early stages of HIV infection, dilated cardiomyopathy usually occurs later on and tends to be associated with low CD4 cell counts.[18,19] The aetiology may be known in some patients with asymptomatic or overt left ventricular dysfunction, such as toxoplasmosis, cryptococcosis, cocaine use, toxo-serology hypertrophic cardiomyopathy, alcoholic heart disease, or drug toxicity. Other factors that may possibly contribute to the development of myocardial dysfunction include post-viral autoimmunity, cachexia, selenium deficiency and the cardiotoxicity of therapeutic (HIV) drugs.

Several studies support a direct role for HIV-1-mediated cardiac injury, but the underlying pathological mechanism is unclear.[20,21] One hypothesis suggests an alteration in T-helper cell function that induces myocardial inflammation through unregulated hypergammaglobulinaemia.[8] Alternatively, HIV may induce circulating cardiac antibodies, ultimately triggering a progressively destructive autoimmune reaction to cardiac tissue.[22] Patients infected with HIV who have severe symptomatic heart failure also tend to have low CD4 cell counts, to demonstrate myocarditis and to have a persistent elevation of cardiac antibodies.

Endocarditis

Marantic endocarditis or non-bacterial thrombotic endocarditis can be associated with malignant neoplasms, hypercoagulable states and chronic wasting disease.[23,24] Estimates place the incidence of marantic endocarditis at 3–5% of patients with AIDS, tending to occur most frequently in older patients. Friable, fibrinous clumps of platelets and red blood cells that stick to the cardiac valves but do not appear to precipitate an inflammatory response are characteristic and it is usually the tricuspid valve that is affected.[25] Systemic embolisms can occur but most events are clinically silent and rarely result in death.[12]

Patients with AIDS may also be affected by infective endocarditis, occurring more frequently in the parenteral drug user.[26] The tricuspid valve is once again the one most frequently affected. Patients usually present with fever, sweats and weight loss, having co-existing pneumonia and/or meningitis. Although prognosis is generally no different from that in the uninfected patient, increased mortality has been reported in the more advanced stages of HIV infection.[27]

Pulmonary hypertension

In recent years, there have been reports of patients with HIV infection developing unexplained or pulmonary hypertension. Risk factors for pulmonary hypertension include intravenous drug use, repeated exposure to the virus and haemophilia. It is reported more frequently in male and/or young patients; incidence may be associated more with demographic profile than any underlying pathological process.[28] Patients tend to present having experienced several months of being easily fatigued and with shortness of breath. Diagnosis can be made on echocardiography, which tends to show a hypertrophied right ventricle with a normal left ventricle. Prognosis is poor, with survival times being quoted in the region of a year.

The pathogenesis of pulmonary hypertension associated with HIV is unclear but it does not appear to be simply a phenomenon of immunodeficiency. Evidence suggests that disturbed endothelial function is unlikely, although many patients have multiple pulmonary infections. Interestingly, electron microscopy has shown the presence of intracytoplasmic inclusions, suggesting that the virus may act by causing the release of secondary mediators. Glycoproteins in the HIV envelope can stimulate macrophages to produce potent vasoconstrictors as well as tumour necrosis factor – these may be involved in the underlying pathology.[29]

Cardiac neoplasm and HIV

The two main malignant neoplasms that appear to affect the hearts of patients with HIV infection are Kaposi's sarcoma and malignant lymphoma. With Kaposi's sarcoma, cardiac involvement in HIV-infected individuals usually occurs as part of a disseminated sarcoma. AIDS-related metastatic Kaposi sarcoma involves either the visceral layer of serous pericardium or the sub-

epicardial fat. There also appears to be a tendency for the sarcoma to involve the sub-epicardial adipose tissue adjacent to major coronary arteries.[30]

Malignant lymphoma is the second most frequently occurring tumour involving the heart and is included in the diagnostic criteria for AIDS.[31] Histologically, the lymphomas are diffuse and aggressive and are usually of small non-cleaved or immunoblastic subtypes.[32] Where a patient suffers functional obstruction, they may benefit from surgical resection, but the overall prognosis of patients with HIV-associated cardiac lymphoma is poor.[33]

Coronary artery disease

Coronary artery disease has been reported in patients with HIV infection[34,35] and, although antiviral treatment has been linked with vascular complications, HIV itself may be responsible.

Atherosclerosis is recognised as a disease of dysfunctional inflammatory processes and altered cellular adhesion. Virus-induced or augmented atherogenesis may be involved in the pathology of coronary artery disease seen in HIV-positive patients. Changes in metabolic regulation are a classic response to infection. This process is no different following infection with HIV – when left unchecked, the body will be exposed to millions of viral particles during proliferation.

