Cardiovascular manifestations of HIV infection

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J R Soc Med 2001;**94**:384–390

Studies published over the past three years have tracked the incidence and course of human immunodeficiency virus (HIV) infection in relation to cardiac illness in both children and adults[1] (Table 1). This recent work shows that subclinical echocardiographic abnormalities independently predict adverse outcomes and identify high-risk groups who can then be targeted for early intervention and therapy[2].

The introduction of highly active antiretroviral therapy (HAART) regimens has greatly modified the course of HIV disease, with longer survival and better quality of life; however, early data from those treated raise concerns about a possible increase in both peripheral and coronary arterial diseases. In global terms HAART is available only to a minority of HIV-infected individuals, and studies before the advent of HAART remain applicable. UNAIDS estimates that 36.1 million people were living with HIV infection at the end of the year 2000[3]. If 9–10% of patients develop symptomatic heart failure over 2–5 years[4], then 3 million cases of HIV-related heart failure will present in that time period[5]. In this review article, I discuss the principal HIV-associated cardiovascular manifestations, with an emphasis on new knowledge about prevalence, pathogenesis and treatment.

DILATED CARDIOMYOPATHY

HIV disease is an important cause of dilated cardiomyopathy[4] (Figure 1), with a prevalence reported as 3.6% among cardiomyopathy patients, increasing as patients with HIV infection live longer[1]. Patients with HIV-infection and dilated cardiomyopathy have a much worse prognosis than those with idiopathic dilated cardiomyopathy, hazard ratio of death 4.0[5,6]. The importance of cardiac dysfunction is reflected by median survival to AIDS-related death—101 days in patients with left ventricular dysfunction and 472 days in patients with a normal heart by echocardiography at similar infection stage[5].

Myocarditis is the best studied cause of dilated cardiomyopathy in HIV disease[4]. HIV virions infect myocardial cells in patchy distributions[4,7] without a clear direct association between HIV and cardiac myocyte dysfunction[4,7]. How virus enters CD4-receptor-negative cells such as myocytes is unknown. Reservoir cells (e.g. dendritic cells) may play a pathogenic role in the interaction between HIV and the myocyte and in the activation of multifunctional cytokines (e.g. tumour necrosis factor-alpha [TNF-α], interleukin-1 [IL-1], interleukin-6, interleukin-10) that contribute to progressive and late tissue damage[6].

Myocarditis and dilated cardiomyopathy are associated with local cytokine production; thus, circulating levels tend to be uninformative[6]. Viral infection in the context of a nonspecific stimulator of monokines such as IL-1 or TNF-α is much more likely to lead to myocarditis and myocyte damage than viral infection alone. TNF-α produces a negative inotropic effect, by altering intracellular calcium homoeostasis and possibly by inducing nitric oxide synthesis, which likewise reduces myocyte contractility[6,8]. The intensity of both TNF-α and inducible nitric oxide synthase staining has been reported much higher in myocardial biopsy samples from patients with HIV-associated cardiomyopathy—specifically in those with a myocardial viral infection independently of antiretroviral treatment—than in those with idiopathic dilated cardiomyopathy.

When children with HIV-infection have received monthly immunoglobulin infusions they have shown improvement in left ventricular dysfunction, an increase in left ventricular wall thickness, and a reduction in peak left ventricular wall stress; these observations suggest that both impaired myocardial growth and left ventricular dysfunction are immunologically mediated[9]. The apparent efficacy of immunoglobulin therapy may be due to inhibition of cardiac autoantibodies (e.g. anti-α-myosin), the prevalence of which is increased in HIV-infected patients with dilated cardiomyopathy[10], by competing for Fc receptors; alternatively, immunoglobulins might dampen the secretion or effects of cytokines and cellular growth factors[11]. Further study is needed to evaluate the efficacy of immunomodulatory therapy in adults and children with declining left ventricular function. In the published series there is no evidence of benefit to HIV-associated cardiomyopathy from HAART. However, the better control of cytomegalovirus infection, which is an important cause of cardiomyopathy in HIV disease, is one way in which HAART might lessen the incidence and improve the clinical course of HIV-associated heart disease. Encephalopathy influences negatively the clinical course of dilated

