

Human immunodeficiency virus-associated heart failure in sub-Saharan Africa: evolution in the epidemiology, pathophysiology, and clinical manifestations in the antiretroviral era

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Abstract

The survival of patients with human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) who have access to highly active antiretroviral therapy (ART) has dramatically increased in recent times. This review focuses on HIV-associated heart failure in sub-Saharan Africa (SSA). In HIV infected persons, heart failure may be related to pathology of the pericardium, the myocardium, the valves, the conduction system, or the coronary and pulmonary vasculature. HIV-associated heart failure can be because of direct consequences of HIV infection, autoimmune reactions, pro-inflammatory cytokines, opportunistic infections (OIs) or neoplasms, use of ART or therapy for OIs and presence of traditional cardiovascular risk factors. Myocardial involvement includes diastolic dysfunction, asymptomatic left ventricular dysfunction, cardiomyopathy, myocarditis, fibrosis, and steatosis. Pericardial diseases include pericarditis, pericardial effusions (rarely causing tamponade), pericardial constriction, and effusive-constrictive syndromes. Coronary artery disease is commonly reported in industrial nations, although its prevalence is thought to be low in HIV-infected persons from SSA.

Keywords HIV; AIDS; Heart failure; Cardiovascular disease; Africa; HIV-associated heart failure; HIV-associated cardiovascular disease

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Introduction

By the end of 2013, 35 million people globally were living with the human immunodeficiency virus (HIV), and new HIV infections in the same year were estimated at 2.1 million, which was 38% lower than in 2001.¹ The number of acquired immunodeficiency syndrome (AIDS) related deaths also continues to decline, with 1.5 million people dying of AIDS-related causes in 2013, down 35% from the peak in 2005.¹ The survival of people living with HIV/AIDS has dramatically increased since the widespread use of antiretroviral therapy (ART).^{2,3} The Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates that 13.6 million people were receiving ART as of June 2014, and that the world is projected to deliver ART to at least 15 million people by 2015.¹ HIV-associated cardiovascular disease (CVD) involves every

segment of the cardiovascular tree and commonly affects all layers of the heart, including the myocardium, valves, pericardium and coronary, pulmonary, cerebrovascular, and peripheral vasculature.⁴

The incidence of HIV/AIDS related heart failure is on the increase, and current evidence suggests that diastolic, rather than systolic, dysfunction is the predominant form of heart failure in the era of ART.^{5–11} The pathophysiology of heart failure in HIV infected persons is multi-factorial and is intimately related to the presence of traditional risk factors for coronary artery disease, myocardial inflammation, myocardial fibrosis, coronary artery disease, pericardial disease, impaired vascular compliance, myocardial steatosis, pulmonary vascular, and renal disease.^{4,10,12,13} There is a paucity of data on optimal management of HIV-associated heart failure, and data are extrapolated from studies conducted on HIV

uninfected persons, particularly from sub-Saharan Africa (SSA). This review will focus on HIV-associated heart failure in SSA.

ART has significantly altered the natural history of HIV infection, lengthened survival, and improved the quality of life of HIV-infected patients.^{2,3} ART use has also been associated with lipid and metabolic abnormalities associated with an increased risk of both peripheral and coronary arterial diseases,^{14–16} which may contribute to the development of heart failure. Consequently, we thought it was timely to place into perspective the evolving concepts and comprehension of HIV-associated heart failure through systematic review and critical appraisal of the literature. For the purposes of this review, HIV refers to the HIV-1 infection.

Historical perspectives

The association between CVD and HIV infection was recognised early in the history of the AIDS pandemic,¹⁷ with the report of the first case of symptomatic dilated cardiomyopathy (DCM) in 1986. Throughout the 1980s and 1990s, the presence of heart failure in HIV infection was mainly in the context of myocarditis and severe systolic dysfunction, which were thought to be related to direct effects of HIV as well as opportunistic infections, autoimmunity, nutritional deficiencies, and prolonged and profound immunosuppression.^{13,18,19}

In the pre-ART era, the prevalence of HIV-associated cardiomyopathy was 30–40% in hospitalised patients in developed countries, with an annual incidence of 15.9 per 1000 patients.²⁰ However, in SSA, data from historic cross-sectional echocardiographic studies of hospitalised patients revealed a prevalence of HIV-associated cardiomyopathy ranging from 9 to 57%,^{21,22} and an in-hospital incidence of 17% over 18 months.²³ These large variations in epidemiology of HIV-associated cardiomyopathy in Africans largely reflected differing study populations, study designs, and case definitions.²⁴ Further, the prevalence of left ventricular (LV) dysfunction in acutely ill, hospitalised patients, independent of HIV infection, may also have artificially inflated the prevalence rates in these older studies.²⁵

Before the availability of ART, the median survival to AIDS-related death was 101 days in patients with overt LV dysfunction, and 472 days in patients with a normal heart on echocardiography, at a similar stage of immunosuppression.¹³ Importantly, the unadjusted hazard ratio for death in HIV-associated DCM compared with idiopathic DCM was 4.0; the ratio adjusted after multivariate analysis was 5.86.²⁶ However, since the introduction of ART, the phenotype of HIV-associated heart failure has changed from severe, dilated cardiomyopathy to subclinical LV dysfunction, with mildly reduced LV systolic and frequent findings of impaired diastolic function.²⁷

In a study performed in 1999 in the Netherlands involving 105 ambulatory HIV patients receiving ART, the prevalence of myocardial systolic dysfunction was low (3%) and none of the patients developed end-stage DCM.²⁸ The authors suggest a myocardial protective effect of ART to explain this low prevalence of cardiac dysfunction compared with the findings of previous studies.²⁸ A retrospective study conducted in Italy among HIV-positive patients on ART showed a lower incidence of cardiac involvement in patients treated with combination ART from 1996 to 1998 compared with those treated with nucleoside reverse transcriptase inhibitors (NRTIs) in earlier years.²⁹

Several historic studies have reported the incidence of HIV-associated heart failure to be much higher in SSA compared with western countries.^{30,31} Further, when treated HIV-infected persons from SSA were compared with those treated in the USA, there were significantly more cardiovascular events observed in Africans, highlighting the potential contribution of systematic challenges in HIV management in the region.³²

Current epidemiology

The prevalence of CVD in HIV infection remains unclear and depends on the population studied, the definition of the specific CVD and the background prevalence of CVD in the population. There is a dearth of population-based studies, and most studies have been based on hospital and clinic patients. Despite this, several recent publications have expanded our understanding of the epidemiology of HIV-associated CVD and heart failure and have highlighted a number of important themes, which we will focus on in this review.

The first relates to unexpectedly low rates of CVD events and mortality in patients receiving ART. In light of the prior evidence that HIV increased the risk of CVD and knowledge that ART was allowing HIV infected persons to survive longer, the assumption has been that there would be a growing and proportionate increase in HIV associated CVD. The second relates to the observation that although HIV does increase the risk of atherosclerotic cardiovascular complications, a significant proportion of the risk is attributable to conventional or traditional modifiable risk factors. The third is that the increasingly earlier introduction and increased uptake of ART appear to have significantly reduced the risks of HIV associated cardiomyopathy, pericardial disease, and possibly HIV associated pulmonary hypertension. Along with this is the observation that the phenotype of heart muscle disease has shifted from systolic dysfunction associated with opportunistic infections to diastolic dysfunction associated with inflammation and fibrosis. Finally in sub-Saharan Africa where the burden of HIV infection is highest (70% of the world's burden reside in 8 SSA countries) the anticipated pandemic of HIV-associated CVD has not materialised. However, this may

be related to insufficient research and technology focusing on these specific questions, particularly in SSA.

