

# Cardiac diseases in HIV and AIDS

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## Abstract

HIV infection is a major global health challenge of our time. With the introduction of highly active antiretroviral therapy and consequent reduction in mortality, the epidemic is now moving into middle-aged populations which are already at increased risk of cardiovascular diseases. The impact of HIV infection on the cardiovascular system is enormous and its adequate knowledge critical to the overall management of the patients. This article provides an review of the clinical spectrum and pathogenesis of HIV-associated cardiovascular diseases. It will no doubt enrich the knowledge of doctors and other health professionals, particularly those who are working in resource-poor settings with high burden of HIV disease

## INTRODUCTION

The Joint United Nations Programme on HIV/AIDS <sup>1</sup> estimates that 4.3 million people were newly infected with HIV in 2007. This brings the total number of HIV-infected people to 40 million worldwide. The pandemic's relentless spread despite about 25 years of efforts to combat the scourge is a source of global concern. Cardiac diseases associated with HIV are now well documented. These include dilated cardiomyopathy, pericarditis and pericardial effusion, pulmonary artery hypertension, vascular disease and arrhythmias. <sup>2</sup> With the present unabating nature of HIV epidemic and the weak hopes of near-future remedies such as HIV vaccines, the global health community might be jolted by an explosion of cardiovascular diseases in people living with HIV and AIDS.

## HIV-ASSOCIATED DILATED CARDIOMYOPATHY

The pathogenesis of HIV-associated dilated cardiomyopathy (HDCM) is unclear. However, myocarditis and direct HIV invasion of myocardial tissue are the most studied causes of dilated cardiomyopathy in HIV infection. <sup>3,4</sup> Other aetiopathogenic mechanisms that have been described are; an autoimmune process induced by HIV, the effect of toxicities of some antiretroviral drugs and medications use for opportunistic infections, and nutritional deficiencies. <sup>3</sup> In many studies, myocardial biopsy revealed myocarditis with cardiotropic viral infections. <sup>5</sup> Some of the viruses that have been implicated include coxsackievirus group B, cytomegalovirus, Epstein Barr and herpes simplex viruses.

Other non-viral microbes reportedly associated with myocarditis in HIV are Cryptococcal neoformans, <sup>6</sup> *Toxoplasma gondii*, <sup>7,8</sup> *Histoplasma capsulatum* and *Mycobacterium avium intracellulare*. <sup>9</sup> In one autopsy series, cardiac toxoplasmosis was diagnosed in 21 of 182 patients with HIV infection. <sup>8</sup> HIV itself directly invades and infects myocardial cells through a mechanism that is still largely unknown. However, reservoir cells may play a role in the interaction between HIV and CD4-receptor-negative cells such as myocardial cells. <sup>5</sup> Long term zidovudine has been reported to cause mitochondrial myopathy in skeletal muscles and may have a similar effect on myocardial muscle. <sup>10,11</sup> HDCM has been associated with advanced immunosuppression and lower CD4 counts and it is an independent risk factor for death. <sup>12</sup>

It is still not clear whether highly active antiretroviral therapy (HAART) has influence on the recovery of ventricular functions. Majority of patients will have a progression of left ventricular dysfunction. Thus, high index of suspicion and early diagnosis, and conventional treatment of heart failure remain the most promising ways of reducing the progression of the disease. <sup>13</sup>

## CORONARY ARTERY DISEASE

Patients with HIV infection have been shown to have an increased risk of coronary artery disease (CAD). <sup>14,15,16,17</sup> Some of the mechanisms that have been implicated as possible factors are discussed below.

