

The Impact Of HIV/AIDS On The Cardiovascular System - A Review Of Current Trends

¹JA Ogunmodede, ¹PM Kolo, ²KA Adekeye, ¹IA Katibi, ¹ABO Omotoso

Departments of Medicine ¹University of Ilorin, PMB 1515, Ilorin, Kwara state, Nigeria
²Ekiti state University Teaching Hospital, PMB 5355, Ado-Ekiti, Ekiti state, Nigeria

Abstract

The Human Immunodeficiency Virus (HIV) infection is undoubtedly one of the most significant pandemics the world has known with its effect spanning over three decades now. Initial emphasis in the management of the condition was on opportunistic infections, but the introduction of Highly Active Anti Retroviral Therapy (HAART) has led to longer survival times for HIV patients and converted the infection to a chronic manageable illness like systemic hypertension or diabetes mellitus. Hence, unlike the situation at the emergence of the pandemic, patients now live long enough to develop organ-related complications and it is believed that managing these will soon dominate the care of patients. We review the literature on current knowledge and trends in the involvement of the heart in HIV infection.

Key words: HIV/AIDS, Cardiovascular system.

Introduction

The Human Immunodeficiency Virus (HIV) infection is one of the greatest health challenges facing the developing world today. Its impact on human suffering, cultures, demographics, economics and even politics has been felt in nearly every society across the globe. Cardiac involvement was initially thought to be relatively uncommon in the early days of the disease. The profound immunocompromising nature of the infection commanded most of the attention and the emphasis was thus on managing opportunistic infections.

There are 36.9 million people living with the HIV and 70% of these live in Sub-Saharan Africa and about 72% of deaths due to HIV/AIDS also occur in Sub-Saharan Africa¹. In Nigeria, the first two HIV cases were identified in 1985 and were reported at an international AIDS conference in 1986¹. Today, Nigeria accounts for the second highest number of people living with HIV/ Acquired Immune Deficiency Syndrome (AIDS) worldwide² and has a national prevalence rate of 3.2%³.

Correspondence to:

Dr JA Ogunmodede
Department of Medicine,
University of Ilorin, PMB 1515, Ilorin,
Kwara state, Nigeria
+2348035495487, ayodeleogunmodede@yahoo.com

AIDS was initially recognized in the United States in 1981⁴ and the HIV was first isolated in 1983. However, it was not until 1984 that the HIV was recognized as the causal agent of AIDS. The HIV causes a pan-systemic infection. Cardiac involvement in HIV/AIDS has been recognized at autopsy since the beginning of the pandemic⁵ and some of the earliest reports of cardiovascular disease related to the syndrome were made in 1986⁶.

Today, cardiac involvement in HIV/AIDS has become very important because recent advances in the management of the disease such as the introduction of the Highly Active Anti-Retroviral Therapy (HAART) are leading to longer survival times for HIV infected individuals and have converted the disease to a chronic illness such as systemic hypertension or diabetes mellitus. Hence patients now live long enough to develop heart disease and other organ-related manifestations of late-stage HIV infection, as well as therapy-related affection of body organs^{7,8,9}. The prevalence of cardiac abnormalities in HIV/AIDS patients will depend on the method of detection and specific characteristics of the population studied. However prevalence rates ranging from 14.9% to 76.9% have been reported^{10,11}. Noteworthy is the fact that cardiac dysfunction could occur early in the course of the disease and could be asymptomatic underlining the importance of early screening and detection¹².

The HIV infection is associated with a wide spectrum of heart diseases causing pericardial, myocardial, endocardial, hemodynamic, vascular, and electrophysiologic abnormalities as well as tumours^{13,14,15}.

Pericardial Disease

The spectrum of pericardial disease in HIV/AIDS ranges from acute or chronic pericarditis to pericardial effusion (PE), cardiac tamponade and eventual constrictive pericarditis^{16,17}.

