The Heart And HIV/ AIDS

Citation
D Olusegun-Joseph, J Ajuluchukwu, C Okany, A Mbakwem, D Oke.. The Heart And HIV/ AIDS. The Internet Journal of Cardiology. 2009 Volume 9 Number 1.

Abstract
HIV/AIDS is one of the leading health problems in the world, especially in sub-saharan Africa, where it is the single greatest health challenge facing the continent. Cardiac involvement impacts on the natural history and prognosis of the disease, however, evidence of cardiac involvement may be clinically quiescent initially. With improved management of opportunistic infections, and the advent of Highly Active AntiRetroviral Therapy (HAART), more organ related manifestations of the disease including heart diseases are emerging. The extra cardiovascular burden will be enormous in view of the increasing prevalence of HIV infection globally. This demands an awareness by clinicians of its cardiovascular manifestations for a complete and rational diagnosis and management. This article presents a concise review of the clinical manifestations, pathophysiology/ pathogenesis and management of Cardiovascular complications in HIV/AIDS.

INTRODUCTION
HIV/AIDS is a multisystemic disease, affecting virtually every organ and system of the body, resulting in progressive dysfunction of affected areas. The heart is not spared in the exploit of this rampaging entity.

Cardiac manifestation was thought to be a rare feature of HIV presentation in the early periods of the disease, mainly because the presentation of the disease was largely dominated by opportunistic infections, malignancies, and manifestations of symptoms of other systems like the central nervous system (CNS), and respiratory system; however, currently there are evidences of increasing cardiac involvements in patients with the disease.

Infection with the HIV virus has become one of the leading cause of acquired heart disease and specifically of symptomatic heart failure. Studies have suggested that HIV may exhibit a cardiac tropism, but the heart may also be affected by other opportunistic viruses, fungi, and protozoa. Cardiac disease associated with HIV may therefore be multifactorial, and can be caused by HIV infection itself, opportunistic infections by other viruses, neoplastic complications, drugs used in the treatment of the disease, or any of the established causes of cardiac disease in other patient populations.

The exact prevalence of cardiac involvement in HIV/AIDS is uncertain. Estimates of prevalence vary widely from 28–73% depending on the screening methods selected, the population studied, and the definition of cardiac abnormality. Other workers, however, puts the prevalence at a conservative estimate of 2-10%.

DISEASE SPECTRUM AND PATHOGENESIS
A wide range of cardiovascular diseases has been identified in HIV/AIDS patients. The spectrum ranges from myocardial diseases to pericardial, endocardial disease, coronary artery disease, malignacies, vascular disease, cardiac arrhythmias and autonomic dysfunction.

MYOCARDIAL DISEASE
Myocardial disease is common in HIV/AIDS. Studies have shown that serious clinical cardiac abnormalities are common in patients with AIDS and are associated with myocarditis. Dilated cardiomyopathy occurs late in the course of HIV infection and is usually associated with a significantly reduced CD4 count.

Cohen et al described the first fatal case of dilated cardiomyopathy in three AIDS patients in 1986. Post mortem examination in two of the patients revealed a globular heart with dilated cardiac chambers, and histological evidence of focal lymphocytic myocarditis.

The pathogenesis of human immunodeficiency virus (HIV) associated cardiomyopathy include infection of myocardial...
cells with HIV type 1 (HIV-1) or coinfection with other cardiotropic viruses, postviral cardiac autoimmunity, autonomic dysfunction, activation of multifunctional cytokines and cardiotoxicity from illicit drugs and pharmacologic agents (such as nucleoside analogues and pentamidine).\textsuperscript{2,19,35-35}

HIV-1 genomic material has been demonstrated within cardiac myocytes in patients with congestive cardiomyopathy at autopsy and biopsy. The presence of HIV in cardiac tissue has been documented by culture, southern blotting, and in-situ hybridization\textsuperscript{17,25,26}. It is, however, unclear how the virus enters CD4 receptor negative cells such as myocytes. Reservoir cells like dendritic cells are said to play a pathogenic role in the interaction between HIV and the myocyte and in the activation of multi-functional cytokines that contribute to progressive and late tissue damage.\textsuperscript{27}