With the life expectancy for HIV infected persons on ART approaching that of the general population, it was assumed that cardiovascular causes of morbidity would be important. A recent publication investigating trends over time in all-cause mortality and for specific causes of death in people with HIV from 1999 to 2011 (from the D:A:D study) found that the crude incidence mortality rate was 12.7 per 1000 person-years, with leading causes of death being AIDS-related (29%), non-AIDS-defining cancers (15%), liver disease (13%), and CVD (11%).³³ Of note, the rates of mortality because of CVD had decreased over time (from 1.8 to 0.9 per 1000 person-years), which was attributed to improved use of non-HIV-specific preventive interventions (though this was not specifically measured in the study). This study concludes that non-AIDS cancer is now the leading non-AIDS cause of death in HIV.³³ Similar to the D:A:D study, the HIV Outpatient Study (HOPS), conducted between 1996 and 2008, showed that death rates gradually declined from 7 per 100 person-years in 1996, to 2 deaths per 100 person-years after 1999.³⁴ This is in sharp contrast to the reports by Zhang and colleagues on the risk of non-AIDS defining events among HIV-infected persons not yet on ART: noting that CVD and other non-AIDS complications remained high and were associated with the severity of immunodeficiency as determined by a CD4 count <200 cells/ μ L.³⁵

The importance of traditional risk factors and their background prevalence in various populations was illustrated in the Veterans Aging Cohort Study of 81 000 people, a third of whom were HIV-infected. While HIV infection was associated with an increased risk of developing atherosclerotic related complications such as myocardial infarction, conventional risk factors accounted for a significant proportion of the risk.³⁶ Two recently published meta-analyses, including observational and randomised controlled trial data have reported that HIV-associated coronary artery and cerebrovascular disease is common.^{37,38} Moreover, compared with HIV uninfected populations, the relative risk (RR) of events was higher both for untreated and ART-treated HIV infected persons (RR=1.61 (1.43 to 1.81) and RR=2.00 (1.70 to 2.37), respectively). The HR was higher for protease inhibitor (PI)-based therapies vs. non-PI treatments. Another meta-analysis of 11 studies conducted during the ART era assessed 2242 well-controlled, asymptomatic HIV infected persons who had a prevalence of systolic dysfunction of 8.3% and diastolic dysfunction of 43.4%.⁵ Risk factors for systolic dysfunction included high-sensitivity C-reactive protein >5 mg/L, tobacco use, and prior myocardial infarction; and for diastolic dysfunction, risk factors were hypertension and older age.⁵

Finally in SSA, the region with the highest burden of HIV, the feared impending pandemic of CVD related to CAD following the introduction of ART has not been manifest. The Heart of Soweto Study, which was designed to investigate the

impact of the HIV/AIDS on de novo manifestations of heart disease, 518 of 5328 cases (9.7%) of newly diagnosed heart disease were HIV infected.³⁸ Of those, almost 29% had LV systolic dysfunction and 38% had HIV-associated cardiomyopathy (including both systolic and diastolic dysfunction); the incidence of coronary artery disease (CAD), was found in just 2.7% of patients.³⁹ Similarly, the sub-Saharan Africa Survey of Heart Failure (THESUS-HF) study, a prospective, multicenter observational survey of 1006 patients from 9 countries with acute heart failure found that HIV was detected in 13% of subjects and that CAD was only present in 7.7% of patients.⁴⁰ A recent review supports these observations, summarising that both systolic and diastolic dysfunction are more common among HIV-infected (vs. uninfected) persons in low- to middle-income countries.⁴¹

While ART has significantly improved outcomes in patients with HIV-associated CVD, ART may also be associated with deleterious effects. ART has been associated with worsening LV systolic function.⁴² Zidovudine has been linked with both systolic and diastolic dysfunction.^{18,43,44} While ART use in HIV-infected patients with heart failure was associated with improvement in LV systolic function compared with non-treated controls, four patients have worsening cardiac function that improved upon discontinuation of zidovudine, stavudine, and didanosine.⁴⁵ ART may be associated with increased risk of lipodystrophy and metabolic complications that increase the risk of CAD, as discussed below (*Table 1*).^{46–48}

Pathophysiology

The pathophysiology of cardiovascular involvement in HIV infection is listed in *Table 2*. The evidence for these putative

Table 1. Abbreviations

Abbreviations	
ACS	Acute coronary syndrome
AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral therapy
CD	Cluster of differentiation
CMR	Cardiovascular magnetic resonance
CVD	Cardiovascular disease
CT	Computed tomography
DAD	Data collection on Adverse events of anti-HIV Drugs trials
DCM	Dilated cardiomyopathy
HIV	Human immunodeficiency syndrome
HOPS	HIV Outpatient Study
LV	Left ventricle/ventricular
NRTI	Nucleoside reverse transcriptase inhibitor
OI	Opportunistic infection
PI	Protease inhibitor
RNA	Ribonucleic acid
RR	Relative risk
SSA	Sub-Saharan Africa
TIMI	Thrombolysis in myocardial infarction
UNAIDS	Joint United Nations Commission on HIV/AIDS

Table 2. Mechanisms of cardiovascular involvement in HIV infection

Mechanisms
1. Direct HIV infection
2. Opportunistic infections
3. Coexistent traditional risk factors
4. Toxicity of HIV components
5. HIV-related malignancies
6. Drug toxicity
7. Nutritional deficiencies
8. Exaggerated pro-inflammatory cytokine response
10. Capillary leak
11. HIV-wasting disease
12. HIV-induced endothelial dysfunction
13. Coagulopathy
14. Vasculitis
15. Myocardial fibrosis
16. Myocardial lipidosis
17. Mitochondrial injury
18. Dysregulated (abnormal) immune processes involving MHC I and anti- α -myosin autoantibodies (autoimmunity)
19. Immune reconstitution inflammatory syndrome

mechanisms is discussed below as it applies to specific pathologies/conditions. Briefly, the pathophysiology of HIV-associated heart failure is multifactorial, with varying amounts of evidence for various presumptive mechanisms. Postulated mechanisms include consequences of direct HIV infection and toxicity of HIV components, opportunistic infections, and autoimmunity.^{49–55} Increased myocardial inflammation, endothelial dysfunction, capillary leak syndrome, and abnormal coagulation have also been implicated in the pathophysiology.^{56–59} HIV-associated wasting disease, malignancies, and nutritional deficiencies have also been associated with cardiovascular abnormalities in HIV infected persons.^{44,60–62} There is increasing evidence of the importance of myocardial fibrosis and steatosis in driving cardiovascular dysfunction in HIV.^{10,12} In the D:A:D study of 4000 HIV infected persons and over 1 million HIV uninfected controls, hypertension, diabetes, dyslipidaemia, and smoking were all found more commonly in the HIV infected cohort.⁶³