Pericardial effusion (PE) in HIV/AIDS is usually infective due to several aetiological factors. These include the direct pathogenic effect of the virus itself causing pericardial inflammation and the effect of other pathogens such as *Mycobacterium tuberculosis*, *Staphylococcus aureus*¹⁸, *Cryptococcus neoformans* and *Herpes simplex*¹⁹. In sub-Saharan Africa, *Mycobacterium tuberculosis* is the cause of pericardial disease in 86-100% of infected patients²⁰.

In the pre-HAART era, PE was the most frequent cardiac manifestation with incidence as high as 11% being reported in some workers¹¹. It could be symptomatic or asymptomatic. The incidence of PE increases with advancing stages of the disease¹² and with increasing disease severity¹³. PE is thought to occur as part of the 'capillary leak syndrome'- a generalized serous effusive process which also occurs in pleural and pericardial surfaces and probably caused by enhanced TNF- α expression in later stages of the disease^{17,33,34}.

Pericardial effusion can be complicated by cardiac tamponade in HIV patients. Early reports of aetiology suggested that *Mycobacterium* species accounted for majority of cases³⁵ with other bacterial organisms and fungi occurring as less frequent aetiological agents. Up to 26% of cases have been reported as idiopathic in some series³⁵. More recent interest has been roused in the aetiology of cardiac tamponade with increasing reports of *norcardia* as an aetiological agent³⁶⁻³⁷. Norcardia infection is frequently limited to pulmonary involvement, tending, however to disseminate in immunocompromised individuals. Clinically and radiologically, it mimics pulmonary tuberculosis. Cases previously reported as idiopathic may have been related to the HIV itself.

The occurrence of constrictive pericarditis among HIV positive individuals is also often linked to the presence of pulmonary tuberculosis. Evaluation of the contribution of pulmonary tuberculosis to the aetiology of constrictive pericarditis in HIV patients is best done through a prospective approach. Most cross-sectional studies and case reports suggest relatively high prevalence rates^{12,23} of but a prospective comparison of tuberculous pericarditis patients with and without HIV suggested that constrictive pericarditis was less likely to occur in the HIV positive patients³⁴. Pericardial disease can also be caused by neoplasia like lymphomas and Kaposi sarcoma (KS)^{31,38}.

Heart Muscle Disease

This may present as myocarditis, dilated cardiomyopathy (DCM) or isolated or combined left or right ventricular dysfunction. Overall prevalence of up to 15% has been reported¹⁵.

Myocarditis

Myocardial involvement in HIV infection is multifactorial and may arise as a result of myocardial invasion by the HIV itself, autoimmune response to viral infection, direct cytopathic effects of opportunistic infections and other viral infections, drug-related cardiac toxicity, nutritional deficiencies or prolonged immunosuppression. The severity of myocarditis ranges from incidental microscopic inflammatory findings at autopsy to clinically

significant cardiac disease that causes chronic cardiac dysfunction¹⁹.

The evidence for myocardial invasion by the virus is anchored on the detection of HIV genomic material in both biopsy and autopsy specimens of cardiac myocytes^{39,41}. It is unclear how the virus enters the CD4 receptor negative myocytes, but it is believed that reservoir cells such as dendritic cells facilitate viral entry into the myocyte resulting in the activation of multifunctional cytokines such as tumour necrosis factor- α (TNF- α), interleukin (IL)-6 and endothelin-1 that trigger inflammatory reactions causing myocarditis. Reservoir cells (resting CD4 or other cells that are infected with HIV but not actively producing HIV virions) may help to propagate and prolong these effects. They hold on to the virus on their surfaces for extended periods and chronically release cytotoxic cytokines causing progressive cardiac tissue damage. Other cardiotropic viruses (which act as opportunistic infections in the HIV infected individual) may co-infect a patient with HIV and have also been implicated in the development of myocarditis. An example of this scenario was reported by Herskowitz *et al* who detected positive hybridization signals for HIV-1 and cytomegalovirus (CMV) in 15% and 48% respectively of HIV patients who had histologic evidence of myocarditis. Other infectious agents such as *Toxoplasma gondii*, Coxsackie virus group B, Epstein-Barr virus, adenovirus may also co-infect HIV patients and trigger cytokine release or auto-antibody formation and reaction with cardiac myocytes. Myocarditis is associated with a poor prognosis, and results in symptomatic heart failure in up to 5% of HIV patients⁴². The HAART era has however seen a reduction in the incidence of myocarditis thus reducing the prevalence of HIV-associated cardiomyopathy by almost 7-fold from the pre-HAART era⁴².