Metabolic complications of HIV have been well documented and are known to include disturbances in lipid and glucose metabolism.[36] During the early stages of HIV infection there are decreases in both high density lipoprotein (HDL) and low density lipoprotein (LDL) cholesterol. With the onset of AIDS, triglyceride levels increase markedly as a result of increases in very low density lipoprotein (VLDL) cholesterol. Although the reduction in HDL cholesterol is accompanied by a fall in LDL cholesterol, the overall change in blood lipids reflect what would normally be considered as a significant worsening of the patient's atherogenic profile. This can only be further affected by the increase in triglycerides that occur later in the disease.[36,37] The impact of prescribing lipid-lowering agents on HIV positive patients to counter the disease-related worsening of the atherogenic profile is being investigated.

Presentation, diagnosis and treatment

Clinical presentation of HIV with cardiac involvement can vary markedly in both its underlying cause and the affected cardiac structures. Presentation can range from asymptomatic to complaints that may include fever, fatigue, chest pain, dyspnoea and/or palpitations.[38,39] In general, the clinical manifestations of HIV-related cardiac conditions are similar to cardiac disease due to other causes. History and physical examination looking for signs and symptoms are perhaps the best means of diagnosis. Dilated cardiomyopathy will produce typical signs of heart failure, whereas endocarditis will result in fever, murmur and embolic phenomena. Specific non-cardiac symptoms may suggest underlying cardiac pathology.

Although ECG can be used for regular monitoring of susceptible patients, echocardiography is perhaps the most useful method for investigating the possibility of cardiac disease in HIV patients. The spectrum of disease is broad, including both left and right ventricular dysfunction and can include conditions such as infiltrative and pericardial diseases that may not otherwise be defined. Transthoracic echocardiogram will demonstrate the presence of pericardial effusion, valvular insufficiency and regional hypokinesis. Since there appears to be little advantage in finding sub-clinical disease, the adoption of routine echocardiography of HIV-infected patients may be uneconomic. An additional means of diagnosis, that of biopsy of the endomyocardium, has been used but its value is controversial; it rarely reveals infections that are likely to respond to therapy and results cannot be confirmed by less invasive techniques.

Treatment of left ventricular dysfunction in HIV disease is primarily symptomatic – although the possibility of reversible aetiology, such as infectious myocarditis that may respond to systemic therapy, should be considered. Pericardiocentesis in tamponade may be therapeutic (and diagnostic), with consideration of underlying infectious aetiology. As yet, there have been no reports of successful treatment of cardiomyopathy with angiotensin-converting enzyme (ACE) inhibitors, or beta blockers, such as carvedilol. For now, it is generally recommended that treatment follows heart failure treatment guidelines.

Advanced HIV and associated cardiac disease has a poor prognosis. Complications resulting from opportunistic infection occur frequently in the latter stages of the disease. Focal left and isolated right ventricular dysfunctions do not appear to be associated with any additional worsening of prognosis, whereas clinical left ventricular dysfunction tends to be rapidly fatal in the later stages of AIDS.

The labile nature of the human immunodeficiency virus and its resistance to eradication has, by necessity, resulted in the

Key messages

- Cardiac involvement occurs frequently in HIV/AIDS patients and it seems likely that the myocardium, pericardium and/or endocardium are involved
- Cardiac conditions frequently observed include myocarditis, pericardial effusion, dilated cardiomyopathy, endocarditis, pulmonary hypertension and malignant neoplasms such as cardiac Kaposi's sarcoma and cardiac lymphoma
- Although treatments used by infected patients have cardiovascular effects and toxicities, there is evidence that the pathology of HIV infection has multiple direct and indirect effects on the heart
- Although good clinical practice would suggest that early recognition and prompt treatment might prevent morbidity and/or mortality from cardiac involvement, it remains to be seen whether or not such an approach will prolong survival in AIDS patients

development of an extensive range of potent compounds that have actions beyond their antiretroviral properties. Multi-drug therapy regimens, namely highly active antiretroviral therapy (HAART), designed to cause maximal suppression of viral replication, are required to minimise viral escape through the development of drug resistance. Many cardiovascular adverse effects resulting from these medications have been described. Although beyond the remit of this current article, increased incidence of coronary artery disease has been documented and may be related to the antiretroviral therapies.[40]

Conclusions

While the increased number of anti-HIV compounds is welcome, the ever increasing array of therapeutic options requires a more detailed understanding of HIV disease; including the potential for viral resistance, drug-drug interactions, mechanism of action, drug hypersensitivity in patients with HIV disease and therapy limiting adverse reactions. The improvement in life expectancy also increases the potential for long-term metabolic consequence of treatment, especially chronic conditions such as atherosclerosis. Although good clinical practice would suggest that early recognition and prompt treatment might prevent morbidity and/or mortality from cardiac involvement, it remains to be seen whether or not such an approach will prolong survival or quality of care in AIDS patients.

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