## **ENDOTHELIAL DYSFUNCTION**

HIV can cause inflammatory reaction in coronary vessels which may initiate endothelial dysfunction (ED) and promote atherosclerosis.<sup>18</sup> ED is a well established mechanism for CAD. HIV infected persons have a substantial impairment of endothelial vasomotor function which is said to be worse among a subset with elevated levels of viral replication particularly intravenous drugs users (IDUs).<sup>19</sup> HIV-1 genomic sequences have been demonstrated in the coronary vessels of HIV infected patients who died of coronary arteritis and acute myocardial infarction.<sup>20</sup>

## **ABNORMAL LIPID METABOLISM AND LIPODYSTROPHY SYNDROME**

Lipid abnormalities have been noted in HIV patients before the introduction of HAART. However, during the last one decade, complex lipodystrophic body changes in association with metabolic abnormalities such as dyslipidaemia and insulin resistance have become a common feature in HIV patients on HAART.<sup>21</sup> Dyslipidaemia has been linked to HIV infection and HAART.<sup>22,23</sup> PIs appear to have drug-specific effects on lipid and glucose metabolism and several of them may induce or worsen dyslipidaemia and insulin resistance in HIV patients independent of body composition abnormalities.<sup>24,25,26,27</sup> However, some PIs, such as atazanavir, do not affect lipid or glucose levels

## **INSULIN RESISTANCE AND IMPAIRED GLUCOSE METABOLISM**

Insulin resistance and hyperglycaemia appear to be more common in HIV infected than non HIV infected individuals.<sup>25</sup> Patients on HAART may even be at more risk of insulin resistance and diabetes mellitus, and certain PIs, such as indinavir, may confer higher risk than others.<sup>27</sup> Systemic hypertension occurs in about one-third of patients with HIV infection. Some studies have reported an association between hypertension and NNRTIs and/or PIs.<sup>27,28</sup> However, hypertension associated with HIV seems to be linked to insulin resistance and metabolic syndrome<sup>29,30</sup>

Prevention of CAD is crucial in HIV patients and is based on the guidelines for non HIV infected individuals. Lifestyle modifications such as cessation of smoking, regular isotonic exercises and healthy diets are the initial step in the treatment of dyslipidaemia. 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.<sup>31</sup> 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.<sup>31,32</sup>

## **PERICARDITIS AND PERICARDIAL EFFUSION**

In the pre-HAART era, pericardial effusion was the most frequent cardiac manifestation with incidence as high as 11% per year.<sup>33</sup> Pericardial diseases can be due to HIV itself, other pathogens such as *Mycobacterium tuberculosis*<sup>34</sup>, *Staphylococcus aureus*<sup>35</sup>, *Cryptococcus neoformans*<sup>36</sup> and herpes simplex<sup>37</sup>, or neoplasm. In sub-Saharan Africa, *Mycobacterium tuberculosis* is the cause of pericardial disease in 86%-100% of HIV infected patients<sup>38,39</sup>

Echocardiography remains the gold standard for the diagnosis of pericardial disease, but computer tomography and/or magnetic resonance imaging may also be useful. In haemodynamically important effusions, pericardiocentesis has to be considered. Pericardiectomy may be an important palliative procedure. Infectious causes such as pulmonary tuberculosis should be well treated.

## **ENDOCARDITIS**

HIV infection per se is not associated with an increased risk of infective endocarditis (IE). However, IDUs who have HIV infection have a ten fold increased risk for IE than non-IDUs. In parts of the world where intravenous drug use is a public health issue, the prevalence of IE has been reported to be as high as 34% in HIV seropositive cohorts.<sup>40,41</sup> Right-sided valves are mostly involved. *Staphylococcus aureus* is the most frequent organism and is responsible for about 75% of cases. Other common bacterial organisms are *Streptococcus pneumoniae* and *Haemophilus influenzae*. Unusual pathogens such as *Candida albicans*, *Aspergillus fumigatus* and *Cryptococcus neoformans* are also frequent. There may also be a higher incidence of Gram-negative organisms.<sup>42</sup> Clinical presentation and prognosis are similar to those in non-HIV individuals. However, mortality from IE in the late stages HIV infection is about 30% higher than in the asymptomatic stage probably due to the low CD4 count.<sup>43</sup>