Cardiomyopathy

DCM is a frequent finding in HIV/AIDS patients. The prevalence ranges from 5% to 23%¹³ and is the commonest form of cardiomyopathy reported in HIV-infected individuals. Several factors are associated with the development of DCM in HIV/AIDS patients. These include preceding myocarditis⁴³, opportunistic infections, selenium deficiency, anti-retroviral drug (ARV) use and disease severity as measured by CD4 count¹. Evidence for the relationship between myocarditis and DCM is strengthened by serological evidence of the detection of elevated viral antibody titres in the serum of DCM patients⁴⁴. Of the 76 HIV patients who developed incident DCM in a large prospective study by Barbaro *et al*, 63 (83%) histologically confirmed myocarditis and HIV RNA was detected in the myocardial cells of 58 (76%) - strongly suggesting a causal relationship between

myocarditis and DCM⁴⁵. Likewise, opportunistic infectious agents such as Epstein Barr virus, Herpes simplex virus^{46,47} and non-virus microbes like *Cryptococcus neoformans*⁴⁸, *Candida albicans*⁴⁹, atypical mycobacteria and *Toxoplasma gondii*⁵⁰, have been detected in the myocardium of HIV positive DCM patients. In one autopsy series, cardiac toxoplasmosis was diagnosed in 21 of 82 patients with HIV infection⁵¹.

The recognized effect of deficiency of trace element selenium as a cause of cardiomyopathies in the general population may also play a role in the HIV infected individual⁵². Selenium is a component of the glutathione peroxidase enzyme system of the myocardium, an important anti-oxidant system in the heart which controls the levels of reactive oxygen species (which are potentially toxic by-products of cardiac myocyte aerobic metabolism) thus reducing the effect of oxidative stress on the heart⁵³. Selenium deficiency occurs frequently in HIV positive individuals, due to the trapping of Selenium by a selenoprotein encoded by the proviral genome⁵⁴. Symptomatic improvement has been reported in selenium-deficient HIV patients who had DCM when given selenium supplementation⁵². Long term zidovudine therapy may also play a role in the aetiology of DCM in HIV/AIDS. Long term zidovudine therapy has been reported to cause mitochondrial myopathy in skeletal muscles and may have a similar effect on myocardial muscle⁵⁵. The outlook of HIV/AIDS patients with DCM is poor. It is an independent risk factor for reduced survival¹⁵ and death¹ among them.

Endocardial Disease

Three forms of endocarditis have been reported in HIV infected patients: Marantic (non-bacterial thrombotic), bacterial, and fungal⁵⁴. The marantic form is the most commonly reported in HIV patients with wasting syndrome⁴⁹ though rarely described in Africans⁵⁵. It can involve all the four heart valves, and its occurrence is usually associated with hypercoagulable states and malignancies⁵⁶. Bacterial endocarditis was observed to be more common in intravenous drug users (IDUs), who carry a 10-12 fold higher risk than non-IDUs⁵⁷ - hence right-sided valves are mostly involved⁴². Reported prevalence rates of bacterial endocarditis ranged from 6.3-34% depending on study population and most cases were reported in the western nations where injection drug use is a major public health issue⁵⁶. However due to behavioural change interventions a general decline in cases has been observed⁵⁸. *Staphylococcus aureus* is the most frequently implicated organism and is responsible for about 75% of cases. Other common bacterial causes are *Streptococcus pneumoniae* and *Haemophilus influenzae*. There may also be a higher incidence of Gram-negative organisms among HIV patients than in