Diastolic dysfunction

In recent times, a high prevalence of diastolic abnormalities in HIV infected persons has been reported, mostly with echocardiography. Diastolic dysfunction has been reported commonly in HIV-infected patients from echocardiographic studies, and to be more severe in those with clinical AIDS.^{7,9,22,64,65} Increasingly, strain imaging has been used to document global and segmental systolic and diastolic dysfunction in HIV-infected patients with preserved LV systolic function and in absence of cardiovascular symptoms.^{66,67} In a study of 50 asymptomatic HIV-infected patients (one patient with grade 1 diastolic dysfunction), longitudinal strain, early, and late diastolic strain rates were impaired in

HIV-infected persons.⁶⁶ In a cross-sectional study of 698 HIV-infected persons, 48% had diastolic dysfunction, which was associated with older age, higher body mass index, higher total cholesterol, arterial hypertension, and diabetes mellitus.⁶⁸ Recently, cardiovascular magnetic resonance (CMR) has been used to demonstrate high rates of systolic and diastolic dysfunction in cohorts of asymptomatic HIV-infected persons with preserved ejection fraction.^{10,12}

Cardiomyopathy and systolic dysfunction

HIV has long been recognised as a significant cause of acquired cardiomyopathy.¹⁷ The current prevalence of HIV-associated cardiomyopathy is substantially lower in industrial countries compared with the pre-ART era, mainly because of the ease of access to ART and reduction in opportunistic infections.^{4,27} In the era of ART, the epidemiology of HIV-associated cardiomyopathy has changed substantially; however, very few studies have measured the incidence at a population level in recent times. In The Heart of Soweto Study, cardiomyopathy was reported in 38% of HIV infected patients studied, comprising systolic and diastolic dysfunction in both symptomatic and asymptomatic patients.³⁹ Pathologic features of HIV-associated cardiomyopathy are similar to those observed in HIV uninfected patients with DCM.⁶⁹ The macroscopic pathological features include dilated cardiac chambers with endocardial fibrosis and mural thrombus. Histologically, there is evidence of myocyte hypertrophy and degeneration, with increased interstitial and endocardial fibrillar collagen and evidence of prior myocarditis.⁶⁹ Echocardiography is the first line imaging modality for diagnosis HIV-associated cardiomyopathy; and is useful for assessment of LV systolic function and for looking for wall motion abnormalities, as well as assessment of diastolic function and differential diagnosis. CMR, where available, should always be considered, and provides an accurate assessment of ventricular morphology and function, myocardial fibrosis, myocardial oedema, late gadolinium enhancement, and prognosis, as well as comprehensive assessment of differential diagnosis. Further, in a study of 60 patients with HIV-associated cardiomyopathy, inotropic contractile reserve during dobutamine stress echocardiography was shown to risk-stratify patients and to predict subsequent improvement in LVEF.⁷⁰ Endomyocardial biopsy (EMB), while not routinely performed, remains the gold standard tool for diagnosis of the aetiological agent of the HIV-associated cardiomyopathy.

Myocarditis

Myocardial inflammation and myocarditis are likely the most studied causes of HIV-associated heart failure. A myocarditis directly because of HIV has been described, but the virus

appears to infect the myocardial cells in a patchy distribution,⁷¹ without a clear association between HIV viral load and cardiomyocyte dysfunction. However, myocarditis in HIV may be related to other micro-organisms. For instance, *Mycobacterium tuberculosis*,⁷² *Mycobacterium avium*,⁷² *Toxoplasma gondii*,⁷³ *Cryptococcus neoformans*,⁷⁴ *Histoplasma capsulatum*,⁷⁵ herpes simplex,⁷⁶ parvovirus,⁷⁶ coxsackievirus B3,²⁶ and cytomegalovirus⁷¹ have been described as causes of myocarditis and pericarditis in HIV infection. In an autopsy series performed in the pre-ART era, myocarditis was documented in 40–52% of patients who died of AIDS.^{72,77} In more than 80% of these patients, no specific etiologic factor was found, whereas the remaining cases were attributable to above-mentioned infectious agents. In another historic study of HIV-associated cardiomyopathy, EMB revealed myocarditis with cardiotropic viral infection in almost all cases.⁷⁸

Shaboodien and colleagues have compared the prevalence of myocarditis and cardiotropic viral genomes in HIV-associated cardiomyopathy cases with HIV-negative idiopathic DCM patients and heart transplant recipients using EMB and the immunohistological criteria of the World Heart Federation (WHF) in 33 patients.⁷⁹ In this study, myocarditis was present in 44% of HIV-associated cardiomyopathy cases, 36% of heart transplant recipients, and 25% of participants with idiopathic DCM. While myocarditis was acute in 50% of HIV- and heart transplant-associated myocarditis, it was chronic in all those with idiopathic DCM. Cardiotropic viral infection was present in all HIV-associated cardiomyopathy and idiopathic DCM cases, and in 90% of heart transplant recipients. Multiple viruses were identified in the majority of cases, with HIV-associated cardiomyopathy, heart transplant recipients, and idiopathic DCM patients having an average of 2.5, 2.2, and 1.1 viruses per individual, respectively.

Vascular stiffness

HIV is well-established as an independent risk factor for the development of arterial stiffness. In a study of 49 children (34 on ART, and 15 untreated) without cardiovascular risk factors, endothelium-dependent vasodilatation was lower in HIV, indicating presence of vascular dysfunction.⁸⁰ Importantly, in this study, impaired arterial stiffness was not associated with adverse cardiovascular outcomes after a mean of 5 years of follow-up on ART. Similarly, a study of 77 adult men (55 on ART and 22 ART-naïve) found that HIV-infected patients had greater carotid intima medial thickness and lower arterial distensibility, which was associated with ART use, but was independent of lipodystrophy.⁸¹ Further, smoking and hypertension were found to be incremental risks to HIV for the development of arterial stiffness.⁸² However, a study of 174 HIV-infected persons on ART, 90% of whom were virologically suppressed, found similar arterial pulse wave

velocity to matched HIV-uninfected controls.⁸³ Arterial stiffness has also been shown to be worse in HIV-infected persons with advanced immunosuppression.^{84,85} Using CMR, HIV infection was associated with impaired pulse wave velocity and aortic distensibility, and the magnitude of effect of treated HIV on vascular stiffness was similar but independent to that of the metabolic syndrome.⁸⁶

Pericardial disease

In HIV infection, cardiac failure may also be related to pericardial disease. In areas of the world, where tuberculosis is endemic, as in SSA, pericardial tuberculosis is an important cause HIV-related pericardial disease. The spectrum of tuberculous-related pericardial disease in HIV may include pericarditis, pericardial effusions, pericardial tamponade, myopericarditis, effusive-constrictive syndromes, pericardial constriction, and calcific pericardial constriction. Tuberculous pericardial involvement usually develops by retrograde lymphatic spread of *M. tuberculosis* from peritracheal, peribronchial, or mediastinal lymph nodes or by hematogenous spread from primary tuberculous infection. Less commonly, the pericardium may be involved by contiguous spread from a tuberculous lesion in the lung or by hematogenous spread from distant secondary skeletal or genitourinary infection.