Malnutrition and wasting are also important predictors of cardiac morbidity and mortality in HIV infection. There is a relationship between vitamins, trace element deficiency (e.g. vitamin E, folic acid, Zinc, and selenium) and cardiomyopathy\textsuperscript{1,2,19,28,29}. The cardiac virulence of coxsackie virus appears to be enhanced by selenium deficiency. Indeed, selenium supplementation has been shown to improve cardiac dysfunction in AIDS patients\textsuperscript{1,2,19,28,29}. Dilated cardiomyopathy in HIV positive patients is associated with poor prognosis\textsuperscript{1}. When compared with patients with idiopathic dilated cardiomyopathy, those with HIV associated dilated cardiomyopathy have greatly reduced survival\textsuperscript{30}. Median survival is 101 days in patients with left ventricular dysfunction compared with 472 days in HIV patients with a normal echocardiogram at the same stage of infection.\textsuperscript{31}

Similarly, a longitudinal, prospective study of HIV infected infants and children found that left ventricular dysfunction was a significant predictor of overall mortality, even after adjustment for age, height, CD4 cell count, and progressive neurological disease\textsuperscript{32}. Asymptomatic left ventricular dysfunction and increased left ventricular mass independently predict accelerated mortality in both adults and children infected with HIV.\textsuperscript{27}

Cardiac dysfunction occurs in all the major risk groups for HIV infection, including homosexual men\textsuperscript{33-35}, intravenous drug users\textsuperscript{36,37}, and in positive children\textsuperscript{32,38}. The reported prevalence of left ventricular dysfunction in HIV infection from several studies in Europe and America varies from 2% to over 40%\textsuperscript{5,13,34,37,38}, with symptomatic heart failure developing in 6% of these patients\textsuperscript{32,38}, most of whom have end-stage AIDS\textsuperscript{8,12,34}.

Studies from Africa also reveal that ventricular dysfunction is not uncommon in people living with HIV/AIDS in the continent. Nzuobontane et al\textsuperscript{4} in 2002 reported a 23.3% prevalence of dilated cardiomyopathy in Cameroonian AIDS patients, none in HIV negative patients. The difference was statistically significant when the AIDS group was compared with the HIV negative group. Low CD4 cell counts was associated with dilated cardiomyopathy in that study, a finding similar to that observed by other workers\textsuperscript{14,37,40}.

Longo-Mbenza et al\textsuperscript{41} in another study in Congo reported that left ventricular diastolic dysfunction is an important feature of HIV associated heart disease as it was found in 85.7% of HIV-infected patients. Left ventricular diastolic dysfunction was accompanied by left ventricular hypertrophy and was more pronounced in AIDS patients than in HIV positive, non-AIDS patients. Concentric left ventricular hypertrophy was observed in 46.9% of patients with HIV infection, while 24.4% had left ventricular dilatation.

Omotoso et al\textsuperscript{42} in ilorin, North central part of Nigeria, reported a 32.1% prevalence of HIV infection in patients with heart failure from dilated cardiomyopathy indicating a possible association between HIV infection and dilated cardiomyopathy. The authors concluded that dilated cardiomyopathy is a major cause of heart failure in this environment and that HIV can play a significant role in its pathogenesis.

Okeahialam et al\textsuperscript{43} in Jos, North central part of Nigeria reported more left ventricular systolic dysfunction in AIDS patients. Most of these patients had normal ventricular size but significantly reduced fractional shortening when compared with the HIV negative controls. Diastolic indices were, however, not reported.

Danbauchi et al\textsuperscript{44} in Zaria, Kaduna state, Northern part of Nigeria reported diastolic dysfunction in 30% of patients with stage III/IV HIV infection. Most of these patients were asymptomatic, further confirming that most cardiac abnormalities in HIV/AIDS patients are clinically quiecent. Isolated right ventricular dysfunction with right ventricular
hypertrophy is also associated with HIV/AIDS and has been reported at postmortem and echocardiographic studies. 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 bronchopneumonia, HIV induced pulmonary arteritis, and pulmonary tuberculosis which is common in these patients. Tricuspid regurgitation may also result in volume overload and was a specific cause of right ventricular dysfunction in a man with non-bacterial thrombotic endocarditis and end stage AIDS.