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Table 1 **HIV-associated cardiovascular abnormalities**

Type	*Possible aetiologies and associations*	*Incidence*
Dilated cardiomyopathy	HIV, *Toxoplasma gondii*, coxsackievirus group B, Epstein–Barr virus, cytomegalovirus, adenovirus, autoimmune response to infection	Estimated 15.9 patients/ 1000 asymptomatic HIV-infected persons (Ref. 4)
	Cocaine, possibly nucleoside analogues, IL-2, doxorubicin, interferon	
	Nutritional deficiency/wasting; selenium, B12, carnitine	
	Thyroid hormone, growth hormone, adrenal insufficiency; hyperinsulinaemia	
	TNF-α, nitric oxide, TGF-β, endothelin-1	
	Hypothermia/hyperthermia, autonomic insufficiency	
	Encephalopathy	
	Acquired immunodeficiency, HIV viral load, length of immunosuppression	
Coronary heart disease/ arterial hypertension	Protease-inhibitor-induced metabolic and coagulative disorders	
	HIV-induced endothelial dysfunction	
	Erythropoietin-induced increase of haematocrit and blood viscosity	
	Vasculitis	
Pericardial effusion	*Staphylococcus*, *Streptococcus*, *Proteus*, *Nocardia*, *Pseudomonas*, *Klebsiella*, enterococcus, *Listeria*	11% per year in AIDS (Ref. 27) Spontaneous resolution in up to 42% (Ref. 27)
	Mycobacterium tuberculosis, *M. avium intercellulare*, *M. kansasii*	
	HIV, *Herpes simplex virus*, *Herpes simplex virus* type 2, cytomegalovirus	
	Cryptococcus, *Toxoplasma, Histoplasma*	
	Kaposi's sarcoma,	
	Capillary leak/wasting/malnutrition	
	Hypothyroidism	
	Prolonged immunodeficiency	
Isolated right ventricular and pulmonary disease	Recurrent bronchopulmonary infections, pulmonary arteritis, microvascular pulmonary emboli due to thrombus or drug injection	
Primary pulmonary hypertension	Plexogenic pulmonary arteriopathy; mediator release from endothelium	0.5% (Ref. 24)

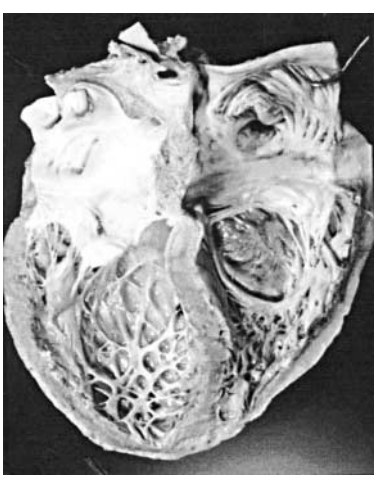

Figure 1 **Dilated cardiomyopathy in AIDS patient.** The heart has a globular shape with rounded apex due to ventricular dilation. The left ventricular cavity is enlarged, with mild myocardial hypertrophy. There is diffuse endocardial fibrous thickening

cardiomyopathy in HIV disease[8]. Several studies have indicated that patients with encephalopathy are more likely to die of congestive heart failure than are patients without encephalopathy, hazard ratio after multivariate analysis 3.4[8]. Immune modulating factors and cytokines have both cardiotoxic and neurotoxic actions and may play a crucial role in the development and progression of dilated cardiomyopathy and encephalopathy, perhaps explaining the association between the two. Proinflammatory cytokines activate inducible NO synthase (iNOS), thus stimulating production of NO, a sequence of events that may contribute to the association between dilated cardiomyopathy and encephalopathy in HIV disease[8]. HIV can persist in reservoir cells in the myocardium and the cerebral cortex even after antiretroviral treatment[8]. The reservoir cells may hold HIV-1 on their surfaces for long periods, and chronic release of cytotoxic cytokines (e.g.

TNF-α, interleukin-6, endothelin-1) could contribute to progressive and late tissue damage in both systems independently of HAART regimens[8].