Historic studies established that in SSA tuberculosis accounted for over 80% of causes of pericardial effusion in HIV-infected persons.^{87,88} Constrictive pericarditis was reported to occur in 30–60% of patients, despite prompt antituberculosis treatment and the use of corticosteroid.⁸⁹ A study of 185 patients with tuberculous pericardial disease (79.5% effusive, 15.1% effusive-constrictive, and 5.4% constrictive or acute dry pericarditis), 40% of whom had clinical features or a confirmed diagnosis of HIV found that patients with HIV infection were more likely to present with dyspnoea and ECG features of myopericarditis.⁹⁰ Additionally, HIV was associated with greater cardiomegaly and haemodynamic instability, but stage of pericardial disease at diagnosis and use of diagnostic tests were not related to clinical HIV status. A different study of 174 patients with tuberculous-associated pericardial disease found the overall mortality rate to be 26%, with mortality higher in HIV infection (40% vs. 17 in uninfected individuals).⁹¹ In this study, independent predictors of mortality included a proven non-tuberculosis final diagnosis, the presence of clinical signs of HIV infection, coexistent pulmonary tuberculosis, and older age. HIV has also been shown to be associated with a lower incidence of constriction in presumed tuberculous pericarditis.⁹² Pericardiectomy, for the management of symptomatic pericardial constriction, is not associated with increased mortality in HIV infection.⁹³ In the largest clinical trial of prednisolone and *Mycobacterium indicus pranii* in tuberculous pericardial disease, 1400 patients (two thirds of whom were HIV-infected) were

included, prednisolone was associated with reduction in incident pericardial constriction and both prednisolone and *M. indicus pranii* were associated with significant increase in the incidence of cancer.⁹⁴ Prednisone was shown to be associated with an increase in HIV-associated malignancy, and clinicians should rather avoid its use in the management of HIV-associated tuberculous pericarditis.

Coronary artery disease

CAD in HIV-infected persons was reported early in HIV epidemic.^{95,96} Current data from industrial countries suggest that there is increasing occurrence of CAD, with a histologically distinctive form of accelerated atherosclerosis.⁹⁷ In these patients, vessel involvement is frequently diffuse and circumferential, affecting the whole artery.^{98,99} A unique finding of HIV-associated CAD is the unusual proliferation of smooth muscle cells, mixed with abundant elastic fibres, resulting in endoluminal protrusions.¹⁰⁰ Endothelial cells have been implicated to be central in development of HIV-associated CAD by altering procoagulant, anticoagulant, and fibrinolytic pathways. There is evidence of increased platelet activation in HIV.⁹⁸ Moreover, altered adhesion of HIV-infected monocytes-macrophages and HIV-associated angitis/vasculitis may also contribute to coronary arteriopathy.⁹⁹ In South Africa, there have been reports of *de novo* arteriothrombosis with evidence of acute coronary syndromes marked by fresh thrombus as opposed to an atherosclerotic occlusion.^{101,102} Atherosclerosis in HIV is a multifactorial pathogenic process with contributions from sequelae of ART (especially PIs) and HIV-mediated endothelial dysfunction.¹⁰³ PIs may lead to increased atherosclerosis via increased dyslipidemia, insulin resistance, increased levels of C peptide, lipodystrophy, and endothelial dysfunction.⁴⁶ In a single centre-study, HIV-infected patients had lower TIMI (thrombolysis in myocardial infarction) risk assessment scores and were more likely to have single-vessel disease.⁴⁷ The distribution of coronary lesions is similar to HIV-uninfected persons, and although a greater incidence of ischemic events is observed, including restenosis and stent thrombosis, the intermediate mortality rate is low.⁴⁸

Myocardial fibrosis

At autopsy, 40% of HIV-infected patients were found to have histological evidence of interstitial fibrosis,¹⁰⁴ although there has been a dearth of studies of myocardial fibrosis in contemporary cohorts of HIV-infected individuals. A recent CMR study reported that focal fibrosis was seen in up to 77% of asymptomatic HIV infected individuals.¹⁰ Similarly, diffuse fibrosis on CMR-determined extracellular volume estimation was found to be more frequent in HIV-infected persons compared with matched controls.¹¹

Myocardial lipidosis

Two recent CMR spectroscopy studies, using proton spectroscopy, have reported higher levels of myocardial steatosis in HIV-infected patients compared with controls.^{10,11} In the second study, intramyocardial lipid levels correlated with impaired strain, ART duration, and visceral adiposity.¹¹

Mitochondrial injury

There is some emerging evidence of impaired mitochondrial injury in HIV-infected individuals.¹⁰⁵ The Tat protein in HIV has been shown to impair mitochondrial membrane permeability, and this is one possible mechanism for mitochondrial injury in HIV infection.¹⁰⁶ There is no evidence of increased mitochondrial genetic abnormalities in HIV-infected persons.¹⁰⁷

Conclusions

The survival of patients with HIV/AIDS who have access to highly active ART has dramatically increased in recent times. CVD and heart failure are common in people with HIV infection and may be related to primary or secondary diseases of the myocardium, the pericardium, and the coronary arteries. In the ART era, diastolic dysfunction has emerged as the dominant form of heart failure. Heart failure may also be related to impaired systolic function, myocarditis and myocardial fibrosis and steatosis. HIV-associated heart failure can be because of direct consequences of HIV infection, autoimmune reactions, pro-inflammatory cytokines, opportunistic infections (OIs) or neoplasms, use of ART or therapy for OIs and presence of traditional cardiovascular risk factors. Physicians working at all levels of medicine should familiarise themselves with cardiovascular basis and assessment of HIV infected persons.

Conflicts of interest

None declared.