Treatment for HIV related cardiomyopathy is generally similar to that for non-ischaemic cardiomyopathy. Appropriate treatment remains worthwhile despite the seemingly poor prognosis. Angiotensin converting enzyme inhibitors are recommended based on general heart failure studies, but may be poorly tolerated because of low systemic vascular resistance from diarrhoeal disease, infection or dehydration. Palliative therapy with diuretics, digoxin, and inotropes can also be beneficial. Patients with myocarditis, however, have enhanced sensitivity to digoxin which must be taken into consideration when commencing these patients on it.

The use of immunosuppressive regimens is controversial and no convincing benefits have been reported other than with intravenous immunoglobulin, whose efficacy may reflect inhibition of cardiac autoantibodies by competition with Fc receptors or dampened effects of cytokines and cellular growth factors.

PERICARDIAL DISEASE

Pericardial disease is a frequent cardiovascular manifestation of HIV infection often associated with shortened survival, independent of CD4 count and albumin values. There is no apparent correlation between clinical stage of HIV infection and severity of pericardial involvement.

The prevalence of pericardial disease at echocardiography ranges from 10–59%, although the majority of these are asymptomatic. The prevalence of pericardial effusion in asymptomatic HIV infected patients is estimated at 22%. Cases of massive effusion with cardiac tamponade, and constrictive pericarditis have also been reported. In Africa pericardial effusion associated with HIV is now the most frequent cause of pericardial disease, and tuberculosis is the major cause of large pericardial effusion in the continent. In a report from South Africa 96% of HIV patients with large pericardial effusions had tuberculous pericarditis.

Pericardial diseases can be caused directly by the virus, involvement of opportunistic infections such as cytomegalovirus, mycobacterium, nocardia, cryptococcus, bacterial infections, malignancy such as Kaposi Sarcoma, non Hodgkin Lymphoma, or part of a generalized effusive serous process also involving pleural and peritoneal surfaces, and is probably a consequence of enhanced cytokine expression. In some cases of lipodystrophy an increase in the cardiac lipid tissue could simulate an extensive pericardial effusion.

Small asymptomatic pericardial effusion can spontaneously resolve in HIV patients, however, the frequency of resolution varies. In a study by Blanchard et al, 42% of the patients studied had spontaneous resolution of their effusion, while in another study by Heidenreich et al, only 13% had spontaneous resolution. Mortality, however, remains increased in HIV infected patients who develop an effusion, even if the effusion resolves over time.

Echocardiography is regarded as the standard investigative tool for the diagnosis of pericardial effusion. Nevertheless, further diagnosis can be performed by computer tomography and/or magnetic resonance tomography when a neoplasm or an increase in the cardiac lipid tissue is suspected. Pericardiocentesis should be carried out in symptomatic patients and those with cardiac tamponade for relief of symptoms. Culture of pericardial fluid or biopsy from patients with symptomatic effusion can help to identify treatable opportunistic infections or malignancy.

In Africa where the incidence of tuberculous infection is high, patients with pericardial effusion often receive empirical antituberculous chemotherapy. Adjunctive corticosteroids have not been shown to have a significant beneficial effect on mortality in HIV-positive patients with tuberculous pericarditis, thus their use cannot be recommended on a routine basis. The effects of HAART on pericardial effusion are largely unexplored.

ENDOCARDIAL DISEASE

Three forms of endocarditis have been reported in HIV infected patients: Marantic (non-bacterial thrombotic), bacterial, and fungal. Marantic or non-bacterial thrombotic endocarditis (NBTE) is a condition in which friable clumps of platelets and red cells adhere to the cardiac valves, and it is most common in HIV patients with wasting syndrome. It can involve all four valves though left sided lesions are more
common.

Unlike bacterial endocarditis, NBTE are not infective, and has been reported in AIDS patients at autopsy. The pathogenesis of NBTE is not fully understood but hypercoagulability, endothelial damage, and immune complex deposition are implicated. Identification was frequent in early postmortem studies of patients with HIV infection, but the condition is now less commonly encountered, suggesting that its prevalence was possibly overestimated in the past.

Bacterial endocarditis in HIV infection is infrequent, appearing almost exclusively in intravenous drug users where prevalence varies from 6.3–34%. Intravenous drug abusers have been reported to have a ten to twelve fold increased risk for infective endocarditis than non-intravenous drug abusers. Right sided valves are predominantly affected.