CORONARY HEART DISEASE AND HYPERTENSION

A possible reason for accelerated coronary artery disease in HIV-infected patients is stimulation of local monocyte-macrophages by the virus. A wide range of inflammatory vascular diseases (e.g. polyarteritis nodosa, Henoch–Schönlein purpura, drug-induced hypersensitivity vasculitis) occur in HIV-infected individuals[12]. Vascular inflammation appears multifactorial and may result from HIV-induced immunological abnormalities and exposure to xenoantigens such as HIV-1 itself, other infectious agents and drugs[12].

Endothelial dysfunction injury, pivotal to the development of cardiovascular and inflammatory disease, has been described in HIV infection[13]. There is evidence of endothelial activation, in the form of soluble adhesion molecules and procoagulant proteins[13]. Virus may gain entry to endothelial cells via CD4 antigen or galactosyl-ceramide receptors. Other possible mechanisms of entry include chemokine receptors. Nevertheless, endothelial activation may also occur via secretion of cytokines in response to mononuclear or adventitial cell activation by virus, or else by the effects of the secreted HIV-associated proteins *gp 120* (envelope glycoprotein) and *tat* (transactivator of viral replication) on endothelium. Enhanced adhesiveness of endothelial cells, endothelial cell proliferation and apoptosis as well as activation of cytokine secretion have all been demonstrated. Selected inflammatory cytokines and viral proteins have been found synergistic in inducing endothelial injury. In HIV infection, dysfunctional or injured endothelial cells potentiate tissue injury, inflammation and remodelling, and accelerate the development of cardiovascular disease[13].

Coronary artery disease is observed with increasing frequency among HIV patients receiving therapy with protease inhibitors (PI) in the ambit of HAART regimens[1]. Despite the clinical benefits of PI therapy, complications such as lipodystrophy, insulin resistance, and high levels of low-density lipoprotein cholesterol and triglyceride develop in up to 60% of patients treated with these regimens[1]. In 10–20% of patients the effects are severe, with unstable angina, myocardial infarction, and stroke developing even in young individuals[14–18].

As regards lipodystrophy, similarities between HIV-associated fat redistribution and metabolic abnormalities with both inherited lipodystrophies and benign symmetric lipomatosis suggest the pathophysiological involvement of nuclear factors such as lamin A/C and drug-induced mitochondrial dysfunction[19]. Moreover, there is some evidence that cytokines and hormones impair fat and glucose homoeostasis in patients with HIV receiving HAART[19]. Three years after the first description of HIV-therapy-associated abnormal fat redistribution, there is still discussion about the case definition, diagnostic procedure and treatment options for both body shape changes and metabolic disturbances[19].

In the evaluation of patients for HAART and in continued therapy, it is wise to look at traditional coronary risk profiles and to alter those that can be favourably modified. Diet and exercise should not be overlooked, because both can be effective without causing further side-effects[20]. Fibric acid derivatives and statins can lower HIV-associated hypercholesterolaemia and hypertriglyceridaemia, although further data are needed on interactions between statins and PI[20,21]. Lovastatin should be avoided in patients receiving drugs that might potentiate the skeletal muscle toxicity of this agent[22]. Hypoglycaemic agents may have some role in management of glucose abnormalities, although troglitazone cannot be recommended for fat abnormalities alone and metformin may cause lactic acidosis[21]. Perhaps a better understanding of PI effects on lipid and metabolic pathways will lead to a new generation of drug therapies without metabolic alterations.

HIV patients are at higher risk of becoming hypertensive than the general population, and hypertension develops at a younger age[23]. Predisposing factors include vasculitis in small, medium, and large vessels in the form of leukocytoclastic vasculitis, atherosclerosis secondary to HAART regimens, and aneurysms of the large vessels such as the carotid and femoral arteries and the abdominal aorta, with impairment of flow to the renal arteries[23].