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References

- UNAIDS estimates. Fast-track: ending the AIDS epidemic by 2030. UNAIDS Scientific Expert panel 2013–2015 (www.unaids.org). Accessed January 2015.
- Weber R, Ruppik M, Rickenbach M, Spoerri A, Furrer H, Battegay M, Cavassini M, Calmy A, Bernasconi E, Schmid P, Flepp M, Kowalska J, Ledergerber B. Swiss HIV Cohort Study (SHCS). Decreasing mortality and changing patterns of causes of death in the Swiss HIV Cohort Study. *HIV Med* 2013; **14**: 195–207.
- Nakagawa F, Lodwick RK, Smith CJ, Smith R, Cambiano V, Lundgren JD, Delpech V, Phillips AN. Projected life expectancy of people with HIV according to timing of diagnosis. *AIDS* 2012; **26**: 335–343.
- Ntsekhe M, Mayosi BM. Cardiac manifestation of HIV infection: an African perspective. *Nat Clin Pract Cardiovasc Med* 2009; **6**: 120–127.
- Cerrato E, D'Ascenzo F, Biondi-Zoccai G, Calcagno A, Frea S, Grosso Marra W, Castagno D, Omedè P, Quadri G, Sciuto F, Presutti D, Frati G, Bonora S, Moretti C, Gaita F. Cardiac dysfunction in pauci symptomatic human immunodeficiency virus patients: a meta-analysis in the highly active antiretroviral therapy era. *Eur Heart J* 2013; **34**: 1432–1436.
- Onur I, Ikitimur B, Oz F, Ekmekci A, Elitok A, Cagatay AA, Adalet K, Bilge AK, Kaya MG. Evaluation of human immunodeficiency virus infection-related left ventricular systolic dysfunction by tissue Doppler strain echocardiography. *Echocardiography* 2014; **31**: 1199–1204.
- Reinsch N, Kahlert P, Esser S, Sundermeyer A, Neuhaus K, Brockmeyer N, Potthoff A, Erbel R, Buck T, Neumann T. Echocardiographic findings and abnormalities in HIV-infected patients: results from a large, prospective, multicenter HIV-heart study. *Am J Cardiovasc Dis* 2011; **1**: 176–184.
- Mondy KE, Gottdiener J, Overton ET, Henry K, Bush T, Conley L, Hammer J, Carpenter CC, Kojic E, Patel P, Brooks JT. SUN Study Investigators. High prevalence of echocardiographic abnormalities among HIV-infected persons in the era of highly active antiretroviral therapy. *Clin Infect Dis* 2011; **52**: 378–386.
- Hsue PY, Hunt PW, Ho JE, Farah HH, Schnell A, Hoh R, Martin JN, Deeks SG, Bolger AF. Impact of HIV infection on diastolic function and left ventricular mass. *Circulation Heart Fail* 2010; **3**: 132–139.
- Holloway CJ, Ntusi N, Suttie J, Mahmood M, Wainwright E, Clutton G, Hancock G, Beak P, Tajar A, Piechnik SK, Schneider JE, Angus B, Clarke K, Dorrell L, Neubauer S. Comprehensive cardiac magnetic resonance imaging and spectroscopy reveal a high burden of myocardial disease in HIV patients. *Circulation* 2013; **128**: 814–822.
- Butt AA, Chang CC, Kuller L, Goetz MB, Leaf D, Rimland D, Gibert CL, Oursler KK, Rodriguez-Barradas MC, Lim J, Kazis LE, Gottlieb S, Justice AC, Freiberg MS. Risk of heart failure with human immunodeficiency virus in the absence of prior diagnosis of coronary heart disease. *Arch Intern Med* 2011; **171**: 737–743.
- Thiara DK, Liu CY, Raman F, Mangat S, Purdy JB, Duarte HA, Schmidt N, Hur J, Sibley CT, Bluemke DA, Hadigan C. Abnormal myocardial function is related to myocardial steatosis and diffuse myocardial fibrosis in HIV-infected adults. *J Infect Dis* 2015; **212**: 1544–1551.
- Barbaro G, Fisher SD, Lipshultz SE. Pathogenesis of HIV-associated cardiovascular complications. *Lancet Infect Dis* 2001; **1**: 115–124.
- Mooser V, Carr A. Antiretroviral therapy-associated hyperlipidemia in HIV disease. *Curr Opin Lipidol* 2001; **12**: 313–319.
- Stein JH, Klein MA, Bellehumeur JL, McBride PE, Wiebe DA, Otvos JD, Sosman JM. Use of human immunodeficiency virus-1 protease inhibitors is associated with atherogenic lipoprotein changes and endothelial dysfunction. *Circulation* 2001; **104**: 257–262.
- Henry K, Melrow H, Huebsch J, Hermundson J, Levine C, Swensen L, Daley J. Severe coronary heart disease with protease inhibitors. *Lancet* 1998; **351**: 1328.
- Cohen IS, Anderson DW, Virmani R, Reen BM, Macher AM, Sennesh J, DiLorenzo P, Redfield RR. Congestive cardiomyopathy in association with the acquired immunodeficiency syndrome. *N Engl J Med* 1986; **315**: 628–630.
- Lipshultz SE. Dilated cardiomyopathy in HIV-infected patients. *N Eng J Med* 1998; **339**: 1153–1155.
- Barbaro G. Cardiovascular manifestations of HIV infection. *Circulation* 2002; **106**: 1420–1425.
- Barbarini G, Barbaro G. Incidence of the involvement of the cardiovascular system in HIV infection. *AIDS* 2003; **17**: S46–S50.
- Hakim JG, Matenga JA, Siziya S. Myocardial dysfunction in human immunodeficiency virus infection: an echocardiographic study of 157 patients in hospital in Zimbabwe. *Heart* 1996; **76**: 161–165.
- Nzuobontane D, Blackett KN, Kuaban C. Cardiac involvement in HIV infected people in Yaounde. *Cameroon Postgrad J Med* 2002; **78**: 678–681.
- Longo-Mbenza B, Tonduang K, Muvova D, Phuati MB, Seghers KV, Kestelot H. A clinical study of cardiac manifestations related to acquired immunodeficiency syndrome (AIDS) in Kinshasa. *Arch Mal Coeur Vaiss* 1995; **88**: 1437–1443.
- Ntsekhe M, Hakim J. Impact of human immunodeficiency virus infection on cardiovascular disease in Africa. *Circulation* 2005; **112**: 3602–3607.
- Artucio H, Digenio A, Pereyra M. Left ventricular function during sepsis. *Crit Care Med* 1989; **17**: 323–327.
- Barbaro G, Di Lorenzo G, Soldini M, Giancaspro G, Grisorio B, Pellicelli A, Barbarini G. Intensity of myocardial expression of inducible nitric oxide synthase influences the clinical course of human immunodeficiency virus-associated cardiomyopathy. Gruppo Italiano per lo Studio Cardiologico dei pazienti affetti da AIDS (GISCA). *Circulation* 1999; **100**: 933–939.
- Remick J, Georgiopoulou V, Marti C, Ofotokun I, Kalogeropoulos A, Lewis W, Butler J. Heart failure in patients with human immunodeficiency virus infection: epidemiology, pathophysiology, treatment, and future research. *Circulation* 2014; **129**: 1781–1789.
- Bijl M, Dieleman JP, Simoons M, van der Ende ME. Low prevalence of cardiac abnormalities in an HIV-seropositive population on antiretroviral combination therapy. *J Acquir Immune Defic Syndr* 2001; **27**: 318–320.
- Pugliese A, Isnardi D, Saini A, Scarabelli T, Raddino R, Torre D. Impact of highly active antiretroviral therapy in HIV-positive patients with cardiac involvement. *J Infect* 2000; **40**: 282–284.
- Obiako OR, Muktar HM. Challenges of HIV treatment in resource-poor countries: a review. *Niger J Med* 2010; **19**: 361–368.
- Niakara A, Drabo YJ, Kambire Y, Nebie LV, Kabore NJ, Simon F. Cardiovascular diseases and HIV infection: study of 79 cases at the National Hospital of Ouagadougou (Burkina Faso). *Bull Soc Pathol Exot* 2002; **95**: 23–26.
- Wester CW, Koethe JR, Shepherd BE, Stinnette SE, Rebeiro PF, Kipp AM, Hong H, Bussmann H, Gaolathe T, McGowan CC, Sterling TR, Marlink RG. Non-AIDS-defining events among HIV-1-infected adults receiving combination antiretroviral therapy in resource-replete versus resource-limited urban setting. *AIDS* 2011; **25**: 1471–1479.
- Smith CJ, Ryom L, Weber R, Morlat P, Pradier C, Reiss P, Kowalska JD, de Wit S, Law M, el Sadr W, Kirk O, Friis-Moller N, Monforte A, Phillips AN, Sabin CA, Lundgren JD. D:A:D Study Group. Trends in underlying causes of