Staphylococcus aureus is the most common organism, detected in more than 50% of cases, followed by Streptococcus pneumoniae and Haemophilus influenzae. They also have a higher risk of developing salmonella endocarditis than immunocompetent patients because they are more likely to develop salmonella bacteremia during salmonella infection due to their impaired immune function. Patients typically present with fever, sweats, weight loss, and co-existing pneumonia and/or meningitis. Infection affecting the left heart with systemic embolism is less common.

The prevalence of infective endocarditis in HIV positive patients is similar to that in the general population and they generally have similar presentation. However, patients with late stage HIV disease have higher mortality from infective endocarditis than do asymptomatic HIV infected patients. Fungal endocarditis is usually the result of systemic fungaemia. Aspergillus fumigatus, cryptococcal and other forms of fungal endocarditis can occur in end-stage AIDS.

Incidence of infective endocarditis in HIV positive patients in Nigeria is not known, but it is not a commonly reported finding. However, Okeahialam et al reported a case of endocarditis with vegetations on the aortic valve. Blood culture in that case yielded Pseudomonas aeruginosa, an unusual pathogen.

Aggressive treatment with conventional antibiotic regimens and surgery when required are appropriate. Medical treatment is reported to be successful in over 70% of cases and surgery also has good outcome, provided that intravenous drug abuse does not resume in the postoperative period. Fortunately, overall incidence of endocarditis in HIV positive patients is falling, a possible benefit of needle exchange and health education schemes.

**MALIGNANT DISEASE**

Two types of malignancy affect the heart in HIV patients: Kaposi’s sarcoma, and malignant lymphoma, of which the former is more common. These malignancies are commoner in patient with AIDS than others, and they often occur in body sites that are unusual in immunocompetent people.

**KAPOSI’S SARCOMA**

Kaposi sarcoma (KS) is the commonest AIDS related neoplasia, affecting 12% to 28% in retrospective autopsy findings. Autran et al in 1983 first described Kaposi’s sarcoma of the heart involving the entire anterior cardiac wall without effusion in an HIV/AIDS patient. Male homosexuals appear to be most at risk, with very aggressive form, often disseminated with potentially fatal visceral involvement in these patients, unlike the classical dermatological form which is more benign.

Myocardial KS usually occurs as part of a disseminated process. This endothelial cell neoplasm shows a predilection for the subpericardial fat around coronary arteries. Visceral and parietal pericardial lesions are most common though involvement of the myocardium, coronary arterial adventitia, great vessels, and epicardium have also been reported.

Generally, KS is seldom associated with cardiac symptoms; however, cases of fatal tamponade and constrictive pericarditis have been reported.

Primary cardiac lymphoma and disseminated lymphoma involving the myocardium as part of widespread tumour involvement has been reported in AIDS patients. Most non-Hodgkin’s lymphomas affecting the heart in HIV infection are high grade, with Burkitt-like cells, reticular cell sarcomas, or large cell immunoblastic sarcomas. The majority originate from B cells and display monoclonal immunoglobulin staining with patchy involvement of the epicardium, myocardium, and endocardium in the form of focal circumscribed nodules, most frequently affecting the right atrium.

In contrast to KS, cardiac lymphoma commonly give rise to clinical symptoms like tamponade, congestive heart failure,
Arrhythmias or progressive heart block. Outcome is usually poor and the optimal approach to treatment is yet to be determined, though clinical remission has been obtained with combination chemotherapy.

**PULMONARY HYPERTENSION**

Human immunodeficiency virus–associated pulmonary hypertension was first described by Kim and Factor in 1987. The incidence of HIV-associated pulmonary hypertension is 1 in 200 compared with 1 in 200,000 in the general population and it is more common in male and young patients. The common risk factors were intravenous drug use, homosexual contacts, and hemophilia. Development and progression bear no relationship to the stage of underlying HIV disease. It affects about 0.5% of hospitalized AIDS patients and is a cause of severe cardiac impairment with associated cor pulmonale and death.

The pathogenesis of pulmonary hypertension is multifactorial and poorly understood. HIV may cause endothelial damage and vasoconstriction through release of endothelin-1, interleukin-6, and tumour necrosis factor. HIV may also be identified in alveolar macrophages which release tumour necrosis factor, oxide anions, and proteolytic enzymes in response to infection. Treatments with oxygen, steroids, calcium channel blockers, epoprostenol, and nitric oxide have all been proposed though efficacy has not been confirmed in controlled clinical trials. Effects of HAART on pulmonary artery endothelial cells are unknown for now.