PULMONARY HYPERTENSION AND RIGHT VENTRICULAR DYSFUNCTION

The incidence of HIV-associated pulmonary hypertension is estimated to be 1/200, much higher than the 1/200 000 found in the general population[1]. Common reasons for pulmonary hypertension in HIV-infected patients are lung infections, venous thromboembolism and left ventricular dysfunction. Pulmonary hypertension found on screening echocardiography or right heart catheterization warrants an aggressive evaluation for treatable pulmonary infections[24].

Primary pulmonary hypertension has been reported in HIV-infected patients without a history of thromboembolic disease, intravenous drug use, or pulmonary infections associated with HIV. One necropsy specimen and one biopsy specimen revealed precapillary muscular pulmonary artery and arteriole medial hypertrophy, fibroelastosis, and eccentric intimal fibrosis without direct viral infection of

pulmonary artery cells[24,25]. This suggests mediator release from infected cells elsewhere and possibly cytokine mediated injury.

The pathogenesis of primary pulmonary hypertension is multifactorial and poorly understood. Primary pulmonary hypertension has been found in haemophilic patients receiving lyophylized factor VIII, in intravenous drug users and in patients with left ventricular dysfunction, obscuring any relationship with the human immunodeficiency virus[1,24,25]. It may be that HIV causes endothelial damage and mediator-related vasoconstriction through stimulation by the envelope *gp 120*, including direct release and effects of endothelin-1 (vasoconstrictor), interleukin-6 and TNF-α in the pulmonary arteries[24,25].

HIV is frequently identified in alveolar macrophages[24,25]. These macrophages release TNF-α, oxide anions and proteolytic enzymes in response to infection. Lymphokines may also have a role in the aetiology of the endothelial proliferation seen in pulmonary hypertension, by promoting leukocyte adhesion to the endothelium[26]. Clinical symptoms and outcome of patients with right ventricular dysfunction are related to the degree of pulmonary hypertension, varying from a mild symptomless condition to severe cardiac impairment with cor pulmonale and death[1,24]. Activation of α_1-receptors and genetic factors (increased frequency of HLA DR6 and DR52) have been also hypothesized for the pathogenesis of HIV-associated pulmonary hypertension[1,26]. The influence of HAART regimens on the clinical course of HIV-associated pulmonary hypertension is unknown.

Figure 2 **Fibrinous pericarditis in AIDS patient induced by *M.avium intracellulare* infection.** Note focal thickening of epicardium suggesting simultaneous involvement of myocardium below

Figure 3 ***Candida albicans* endocarditis of tricuspid valve in drug abuser with AIDS (necropsy finding).** A large polypoid thrombotic lesion is seen on the posterior leaflet

PERICARDIAL EFFUSION

The incidence of pericardial effusion among those meeting criteria for AIDS is 11% per year[27]. The prevalence of symptomless pericardial effusion in AIDS patients is estimated at 22%[27]. HIV infection should be included in the differential diagnosis of unexplained pericardial effusion or tamponade. AIDS patients with pericardial effusion survive a median of 6 months—considerably less time than AIDS patients without effusion. Survival is independent of CD4 count and albumin levels[27].

Pericardial effusion in HIV disease may be related to opportunistic infections (Figure 2) or to malignancy (Kaposi's sarcoma, non-Hodgkin lymphoma), but most often a clear aetiology is not found[27]. The effusion may be part of a generalized serous effusive process also involving pleural and peritoneal surfaces. This capillary leak syndrome is probably related to enhanced cytokine expression (e.g. TNF-α) in the later stages of HIV disease[1,27]. Pericardial effusion spontaneously resolves in up to 42% of patients[1,27]. Pericardiocentesis is currently recommended only for large or poorly tolerated effusions, for diagnostic evaluation of systemic illness or in the presence of cardiac tamponade[1]. Even if the effusion resolves over time[1], these patients still have excess mortality. The effects of HAART therapy on pericardial effusion are largely unexplored.

ENDOCARDIAL INVOLVEMENT

The prevalence of infective endocarditis in HIV-infected patients is similar to that in other patients of similar behaviour risk—i.e. intravenous drug use[1]. Estimates of endocarditis occurrence vary from 6.3% to 34% of HIV-infected patients who use intravenous drugs[1,7]. Right-sided valves are predominantly affected and the most frequent pathogens are *Staphylococcus aureus*, *Candida albicans* (Figure 3), *Aspergillus fumigatus*, *Histoplasma capsulatum*, and *Cryptococcus neoformans*[1,7]. Patients with and without HIV generally have similar presentation and survival rates from infective endocarditis. However, patients with late-stage HIV disease have higher mortality from infective endocarditis than do those with earlier disease[1].

