Cardiac Sequelae of Human Immunodeficiency Virus Disease

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Abstract: Presently, patients with human immunodeficiency virus infection are living longer and are frequently encountered in medical practice. HIV infection is a systemic disease, which affects a wide spectrum of organs. Cardiac involvement is frequent, and the consequent clinical manifestations are a common reason to seek medical advice. In this review, we discuss the different cardiac sequelae of HIV infection.

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The burden of the worldwide epidemic of HIV infection continues to increase, especially in the developing world. However, with the advent of potent antiretroviral therapies, more patients are surviving longer, which is allowing clinicians to witness new clinical manifestations of chronic HIV infection.[1]

Pulmonary hypertension, coronary artery disease (CAD), myocardial diseases, endocardial disease, pericardial disease, arrhythmias and cardiac tumors are pathologies that may be encountered in HIV-infected patients. In this review, our goal is to update the reader on more recent reports of the above-mentioned cardiovascular outcomes.

PULMONARY ARTERIAL HYPERTENSION

HIV-associated pulmonary arterial hypertension (HIV-PaHT) is a very rare complication with an estimated prevalence of 1 in 200 (0.5%) HIV-infected individual (Table 1); this has not changed in the post–highly active antiretroviral therapy (HAART) era.[2]

The pathogenesis of HIV-PaHTN is complex and is still poorly understood; however, both viral infection and patient factors are thought to play roles.[3] It has been hypothesized that the HIV stimulates host cells to release cytokines and growth factors, including the potent vasoconstrictors, endothelin-1, interleukin 6, tumor necrosis factor α and platelet-derived growth factor α.[4] These complex interactive changes will result in endothelial damage, laminar intimal fibrosis, smooth muscle and fibroblast proliferation and plexiform lesion formation, quite similar to those found in PaHTN from other causes.[5] More recent evidence suggests that the patient's immunologic response, virus HIV-negative factor (Nef), HIV transactivator of transcription (Tat) accessory proteins and human herpes virus-8 coinfection may play an important role in the cascade of events.[6,7]

The prognosis is poor and the reported mortality rate is high. PaHTN in HIV population is an independent predictor of mortality with 1-year survival rate reported to be 51% to 88%.[5,8] The severity of HIV infection and CD4 cell count has no apparent correlation with this complication. The effect of highly active antiretroviral therapy regimens on the clinical course is still not well defined and is presently being investigated; however, it has been suggested that long-duration treatment with HAART might reduce mortality.[8]

At present, the treatment of HIV-PaHTN is similar to that of patients with idiopathic pulmonary arterial hypertension. There have been reports of the use of diuretics, anticoagulation, phosphodiesterase V inhibitors and calcium channel blockers to treat HIV-PaHTN. However, HAART, prostacyclin analogs (eg, epoprostenol) and endothilin receptor inhibitors (eg, bosentan) were found to be effective in reducing the pulmonary arterial pressure in this population in several small studies. Heart-lung transplantation is the last treatment option in this subgroup of patients.[9,10]

CORONARY ARTERY DISEASE

As the longevity of individuals with HIV has been increasing because of HAART, the clinicians would be expected to see more HIV-infected patients with CAD. HIV infection increases the risk of atherosclerosis and the development of CAD at earlier ages in comparison with noninfected subjects.[11–15] Recently, it has been shown that cardiovascular mortality accounted for 6.5% of total deaths among HIV-infected patients from Europe and North America and for 8% among HIV-infected people in France. HIV patients have higher rates of CAD when compared with the general population; the standardized mortality ratio was 1.5 in a French database and a risk ratio of 1.7 in North American cohort. Moreover, the HIV patients were reported to have their first myocardial infarction in their late 40s, far earlier than that reported in the general population.[16,17] During the pre-HAART era, the risk of ischemic heart disease was slightly, but not significantly, higher in HIV-infected patients than in control subjects (adjusted relative risk, 1.39; 95% confidence interval, 0.82–2.36) (Table 1). However, during the post-HAART period, there was a substantial increase in the risk of ischemic heart disease in the HIV population (adjusted relative risk, 2.12; 95% confidence interval, 1.62–2.76).[11] The 3-year risk for myocardial infarction was found to increase from 0.30% in patients who are not on HAART to 1.07% in patients receiving antiretroviral agents.[16]

The viruses itself as well as HAART are potential causes of CAD. In addition to the conventional cardiovascular risk factors, which are found to be at higher, rates in this population.[16–18]

HAART, protease inhibitors (PIs) in particular and some nucleoside reverse transcriptase inhibitors might potentially increase the risk of CAD. The metabolic changes that are produced by PIs, including increased glucose levels and lipodystrophy as a result of decreased insulin sensitivity, can lead to acceleration in the process of atherosclerosis.[19–21] Although all PIs may lead to these derangements to different degrees, the D:A:D study suggested that cumulative exposure to indinavir and the lopinavir-ritonavir combination in particular