other individuals⁵⁹. Infective endocarditis is not a commonly reported finding in HIV positive patients in Nigeria, the first reported case was by Okeahialam *et al*⁶⁰ in Jos, North Central Nigeria of a patient who had aortic valve involvement and vegetations with blood culture yielding *Pseudomonas aeruginosa*.

The presentation of bacterial IE in HIV positive patients is similar to that in the general population, however patients with late stage HIV disease have a higher mortality from IE than do asymptomatic HIV infected patients⁶¹. Fungal endocarditis usually occurs as a part of systemic fungaemia. *Aspergillus fumigatus*^{61,62} cryptococcal and other forms of fungal endocarditis have been reported, though in end-stage AIDS⁶².

Ventricular Dysfunction

Left ventricular (LV) diastolic and systolic dysfunction are common findings in HIV/AIDS disease. Reported prevalence rates vary between 14.5-85.7% depending on patient selection and disease stage and severity^{18,63,64}. Affected patients can be symptomatic or asymptomatic and can develop LV dysfunction both in the early and late phases of the disease. Indeed, Barbaro *et al* in an echo study of 1,236 asymptomatic HIV patients in the early stages of the disease, detected significant impairment of systolic and diastolic function compared to healthy controls⁶⁵. Interestingly, patients can remain asymptomatic of LV dysfunction even in clinically advanced stages of the disease⁶⁶.

Factors that predispose to the development and severity of LV dysfunction include previous opportunistic infections⁶⁷ CD4 count⁶⁸, use of HAART and duration of its use. Danbauchi *et al* reported that the systolic function of HIV patients on HAART for 2 years was significantly better than that of patients on HAART for just 1 year⁶⁹.

Isolated right ventricular dysfunction with right ventricular hypertrophy is also associated with HIV/AIDS and has been reported at both postmortem⁷⁰ and echo studies^{13,71-73}. Most cases of isolated right ventricular dysfunction are probably not due to primary myocardial disease from HIV, but rather secondary to changes in the pulmonary circulation from recurrent pulmonary infections such as bronchopneumonia and pulmonary tuberculosis (which are common in these patients)⁷², HIV induced pulmonary arteritis⁷⁴ and microvascular pulmonary emboli due to thrombosis or drug injection⁴⁹.

Coronary Artery Disease

Patients with HIV infection have been shown to have an increased risk of coronary artery disease (CAD)^{75,76}. HIV-1 genomic sequences have been demonstrated in the coronary vessels of HIV infected

patients who died of acute myocardial infarction (MI)^{75,76}.

Implicated mechanisms of the development of CAD include endothelial dysfunction, abnormal lipid metabolism and lipodystrophy syndrome, insulin resistance and impaired glucose metabolism associated with ARV use, which occurs in HIV patients⁷⁵. Endothelial dysfunction (ED), also called endothelial activation, is triggered by the entry of the virus into the coronary endothelial cells via CD4 receptors or galactosyl-ceramide receptors on endothelial cells³². Viral entry triggers an inflammatory reaction and the elaboration of circulating markers of endothelial dysfunction such as soluble adhesion molecules and pro-coagulant proteins in coronary vessels which promote atherosclerosis⁵⁵. Also, there is stimulation of the release of vasoconstrictors such as endothelin-1, IL-6, TNF- α and a reduction in endothelial nitrous oxide (NO) and prostacyclin production. This converts the usually thrombo-resistant and cellular non-adhesive endothelium to a thrombogenic, adhesive one with increased atherogenesis.