As the autoimmune response to bacterial endocarditis is often largely responsible for associated valvular destruction,

HIV-infected patients may have an altered course. For example, HIV-infected patients have a higher risk of developing salmonella endocarditis than immunocompetent patients because they are more likely to develop salmonella bacteraemia during salmonella infection. However, they respond better to antibiotic therapy, and may be less likely to sustain valvular damage because of impaired immune function[1].

Non-bacterial thrombotic endocarditis, also known as marantic endocarditis, is most common in patients with HIV wasting syndrome[1]. It is characterized by friable endocardial vegetations, consisting of platelets within a fibrin mesh with few inflammatory cells. The lesions may involve any of the four valves but are more common on the left side. Systemic or pulmonary embolization can cause serious end-organ damage in spleen, kidneys and myocardium. Systemic embolization from marantic endocarditis is a rare cause of death in AIDS patients[1].

DRUG CARDIOTOXICITY

An association between zidovudine and dilated cardiomyopathy has been reported in both adult and paediatric patients[28,29]. Studies performed on transgenic mice suggest that zidovudine is associated with diffuse destruction of cardiac mitochondrial ultrastructures and inhibition of mitochondrial DNA replication[30]. Lactic acidosis related to mitochondrial dysfunction may further contribute to myocardial cell dysfunction[31]. However, from a clinical point of view, in a study of selected HIV-infected children zidovudine neither worsened nor ameliorated cardiomyopathy[32]. Infants born to HIV-positive mothers were followed from birth to age 5 years with serial echocardiographic studies every 4–6 months. No association with acute or chronic abnormalities in left ventricular structure or function was found with perinatal exposure to zidovudine[33]. Other antiretroviral drugs, such as didanosine and zalcitabine, do not seem either to promote or to prevent dilated cardiomyopathy[4].

In AIDS patients with Kaposi's sarcoma, reversible cardiac dysfunction was associated with prolonged high-dose therapy with interferon alpha[1,34]. High-dose interferon alpha treatment is not associated with myocardial dysfunction in other patient populations, so a synergistic effect with HIV infection has been proposed[35].

Doxorubicin, used to treat AIDS-related Kaposi's sarcoma and non-Hodgkin lymphoma, has a dose-related effect on dilated cardiomyopathy[36], as does foscarnet sodium when used to treat cytomegalovirus oesophagitis[37]. The prevalence of hypertension associated with erythropoietin therapy is 47%; the effect may be related to the increase in haematocrit and blood viscosity[38].

Cardiac arrhythmias (ventricular tachycardia or ventricular fibrillation, *torsade de pointes* [related to prolongation of QTc interval], atrioventricular conduction abnormalities) have been described with the administration of amphotericin B[39], ganciclovir[40], co-trimoxazole[41] and pentamidine[42]. Prolongation of QTc interval has been described also with the administration of macrolide antibacterials (erythromycin, clarithromycin)[42]. In HIV-infected patients cisapride, a prokinetic agent often used for the treatment of gastro-oesophageal reflux, may increase the risk of *torsade de pointes* when administered in combination with other drugs such as macrolide antibacterials, azole antifungal agents (fluconazole, itraconazole, ketoconazole), all PI (amprenavir, indinavir, nelfinavir, ritonavir, saquinavir), and drugs that have potential additive effects on the QT interval (adenosine, class Ia and III antiarrhythmic drugs)[43].