- death in people with HIV from 1999 to 2011 (D:A:D): a multicohort collaboration. *Lancet* 2014; **384**: 241–248.
34. Palella FJ Jr, Baker RK, Moorman AC, Chmiel JS, Wood KC, Brooks JT, Holmberg SD. HIV Outpatient Study Investigators. Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. *J Acquir Immune Defic Syndr* 2006; **43**: 27–34.
 35. Paisible AL, Chang CC, So-Armah KA, Butt AA, Leaf DA, Budoff M, Rimland D, Bedimo R, Goetz MB, Rodriguez-Barradas MC, Crane HM, Gibert CL, Brown ST, Tindle HA, Warner AL, Alcorn C, Skanderson M, Justice AC, Freiberg MS. HIV infection, cardiovascular disease risk factor profile, and risk for acute myocardial infarction. *J Acquir Immune Defic Syndr* 2015; **68**: 209–216.
 36. Zhang S, van Sighem A, Kesselring A, Gras L, Prins J, Hassink E, Kauffmann R, Richter C, de Wolf F, Reiss P. ATHENA national observational HIV cohort study. Risk of non-AIDS-defining events among HIV-infected patients not yet on antiretroviral therapy. *HIV Med* 2015; **16**: 265–272.
 37. Islam FM, Wu J, Jansson J, Wilson DP. Relative risk of cardiovascular disease among people living with HIV: a systematic review and meta-analysis. *HIV Med* 2012; **13**: 453–468.
 38. Freiberg MS, Chang C-CH, Kuller LH, Skanderson M, Lowy E, Kraemer KL, Butt AA, Bidwell Goetz M, Leaf D, Oursler KA, Rimland D, Rodriguez Barradas M, Brown S, Gibert C, McGinnis K, Crothers K, Sico J, Crane H, Warner A, Gottlieb S, Gottdiener J, Tracy RP, Budoff M, Watson C, Armah KA, Doeblner D, Bryant K, Justice AC. HIV infection and the risk of acute myocardial infarction. *JAMA Intern Med* 2013; **173**: 614–622.
 39. Sliwa K, Carrington MJ, Becker A, Thienemann F, Ntsekhe M, Stewart S. Contribution of the human immunodeficiency virus/acquired immunodeficiency syndrome epidemic to de novo presentations of heart disease in the Heart of Soweto Study cohort. *Eur Heart J* 2012; **33**: 866–874.
 40. Damasceno A, Mayosi BM, Sani M, Ogah SS, Mondo C, Ojji D, Dzuzie A, Kouam CK, Suliman A, Schrueder N, Yonga G, Ba SA, Maru F, Alemayehu B, Edwards C, Davidson BA, Cotter G, Sliwa K. The causes, treatment and outcome of acute heart failure in 1006 Africans from 9 countries. *Arch Intern Med* 2012; **172**: 1386–1394.
 41. Bloomfield GS, Alenezi F, Barasa F, Lumsden R, Mayosi BM, Valesquez EJ. Human immunodeficiency virus and heart failure in low- and middle-income countries. *JACC Heart Fail* 2015; **3**: 579–590.
 42. Barbaro G. Metabolic and cardiovascular complications of highly active antiretroviral therapy for HIV infection. *Curr HIV Res* 2006; **4**: 79–85.
 43. Lipshutz SE, Orav EJ, Sanders SP, Hale AR, McIntosh K, Colan SD. Cardiac structure and function in children with human immunodeficiency virus infection treated with zidovudine. *N Eng J Med* 1992; **327**: 1260–1265.
 44. Luo L, Ye Y, Liu Z, Zuo L, Li Y, Han Y, Qiu Z, Li L, Zeng Y, Li TS. Assessment of cardiac diastolic dysfunction in HIV-infected people without cardiovascular symptoms in China. *Int J STD AIDS* 2010; **21**: 814–818.
 45. Pepeta L, Cilliers AM. Impact of highly active antiretroviral therapy on paediatric human immunodeficiency virus-associated left ventricular dysfunction within the Johannesburg teaching hospital complex. *Cardiol Young* 2012; **22**: 564–573.
 46. Klein D, Hurley LB, Quesenberry CP Jr, Sidney S. Do protease inhibitors increase the risk for coronary heart disease in patients with HIV-1 infection? *J Acquir Immune Defic Syndr* 2002; **30**: 471–477.
 47. Hsue PY, Giri K, Erikson S, Macgregor JS, Younes N, Shergill A, Waters DD. Clinical features of acute coronary syndromes in patients with human immunodeficiency virus infection. *Circulation* 2004; **109**: 316–319.
 48. Calza L, Manfredi R, Pocater D, Chiodo F. Risk of premature atherosclerosis and ischemic heart disease associated with HIV infection and antiretroviral therapy. *J Infect* 2008; **57**: 16–31.
 49. Lewis W. Cardiomyopathy in AIDS: a pathophysiological perspective. *Prog Cardiovasc Dis* 2000; **43**: 151–170.
 50. Welch K, Finkbeiner W, Alpers CE, Blumenfeld W, Davis RL, Smuckler EA, Beckstead JH. Autopsy findings in the acquired immune deficiency syndrome. *JAMA* 1984; **252**: 1152–1159.
 51. Cammarosano C, Lewis W. Cardiac lesions in acquired immune deficiency syndrome (AIDS). *J Am Coll Cardiol* 1985; **5**: 703–706.
 52. Reilly JM, Cunnion RE, Anderson DW, O'Leary TJ, Simmons JT, Lane HC, Fauci AS, Roberts WC, Virmani R, Parrillo JE. Frequency of myocarditis, left ventricular dysfunction and ventricular tachycardia in the acquired immune deficiency syndrome. *Am J Cardiol* 1988; **62**: 789–793.
 53. Grody WW, Cheng L, Lewis W. Infection of the heart by the human immunodeficiency virus. *Am J Cardiol* 1990; **66**: 203–206.
 54. Currie PF, Boon NA. Immunopathogenesis of HIV-related heart muscle disease: current perspectives. *AIDS* 2003; **17**: S21–S28.
 55. Currie PF, Goldman JH, Caforio AL, Jacob AJ, Baig MK, Brett RP, Haven AJ, Boon NA, McKenna WJ. Cardiac autoimmunity in HIV related heart muscle disease. *Heart* 1998; **79**: 599–604.
 56. Gresele P, Falcinelli E, Sebastiano M, Baldelli F. Endothelial and platelet function alterations in HIV-infected patients. *Thromb Res* 2012; **129**: 301–318.
 57. Monsuez JJ, Escaut L, Teicher E, Charniot JC, Vittecoq D. Cytokines in HIV-associated cardiomyopathy. *Int J Cardiol* 2007; **120**: 150–157.
 58. Yearley JH, Mansfield KG, Carville AA, Sokos GG, Xia D, Pearson CB, Shannon RP. Antigenic stimulation in the simian model of HIV infection yields dilated cardiomyopathy through effects of TNF alpha. *AIDS* 2008; **22**: 585–594.
 59. Barbaro G, Di Lorenzo G, Soldini M, Giancaspro G, Grisorio B, Pellicelli A, Barbarini G, Gruppo Italiano per lo Studio Cardiologico dei pazienti affetti da AIDS (GISCA). Intensity of myocardial expression of inducible nitric oxide synthase influences the clinical course of human immunodeficiency virus-associated cardiomyopathy. *Circulation* 1999; **100**: 933–939.
 60. Chariot P, Perchet H, Monnet I. Dilated cardiomyopathy in HIV-infected patients. *N Engl J Med* 1999; **340**: 732–735.
 61. Ioachim HL, Cooper MC, Hellman GC. Lymphomas in men at high risk for acquired immune deficiency syndrome (AIDS). A study of 21 cases. *Cancer* 1985; **56**: 2831–2842.
 62. Grinspoon S, Mulligan K. Weight loss and wasting in patients infected with human immunodeficiency virus. *Clin Infect Dis* 2003; **236**: S69–S78.
 63. Triant VA, Lee H, Hadigan C, Grinspoon SK. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. *J Clin Endocrinol Metab* 2007; **92**: 2506–2512.
 64. Nayak G, Ferguson M, Tribble DR, Porter CK, Rapena R, Marchicelli M, Decker CF. Cardiac diastolic dysfunction is prevalent in HIV-infected patients. *AIDS Patient Care STDS* 2009; **23**: 231–238.
 65. Hsue P, Farah H, Bolger AF, Palav S, Ahmed SY, Schnell A, Deeks SG, Martin JN, Bhavne P, Cogswell R, Waters DD. Diastolic dysfunction is common in asymptomatic HIV patients. *Circulation* 2007; **116**: II_499.
 66. Mendes L, Silva D, Miranda C, Sa J, Duque L, Duarte N, Brito P, Bernardino L, Pocas J. Impact of HIV on cardiac deformation. *Rev Port Cardiol* 2014; **33**: 501–5019.
 67. Lai H, Redheuil A, Tong W, Bleunke DA, Lima JAC, Ren S, Lai S. HIV infection and abnormal regional ventricular function. *Int J Cardiovasc Imaging* 2009; **25**: 809–817.
 68. Reinsch N, Neuhaus K, Esser S, Pothoff A, Hower M, Brockmeyer NH, Erbel R, Neumann T. German Competence Network for Heart Failure; German Competence Network for HIV/AIDS.