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TABLE 1. Clinical presentations of the various HIV-related cardiac involvements

HIV-related cardiac involvement	Clinical presentation	Epidemiology	
		Pre-HAART	Post-HAART
Pulmonary arterial hypertension[2]	Nonspecific symptoms. Exertional dyspnea, pedal edema and fatigue are common symptoms; causes right ventricular dysfunction, cor pulmonale and death; poor prognosis	Prevalence = 0.5%	Same
Coronary artery disease[16,17]	Silent ischemia, stable angina or acute coronary syndrome; patients usually young (<50 yr)	Adjusted relative risk = 1.39	Adjusted relative risk = 2.12; increased risk of MI by 13% per year
Dilated cardiomyopathy[28,a]	Frequently asymptomatic but can present with decompensation (NYHA class III or IV); changes in echocardiogram: LV dilatation, global hypokinesis and reduced systolic function; poor prognosis	Prevalence 30%–40%; annual incidence of 15.9/1000	Prevalence decreased by about 33%
Endocarditis[34]	Infective endocarditis: fever and sepsis; affects intravenous drug users; involves right-sided valves; *Staphelcoccus aureus* are most frequent pathogens	20.5 per 1000 person-years	6.6 per 1000 person-years
	Marantic endocarditis: seen in HIV wasting syndrome; affects left-sided valves	Prevalence 3%–5%	Not available
Pericardial disease[27,28,a]	Commonly asymptomatic, but can present with fever and chest pain of pleuritic nature (pericarditis); pericardial effusion is common and poor prognostic sign	Prevalence = 11% in asymptomatic AIDS	Prevalence decreased by 35%
Arrhythmias[41,44,45]	QTc interval prolongation, torsades de pointes, heart blocks and sudden cardiac death	Prevalence (QTc prolongation) 69%	Prevalence (QTc prolongation) 10%–20%
Cardiac tumors[27,39]	Kaposi's sarcoma: pericardial effusion, and in some cases, tamponade.	Prevalence = 12%–28%	Decreased by 50%.
	Non-Hodgkin's lymphoma: infiltrative cardiac disease causing heart failure, intracavitary masses, arrhythmia, superior vena cava obstruction	Not available	Not available

[a] No clinical studies have quantified the reduction rates.
HAART, highly active antiretroviral therapy; NYHA, New York Heart Association functional classification; MI, myocardial infarction.

was associated with increased risk of myocardial infarction by 12% and 13% per year, respectively.[18]

The data regarding nucleoside reverse transcriptase inhibitors as a risk for CAD are less clear. These agents cause mitochondrial toxicity, insulin resistance and lipid disturbances.[19] In the D:A:D study, abacavir and didanosine were associated with increased risk of myocardial infarction.[18] Choi et al[20] also found that the exposure to abacavir within 6 months is independently associated with higher rates of cardiovascular events, myocardial infarction in particular. However, other studies could not confirm this relationship, especially after controlling for chronic kidney disease and the other traditional cardiovascular risk factors.[17,21,22] Non-nucleoside reverse transcriptase inhibitors and integrase inhibitors have not been suspected of causing CAD.[23,24]

Interestingly, there is growing evidence suggesting that the HIV itself can independently increase the risk of accelerated CAD.[21–24] Monocyte-macrophage activation induced by the virus is one possible mechanism in the multifactorial vascular inflammation process. Moreover, alteration of the immunologic response in this population, in addition to the exposure to various xenoantigens from HIV itself and other viral and bacterial infections have been claimed to induce an inflammatory condition that may speed up atherogenesis.[24]

Endothelial dysfunction, a marker of early stages of atherosclerosis, has also been reported in HIV infection and has been associated with increased viral load.[21,22] The HIV has the ability to directly change the normal function of the endothelium.[22,23] The latter interaction results in elevated levels of the various prothrombotic plasma markers, such as von Willebrand factor, β2 microglobulin and thrombomodulin.[21,25] Also, researchers found increased levels of the circulating inflammatory molecules, such as interleukin 6 and D-dimer, in patients with elevated viral loads.[25]

Prevention of CAD is the mainstay of the management. Interruption of HAART therapy in chronically treated HIV patients should be avoided. It has been demonstrated by the SMART study that the rates of death and cardiovascular events increased significantly in patients who were assigned to a CD4-guided drug conservation arm in comparison with continuous therapy arm.[25]

Controlling and modifying the risk factors and comorbidities are of paramount importance. The fasting serum concentrations of lipids should be evaluated before starting HAART, at