NUTRITIONAL DEFICIENCIES

Nutritional deficiencies are common in HIV infection, particularly in late-stage disease, and may contribute to ventricular dysfunction independently of HAART regimens. Poor absorption and diarrhoea both lead to electrolyte imbalances and deficiencies in elemental nutrients. Deficiencies of trace elements have been associated directly or indirectly with cardiomyopathy[44]. For example, selenium deficiency increases the virulence of coxsackievirus to cardiac tissue[45]. Selenium replacement reverses cardiomyopathy and restores left ventricular function in nutritionally depleted patients[44]. Levels of vitamin B12, carnitine, growth hormone and thyroid hormone may also be altered in HIV disease; all have been associated with left ventricular dysfunction[44]. Electrolyte imbalances (e.g. hypokalaemia, hypocalcaemia, hypomagnesaemia), related to malnutrition or to chronic diarrhoea, may further contribute to induction of ventricular arrhythmias (*torsade de pointes* and ventricular fibrillation) by prolongation of the QTc interval.

CARDIAC INVOLVEMENT IN AIDS-RELATED TUMOURS

Cardiac Kaposi's sarcoma in AIDS may cause visceral and parietal pericardial lesions and, less frequently, myocardial lesions. The prevalence has ranged from 12% to 28% in retrospective necropsy studies in the pre-HAART era[1–7] (Figure 4). Cardiac Kaposi's sarcoma is not usually obstructive or associated with clinical cardiac dysfunction, morbidity or mortality[1].

Malignant lymphoma involving the heart is infrequent in AIDS[1,7,46]. Lymphomatous infiltration may be diffuse or may result in discrete isolated lesions, which are usually derived from the Burkitt or immunoblastic B cells. The

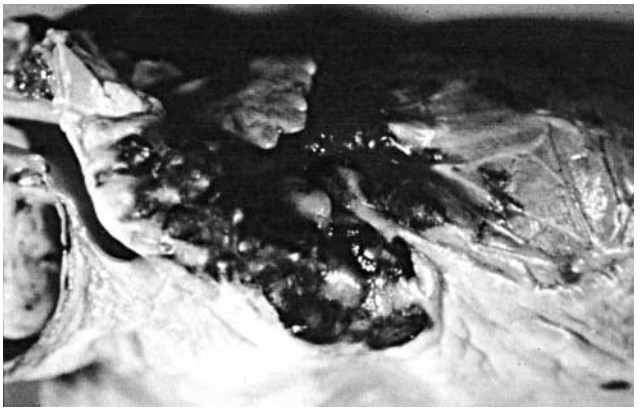

Figure 4 **Cardiac Kaposi's sarcoma in AIDS patient.** The epicardial lesions appear as red purple coalescent plaques

lesions tend to be nodular or polypoid, and they predominantly involve the pericardium, with variable myocardial infiltration[1,7]. The prognosis of patients with HIV-associated cardiac lymphoma is generally poor, although clinical remission has been observed with combination chemotherapy[1].

The better control of human herpes virus 8 and Epstein–Barr virus infection, which are involved in the development of HIV-associated tumours, may account for the reduction, since the advent of HAART, in overall incidence of cardiac involvement by both Kaposi's sarcoma and non-Hodgkin lymphomas.

CONCLUSIONS

As therapies improve, late complications of HIV infection are becoming more prevalent. Cardiac and pulmonary complications of HIV disease are generally late manifestations and may be due to prolonged immunosuppression and a complex interplay of mediator effects from opportunistic infections, viral infections, autoimmune response to viral infection, drug-related cardiotoxicity and nutritional deficiencies. Careful clinical evaluation is required for patients who receive antiretroviral treatment (with zidovudine and PI) or drugs with recognized cardiotoxic action (doxorubicin, interferon alpha, pentamidine), for patients whose CD4 count is below 400/μL, and for patients with HIV-associated encephalopathy. HIV-associated heart disease may be an important model for the mechanisms behind dilated cardiomyopathy. The study of immunological factors may provide useful information about testable therapies for HIV-associated cardiomyopathy. Such findings would also have important implications for non-HIV-related cardiovascular diseases. Since the role of infection and inflammation in many other cardiovascular diseases is beginning to be recognized, discovery of the molecular mechanisms of HIV-related heart disease might provide the basis for rational therapy in a broader range of patients[5].

Acknowledgment I thank Giulia D'Amati MD, Department of Experimental Medicine and Pathology, University 'La Sapienza', Rome, for providing the illustrations.

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