- Prevalence of cardiac diastolic dysfunction in HIV-infected patients: results of the HIV-HEART study. *HIV Clin Trials* 2010; **11**: 156–162.
69. Barbaro G. Evolution and pathogenesis of the involvement of the cardiovascular system in HIV infection. *Adv Cardiol* 2003; **40**: 15–22.
 70. Wever-Pinzon O, Bangalore S, Romero J, Silva Enciso J, Chaudhry FA. Inotropic contractile reserve can risk-stratify patients with HIV cardiomyopathy: dobutamine stress echocardiographic study. *JACC Cardiovasc Imaging* 2011; **4**: 1231–1238.
 71. Barbaro G, Di Lorenzo G, Grisorio B, Barabarin G. Cardiac involvement in the acquired immunodeficiency syndrome: a multicenter clinical pathological study. *AIDS Res Hum Retroviruses* 1998; **14**: 1071–1077.
 72. Barbaro G. Cardiovascular manifestations of HIV infection. *J R Soc Med* 2001; **94**: 384–90.
 73. Adair OV, Randive N, Krasnow N. Isolated toxoplasma myocarditis in acquired immune deficiency syndrome. *Am Heart J* 1989; **118**: 856–857.
 74. Kinney EL, Monsuez JJ, Kitzis M, Vittecoq D. Treatment of AIDS-associated heart disease. *Angiology* 1989; **40**: 970–976.
 75. Hofman P, Drici MD, Gibelin P, Michiels JF, Thyss A. Prevalence of toxoplasma myocarditis in patients with the acquired immunodeficiency syndrome. *Br Heart J* 1993; **70**: 376–381.
 76. Freedberg RS, Gindea AJ, Dieterich DT, Greene JB. Herpes simplex pericarditis in AIDS. *N Y State J Med* 1987; **87**: 304–306.
 77. Anderson DW, Virmani R, Reilly JM, O'Leary T, Cunnion RE, Robinowitz M, Macher AM, Punja U, Villaflor ST, Parrillo JE et al. Prevalent myocarditis at necropsy in the acquired immunodeficiency syndrome. *J Am Coll Cardiol* 1988; **11**: 792–729.
 78. Herskowitz A, Wu TC, Willoughby SB, Vlahov D, Ansari AA, Beschoner WE, Baughman KL. Myocarditis and cardiotropic viral infection associated with severe left ventricular dysfunction in late-stage infection with human immunodeficiency virus. *J Am Coll Cardiol* 1994; **24**: 1025–1032.
 79. Shaboodien G, Maske C, Wainwright H, Smuts H, Ntsekhe M, Commerford PJ, Badri M, Mayosi BM. Prevalence of myocarditis and cardiotropic virus infection in Africans with HIV-associated cardiomyopathy, idiopathic dilated cardiomyopathy and heart transplant recipients: a pilot study: cardiovascular topic. *Cardiovasc J Afr* 2013; **24**: 218–23.
 80. Bonnet D, Aggoun Y, Szezepanski I, Bellal N, Stephane B. Arterial stiffness and endothelial dysfunction in HIV-infected children. *AIDS* 2004; **18**: 1037–1041.
 81. van Vonderen MGA, Smulders YM, Stehouwer CDA, Danner SA, Gundy CM, Vos F, Reiss P, Agtmael M. Carotid intima-medial thickness and arterial stiffness in HIV-infected patients: the role of HIV, antiretroviral therapy and lipodystrophy. *JAIDS* 2009; **50**: 153–161.
 82. Mascolini M, NATAP investigators. Classic risk factors, but not HIV, linked to arterial stiffness in middle-aged. EACS 14 Conference reports: Opportunistic infections and complications. Brussels, December 2013.
 83. Echeverria P, Bonioch A, Molto J, Jou A, Puig J, Ornelas A, Perez-Alvarez N, Clotet B, Negro E. Pulse wave velocity as index of arterial stiffness in HIV-infected patients compared to a healthy population. *J AIDS* 2014; **65**: 50–56.
 84. Monteiro P, Miranda-Filho DB, Bandeira F, Lacerda HR, Chaves H, Alberquerque MFPM, Montarroyos UR, Ximenes RAA. Is arterial stiffness in HIV-infected individuals associated with HIV-related factors? *Braz J Med Biol Res* 2012; **45**: 818–826.
 85. Charakida M, Loukogeorgakis SP, Okorie MI, Masi S, Halcox JP, Deanfield JE, Klein NJ. Increased arterial stiffness in HIV-infected children: risk factors and antiretroviral therapy. *Antivir Ther* 2009; **14**: 1075–1079.
 86. Rider OJ, Asaad M, Ntusi N, Wainwright E, Clutton G, Hancock G, Banerjee R, Pitcher A, Samaras K, Clarke K, Neubauer S, Dorrell L, Holloway CJ. HIV is an independent predictor of aortic stiffness. *J Cardiovasc Magn Reson* 2014; **16**: 57.
 87. Cegielski JP, Lwakatara J, Dukes CS, Lema LE, Lallinger GJ, Kitinya J, Reller LB, Sheriff F. Tuberculous pericarditis in Tanzanian patients with and without HIV infection. *Tuber Lung Dis* 1994; **75**: 429–434.
 88. Longo-Mbenza B, Tonduang K, Seghers KV, Mubagwa D. HIV infection and pericardial disease invasion in Africa. *Arch Mal Coeur Vaiss* 1997; **90**: 1377–1384.
 89. Sagrista-Sauleda J, Permanyer-Miralda G, Soler-Soler J. Tuberculous pericarditis: ten-year experience with a prospective protocol for diagnosis and treatment. *J Am Coll Cardiol* 1988; **11**: 724–728.
 90. Mayosi BM, Wiysonge CS, Ntsekhe M, Volmink JA, Gumede F, Maartens G, Aje A, Thomas BM, Thomas KM, Awotodu AA, Thembela B, Mntla P, Maritz F, Blackett KN, Nkounlack DC, Burch VC, Rebe K, Parish A, Sliwa K, Alam N, Brown BG, Gould T, Visser T, Shey MS, Magula NP, Commerford PJ. Clinical characteristics and initial management of patients with tuberculous pericarditis in the HIV era: the Investigation of the Management of Pericarditis in Africa (IMPI Africa) registry. *BMC Infect Dis* 2006; **6**: 2.
 91. Mayosi BM, Wiysonge CS, Ntsekhe M, Gumede F, Volmink JA, Maartens G, Aje A, Thomas BM, Thomas KM, Awotodu AA, Thembela B, Mntla P, Maritz F, Blackett KN, Nkounlack DC, Burch VC, Rebe K, Parrish A, Sliwa K, Zezi BZ, Alam N, Brown BG, Gould T, Visser T, Magula NP, Commerford PJ. Mortality in patients treated for tuberculous pericarditis in sub-Saharan Africa. *S Afr Med J* 2008; **98**: 36–40.
 92. Ntsekhe M, Wiysonge CS, Gumede F, Maartens G, Commerford PJ, Volmink JA, Mayosi BM. HIV infection is associated with a lower incidence of constriction in presumed tuberculous pericarditis: a prospective observational study. *PLoS One* 2008; **3**: e2253.
 93. Mutyaba AK, Balkaran S, Cloete R, du Plessis N, Badri M, Brink J, Mayosi BM. Constrictive pericarditis requiring pericardiectomy at Groote Schuur Hospital, Cape Town, South Africa: causes and perioperative outcomes in the HIV era (1990-2012). *J Thorac Cardiovasc Surg* 2014; **148**: 3058–3065.
 94. Mayosi BM, Ntsekhe M, Bosch J, Pandie S, Jung H, Gumede F, Pogue J, Thabane L, Smieja M, Francis V, Joldersma L, Thomas KM, Thomas B, Awotodu AA, Magula NP, Naidoo DP, Damasceno A, Chitsa Banda A, Brown B, Manga P, Kirenga B, Mondo C, Mntla P, Tsitsi JM, Peters F, Essop MR, Russell JB, Hakim J, Matenga J, Barasa AF, Sani MU, Olunuga T, Ogah O, Ansa V, Aje A, Danbauchi S, Ojji D, Yusuf S, IMPI Trial Investigators. Prednisolone and *Mycobacterium indicus pranii* in tuberculous pericarditis. *N Engl J Med* 2014; **371**: 1121–1123.
 95. Glesby MJ. Coronary heart disease in HIV-infected persons. *AIDS Read* 2003; **13**: S15–S19.
 96. Paton P, Tabib A, Loire R, Tete R. Coronary artery lesions and human immunodeficiency virus infection. *Res Virol* 1993; **144**: 225–231.
 97. Tabib A, Leroux C, Mornex JF, Loire R. Accelerated coronary atherosclerosis and arteriosclerosis in young human immunodeficiency virus-positive patients. *Coron Artery Dis* 2000; **11**: 41–46.
 98. Mehta NJ, Khan IA. HIV-associated coronary artery disease. *Angiology* 2003; **54**: 269–275.
 99. Lewis W. Atherosclerosis in AIDS: potential pathogenetic roles of antiretroviral therapy and HIV. *J Mol Cell Cardiol* 2000; **32**: 2115–2129.
 100. Khunnawat C, Mukerji S, Havlichek D, Touma R, Abela GS. Cardiovascular manifestations in human immunodeficiency virus-infected patients. *Am J Cardiol* 2008; **102**: 635–642.
 101. Becker AC, Sliwa K, Stewart S, Libhaber E, Essop AR, Zambakides CA, Essop MR. Acute coronary syndromes in treatment-naïve black South Africans with human immunodeficiency