Though lipid abnormalities were noted in HIV patients before the introduction of HAART⁷⁷, dyslipidaemia has been linked to both HIV infection and HAART, particularly therapy with protease inhibitors (PI's). The occurrence of HAART-induced premature atherosclerosis has been strengthened by autopsy studies one of which reported a significant increase of atherosclerotic plaques in HIV-infected patients over the 2 decades following the discovery of the disease⁷⁸. PI's appear to have drug-specific effects on lipid and glucose metabolism and several of them may induce or worsen dyslipidaemia in HIV patients independent of body anthropometric abnormalities. Robinson and Meng working separately also found an augmented rate of coronary artery calcification in HIV patients treated with PI's^{75,78}.

The use of some ARVs especially PIs also predisposes HIV infected individuals to developing insulin resistance and hyperglycaemia thus increasing their risk of adverse coronary events⁷⁹. Indeed a large prospective study of 23,468 patients found a 26% relative increase in the incidence of MI per year of exposure to combination ARV⁸⁰. The presence of other cardiovascular risk factors in an HIV patient may confound evaluation of HIV as a possible risk factor for the development of acute myocardial infarction. Considering, in addition, the up-regulation of some cardiovascular risk factors in HIV patients especially those on HAART, it is important to distinguish the effect of the virus on the risk of acute MI from the effect of co-existent cardiovascular risk factors. Frieberg et al in a large prospective study of 89,459 patients, adjusted statistically for the presence of cardiovascular risk factors such as smoking, alcohol, systemic

hypertension, DM and dyslipidemia and reported a 50% increased risk of acute MI in HIV positive patients compared to HIV negative controls⁸¹. However, Paisible *et al* have also showed that the effect of HIV on incident acute MI was related to the virus. In their prospective study of 81,322 HIV patients, when groups of HIV positive patients with different burdens of existing cardiovascular risk factors were matched with groups of HIV negative individuals with similar risk factor burden, the risk of acute MI was still greater among the HIV positive patients irrespective of whether the burden of risk factors was high or low in the matched groups⁸². The presence of biomarkers of inflammation is also associated with the occurrence of MI. The presence of high levels of C-reactive protein in HIV patients is associated with a four-fold increase in the odds for developing MI among HIV negative individuals with normal C-reactive protein⁸³.

With the association of HIV with several cardiovascular diseases, it is not unexpected that it may contribute to the occurrence of sudden cardiac death in affected patients. Tseng et al in a retrospective study found that the rate of sudden cardiac death among HIV infected individuals was about 4.5 times that in the general population⁸⁴. Precise mechanisms of this are still subject to research, but are thought to be related to inflammation, antiretroviral therapy interruption, and concomitant medications⁸⁵⁻⁸⁷.

Novel cardiovascular risk factors have also been studied in HIV patients as a means of predicting the occurrence of incident cardiovascular disease and sudden death. Such biomarkers such as Growth differentiation factor-15 (GDF-15), ST2, and high-sensitivity troponin-I (hs-TnI) known to be associated with incident cardiovascular disease in the general population have been studied in HIV patients^{10,88}. They are elevated in HIV-infected patients and associated with LV diastolic dysfunction, pulmonary hypertension and, together with high-sensitivity C-reactive protein and plasma D-dimer, all independently predict all-cause mortality even in patients with adequate viral suppression¹⁰.

Pulmonary Hypertension

Patients infected with HIV have an increased risk of developing pulmonary arterial hypertension (PAH)⁷⁴. HIV associated PAH unlike primary PAH is more commonly seen in male patients with a ratio of 1.5:1 compared to females and an incidence rate of 0.5% has been reported¹³. PAH is thought to be mediated through a variety of virus-induced humoral factors that lead to the re-modelling of pulmonary resistance vessels⁸⁹. Though the precise pathogenetic mechanism is not clear, the development of PAH is believed to be caused by the elaboration of cytokines such as endothelin-1, IL-1, IL-6 and TNF- α by HIV-

infected pulmonary macrophages and dendritic cells leading to pulmonary endothelial activation, endothelial cell proliferation and vasoconstriction^{90,91}. Studies on the impact of HAART on hemodynamic improvement in patients with HIV associated PAH have yielded conflicting results^{92,93}. However the use of HAART with epoprostenol significantly decreased mortality among HIV-1 infected patients with PAH⁹⁴.