**CARDIAC ARHYTHMIAS**

Rhythm abnormalities and sudden death are well recognized in HIV infection, and they account for more than 20% of cardiac-related deaths. These may be secondary to other cardiac pathologies or may be a consequence of treatment.

Ventricular arrhythmias are associated with some drugs used in the treatment of opportunistic infections. Pentamidine, used for the treatment of Pneumocystis carinii infection, is structurally similar to procainamide and can cause torsade de pointes ventricular tachycardia when used intravenously and intramuscularly.

Castillo et al reported a case of acquired long QT syndrome in a patient placed on efavirenz, a novel nonnucleoside reverse transcriptase inhibitor. The temporal relationship between the initiation of treatment and the onset of electrocardiographic abnormalities, the absence of other apparent precipitating factors, as well as the normalization of QT interval and the resolution of the arrhythmia after discontinuation of the drug, strongly suggest a causal relationship between efavirenz and this adverse clinical event.

Cardiac arrhythmias can also occur as a result of autonomic dysfunction which is common in HIV patients. This may predispose to syncopal attacks or even death.

**CORONARY ARTERY DISEASE**

Patients with HIV infection have been shown to have an increased risk of coronary artery disease (CAD). Accelerated coronary artery disease in HIV infected patients may result from atherogenesis stimulated by virus infected monocyte-macrophages, possibly caused by altered leucocyte adhesion or arteritis.

Inflammatory reaction in coronary vessels which may initiate endothelial dysfunction (ED) and promote atherosclerosis have been reported in HIV patients. Solages et al reported that HIV infected persons have a substantial impairment of endothelial vasomotor function which is worse among a subset with elevated levels of viral replication particularly intravenous drugs users (IDU). Also HIV-1 genomic sequences have been demonstrated in the coronary vessels of HIV infected patients who died of coronary arthritis and acute myocardial infarction.

HIV infection has been associated with increasing metabolic abnormalities like insulin resistance, hyperglycemia, dyslipidemia and hypertension which are traditional risk factors for coronary artery disease. Furthermore, coronary artery disease is observed with increasing frequency among HIV patients following the introduction of highly active antiretroviral therapy (HAART), especially among patients receiving protease inhibitors.

Despite the clinical benefits of protease inhibitors, complications such as lipodystrophy, insulin resistance, and high concentrations of low density lipoprotein and triglycerides have been described in up to 60% of patients treated with HAART regimens. Friis-Moller et al, in a study that included more than 23,000 patients, found a 26% increase in the incidence of myocardial infarction with each year of antiretroviral therapy.

HIV patients with cardiovascular risk factors should undergo annual cardiac evaluation, including ECG and echocardiography. Symptomatic patients should have further evaluation including exercise ECG, stress echocardiography,
coronary angiography if needed\(^9\).

Prevention of CAD in HIV patients is based on the guidelines for non HIV infected individuals. Lifestyle modifications such as cessation of smoking, regular isotonic exercises and healthy diets play an important role and can be effective as an initial step in managing these complications without causing further side effects\(^1\). The consumption of fruits, vegetable and low cholesterol products should be encouraged. Even modest reductions in body weights, in the obese HIV patients, may improve dyslipidaemia, hypertension, insulin resistance and the levels of inflammatory and thrombotic markers\(^1\). This may be followed by the use of lipid lowering drugs, but with a caution as some of these drugs may interact with the HAART\(^5,118\).

**VASCULAR DISEASE**

A number of vascular diseases, both infective and non infective have been reported in the setting of HIV infection\(^6\). Polyarteritis nodosa, Henoch-Schönlein purpura, and drug-induced hypersensitivity vasculitis have been reported\(^6\). Features similar to those in Kawasaki syndrome, coronary arteritis, and Takayasu arteritis also have been described\(^6\).

Young Africans who have no evidence of atherosclerosis, syphilis or any other cause of vascular disease are increasingly been found to have large vessel vasculitis involving the aorta and its major branches\(^119\). The typical pathologic process has been described as either an idiopathic focal necrotizing vasculitis with aneurysmal dilatation or a granulomatous vasculitis with fibroproliferative occlusion\(^70,119\).

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