- virus infection. *J Interv Cardiol* 2010; **23**: 70–77.
102. Becker AC, Jacobson B, Singh S, Sliwa K, Stewart S, Libhaber E, Essop MR. The thrombotic profile of treatment-naïve HIV-positive Black South Africans with acute coronary syndromes. *Clin Appl Thromb Hemost* 2011; **17**: 264–272.
103. Rerkpattanapipat P, Wongpraparut N, Jacobs LE, Kotler MN. Cardiac manifestations of acquired immunodeficiency syndrome. *Arch Intern Med* 2000; **160**: 602–608.
104. Segal BH, Factor SM. Myocardial risk factors other than human immunodeficiency virus infection may contribute to histologic cardiomyopathic changes in acquired immune deficiency syndrome. *Mod Pathol* 1993; **6**: 560–564.
105. Lopes de Campos WR, Chirwa N, London G, Rotherham LS, Morris L, Mayosi BM, Khati M et al. HIV-1 subtype C unproductively infects human cardiomyocytes in vitro and induces apoptosis mitigated by anti-Gp120 aptamer. *PLoS One* 2014; **9**: e110930.
106. Lecour H, Borgne-Sanchez A, Charloin O, El-Khoury R, Brabant M, Langonné A, Porceddu M, Brière JJ, Buron N, Rebouillat D, Péchoux C, Deniaud A, Brenner C, Briand JP, Muller R, Rustin P, Jacotot E. HIV-1 Tat protein directly induces mitochondrial membrane permeabilisation and inactivates cytochrome c oxidase. *Cell Death Dis* 2012; **3**: e282.
107. Shaboodien G, Engel ME, Syed FF, Poulton J, Badri M, Mayosi BM. The mitochondrial DNA T16189C polymorphism and HIV-associated cardiomyopathy: a genotype–phenotype association study. *BMC Med Genet* 2009; **10**: 37.