Other poor prognostic factors are affection of the left-sided valves and involvement of Gram-negative organisms or fungi.<sup>44,45</sup> Non-bacterial thrombotic endocarditis also occurs and was noted in 3%-5% of patients in Western series in the pre-HAART times.<sup>41</sup> Ironically, this endocarditis which has a predilection for patients with the wasting syndrome has

been rarely described in Africa. <sup>46</sup>

## HIV-ASSOCIATED VASCULAR DISEASE

There is substantial clinical evidence for the development of vascular disease in HIV infected patients. <sup>47</sup> The large vessel vasculitis involving the aorta and its major branches is increasingly being recognized in young Africans who have no evidence of atherosclerosis, syphilis or any other cause of vascular disease. <sup>48,49</sup> The typical pathologic process has been described as either an idiopathic focal necrotizing vasculitis with aneurysmal dilatation or a granulomatous vasculitis with fibroproliferative occlusion. <sup>50,51</sup>

## HIV-ASSOCIATED PULMONARY HYPERTENSION

The association between HIV and pulmonary hypertension is well established and documented. <sup>52</sup> Although the pathogenesis of HIV-associated pulmonary hypertension (HAPA) is not clear, several hypotheses have been proposed. While the direct role of HIV is still questionable, the indirect role of pleomorphic cytokines carries significant weight. <sup>53</sup> HIV-infected pulmonary macrophages and dendritic cells elaborate cytokines such as endothelin-1, interleukin-1?, and interleukin-6 and tumor necrotic factor-?, which trigger pulmonary endothelial cell proliferation and vasoconstriction. <sup>53,54</sup> Plexogenic pulmonary arteriopathy is the most common histological finding. Progressive dyspnoea and pedal oedema are the most frequent symptoms. The appearance of unexplained cardiopulmonary symptoms in HIV infected patients should arouse a suspicion of HAPA. Therapeutic responses to HAART, pulmonary vasodilators and anticoagulants are variable. <sup>55</sup>

## CARDIAC ARRHYTHMIAS

It is noteworthy to state that any of the cardiovascular disease associated with HIV can be complicated with cardiac arrhythmias. Some medications used in HIV/AIDS can also predispose to arrhythmias. Drugs such as efavirenz, foscarnet and pentamidine can cause QT prolongation which may result into torsade de pointes ventricular tachyarrhythmias. <sup>56</sup> If arrhythmias occur, serum electrolytes and plasma glucose concentrations should be determined and any abnormality appropriately corrected. Magnesium may be used to terminate torsade de pointes ventricular tachyarrhythmias.

## AIDS RELATED NEOPLASMS

Kaposi sarcoma (KS) and non-Hodgkin lymphoma (NHL) involving the myocardium and pericardium have been

described in patients with HIV particularly in the advanced stages of the infection. <sup>42,57</sup> Cardiac KS is often occult and rarely diagnosed in life. The introduction of HAART has led to a reduction in cardiac KS and NHL. This reduction may be due to immunologic recovery and prevention of human herpes virus-8 and Epstein Barr virus infections which play aetiologic role in these neoplasms. <sup>57</sup>

## CONCLUSION

There is no doubt that the HIV epidemic has the potential to catastrophically worsen the epidemiology of cardiovascular diseases across the globe, but particularly in the worst hit resource-constraint regions. Therefore prevention, diagnosis and treatment of HIV associated cardiovascular diseases should become an integral part of current management concepts of HIV infection.

**Figure 1**

PRACTICAL POINTS
Cardiac diseases associated with HIV are now well documented
Myocarditis and direct HIV invasion are the most studied causes of dilated cardiomyopathy in HIV infection
Patients with HIV infection have been shown to have increased risk of coronary artery disease
In sub Sahara Africa, Mycobacterium tuberculosis is the commonest cause of pericardial disease in HIV infected patients
HIV infection per se is not associated with an increased risk of infective endocarditis
There is substantial evidence of development of vascular disease in HIV infected patients
The association between HIV and pulmonary hypertension is well established
The introduction of HAART has led to a reduction in cardiac Kaposi sarcoma and non-Hodgkin lymphoma in HIV and AIDS

## CORRESPONDENCE TO

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