Cardiac Tumours

Kaposi sarcoma (KS) and Non-Hodgkin lymphoma (NHL) have been described in patients with HIV particularly in the advanced stages of the infection⁹⁵. Cardiac KS is often occult and rarely diagnosed in life. It may cause pericardial, and less commonly, myocardial lesions⁹⁶. The Epstein Barr virus has been implicated in its aetiology. Myocardial KS usually occurs as part of a disseminated process⁹⁶. Lymphoma involving the heart is usually of B-cell origin^{97,98}. It is usually diffusely infiltrative, but can form nodules and even intracavitary masses⁹⁶. Cardiac lymphoma can cause congestive heart failure, atrial and ventricular arrhythmias, and heart block. The prognosis is generally poor, though a case has been reported of a patient whose tumour was shown by echo to have regressed with chemotherapy⁹⁶.

Electrophysiologic Abnormalities In HIV/AIDS

The electrocardiogram (ECG) is the least expensive and most widely available tool for cardiac evaluation. It is well established that ECG abnormalities are predictive of incident cardiovascular disease in the general population independent of the traditional risk factors^{97,98}. This will probably be much more so in the HIV/AIDS population in whom the infection already increases the baseline risk for cardiovascular diseases.

ECG abnormalities are very common among HIV patients. Prevalence rates of 44-57.2% have been reported variously depending on patient selection^{65,99,100}. The spectrum of ECG abnormalities reported in HIV/AIDS patients includes left atrial enlargement (LAE), left ventricular hypertrophy (LVH)¹⁰¹, left and right bundle branch blocks, atrioventricular blocks, atrial fibrillation, atrial flutter and ST-T abnormalities and QT interval prolongation¹⁰²⁻¹⁰⁴. The occurrence of electrical abnormalities in HIV/AIDS patients is related to several factors. These include alterations in cardiac innervation due to autonomic dysfunction, the effect of drugs used in managing the patients such as pentamidine, pyrimethamine, methadone, trimethoprim-sulfamethoxazole, clarithromycin, ciprofloxacin and ARVs such as efavirenz and PI's¹⁰⁵ and the effect of the HIV itself as a result of associated conditions such as anaemia and intercurrent infections^{102,106}.

Specifically, a relatively high incidence of QT interval prolongation in HIV/AIDS patients has been reported ranging from 20-65% depending on QTc cut-off values^{101,107,108}. The factors associated with QTc prolongation include known causes of QTc prolongation in the general population such as female gender, diabetes mellitus and systemic hypertension¹⁰⁷. However, in the HIV-infected population, age, caucasian origin, the duration of HIV infection, some ARVs and known prolongators of QTc which are used in the treatment of opportunistic infections (such as pentamidine, pyrimethamine, methadone, trimethoprim-sulfamethoxazole, clarithromycin, ciprofloxacin), have been implicated¹⁰⁶. It is well known that prolongation of the QTc interval can predispose patients to potentially fatal ventricular tachyarrhythmias, particularly torsades de pointes, and thus is an independent predictor of cardiovascular morbidity and mortality¹⁰⁹.

Conclusion

The HIV pandemic has been one of man's greatest public health challenges in the last few decades of its existence. As the pandemic stabilizes, and incidence of new cases diminishes, the next challenge will include the management of chronic systemic complications of the infection such as cardiovascular diseases. There will be need for increased vigilance among healthcare providers of HIV/AIDS patients for such systemic complications as this and initial screening of confirmed cases and strategies for holistic management of the infection may have to be reviewed.

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