Infectious and Non-infectious Etiologies of Cardiovascular Disease in Human Immunodeficiency Virus Infection

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Abstract:

Background:
Increasing rates of HIV have been observed in women, African Americans, and Hispanics, particularly those residing in rural areas of the United States. Although cardiovascular (CV) complications in patients infected with human immunodeficiency virus (HIV) have significantly decreased following the introduction of antiretroviral therapy on a global scale, in many rural areas, residents face geographic, social, and cultural barriers that result in decreased access to care. Despite the advancements to combat the disease, many patients in these medically underserved areas are not linked to care, and fewer than half achieve viral suppression.

Methods:
Databases were systematically searched for peer-reviewed publications reporting infectious and non-infectious etiologies of cardiovascular disease in HIV-infected patients. Relevant articles cited in the retrieved publications were also reviewed for inclusion.

Results:
A variety of outcomes studies and literature reviews were included in the analysis. Relevant literature discussed the manifestations, diagnosis, treatment, and outcomes of infectious and non-infectious etiologies of cardiovascular disease in HIV-infected patients.

Conclusion:
In these medically underserved areas, it is vital that clinicians are knowledgeable in the manifestations, diagnosis, and treatment of CV complications in patients with untreated HIV. This review summarizes the epidemiology and causes of CV complications associated with untreated HIV and provide recommendations for management of these complications.

Keywords: AIDS, HIV, Antiretroviral therapy, Cardiovascular disease, Infectious diseases, Opportunistic infections.

INTRODUCTION
The hallmark of human immunodeficiency virus (HIV) results from a progressive deficiency of the CD4\textsuperscript{+} T-cells leading to profound immunodeficiency [1, 2]. Once HIV enters the body, the virus disseminates rapidly in the absence of an adaptive immune response, establishing a persistent infection characterized by high levels of viremia in lymphoid tissues and reduction of CD4\textsuperscript{+} T-cells. Continuous viral replication also results in chronic immune activation, leading to nonspecific inflammation and microbial translation, further depleting CD4\textsuperscript{+} T-cells. Immune activation is associated
with increased expression of activation markers on natural killer (NK) cells, B cells, CD4+ T-cells, and CD8 T-cells, as well as increased turnover rates of these cells. The function of these cells is compromised, which may result in poor control of other viruses and infectious agents.

New trends in HIV transmission include an increased number of cases in women, African Americans, and Hispanics, many of whom are not linked to appropriate prevention, care and treatment services [3, 4]. Incidence rates of AIDS are also increasing in certain rural areas of the United States, including Appalachia, the Southeast Region, the Mississippi Delta, and the US-Mexico Border [5]. Previous studies have identified additional barriers that residents of rural areas face when attempting to access HIV testing and treatment, such as geographic isolation, lack of education, unemployment, poverty, lack of childcare services, as well as cultural discrimination. Despite the advancements to combat the disease, many patients in these medically underserved areas are not linked to care, and fewer than half achieve viral suppression [6]. Unfortunately, suppressing viral replication is a vital component of HIV treatment as it has been associated with improved health outcomes and decreased rates of transmission [7, 8].

In areas where patients do not have access to or choose not to take advantage of appropriate care, clinicians should be aware of the potential of HIV-related complications. Complications of HIV occur as a result of impaired cell-mediated immunity and include opportunistic infections, malignancies, or multiple organ system dysfunction [9]. Reports of multiorgan involvement including neurologic, pulmonary, gastrointestinal, and hematologic systems have previously been published. Cardiac involvement due to HIV was first described by Autran et al in 1983, who presented the case of a 24 year old Haitian female with cardiac Kaposi sarcoma (KS) [10].

Most studies and reports describing the complications of cardiovascular disease (CVD) in HIV-infected patients were performed prior to the introduction of antiretroviral (ARV) therapy [11, 12]. More than 1.1 million individuals in the United States were infected with HIV as of 2011, and the number of persons living with an AIDS diagnosis was highest in the South [13]. Due to suboptimal HIV care in this region and average rates of nonadherence to ARV therapy ranging from 50-70%, awareness of HIV-associated cardiac complications is essential [13, 14]. This review will focus on the manifestations, diagnosis, and treatment of cardiovascular (CV) complications observed in patients with untreated HIV, which may include pericardial effusions, disease of the myocardium, pulmonary arterial hypertension (PAH), HIV-related cardiac malignancies, valvular disease, and vascular disease including coronary artery disease (CAD) and stroke.

METHODS

Adult English-language peer-reviewed articles and case series examining infectious and non-infectious etiologies of cardiovascular disease in HIV-infected patients were evaluated for inclusion in the paper. Relevant articles cited in the retrieved publications were also reviewed for inclusion. Articles were identified through PubMed. The following terms were included in the search strategy: ‘cardiovascular disease’, ‘human immunodeficiency virus’, ‘acquired immunodeficiency virus’, ‘opportunistic infections’.

PERICARDIAL EFFUSION

Pericardial effusion is one of the most commonly identified CVD complications affecting HIV-infected patients, developing in almost 20% of patients [15 - 20]. Clinical manifestations include asymptomatic pericardial effusion, pericarditis, cardiac tamponade, and constrictive pericarditis. The incidence of pericardial effusions was determined to be 11% per year in a study of 195 HIV-infected patients who underwent serial echocardiograms every 3 to 6 months over a 5-year period [19].

A significantly shorter 6 month survival was observed in patients with pericardial effusions compared to those without effusions (36% versus 93%, respectively) [19]. The overwhelming majority of pericardial effusions found in this patient population are classified as small, and spontaneous resolution has been reported to occur in 13-42% of patients in previous studies. However, increased mortality persists regardless of resolution [19 - 21].

While the majority of effusions were asymptomatic without an identifiable etiology, those that were symptomatic were caused by an identifiable infectious process or neoplasm in up to two-thirds of cases [18]. Fever, pleuritic chest pain, and dyspnea are the most common clinical findings in symptomatic patients with pericardial effusions [22]. Although diagnostic evaluation is not required for small, asymptomatic pleural effusions, pericardiocentesis is necessary in those with symptomatic, large effusions, regardless of tamponade, to identify the etiologic cause, as the majority are treatable. Even with pericardiocentesis, many studies reported low rates of definitive etiologic
One of the most studied causes of cardiomyopathy in HIV-infected patients is the direct invasion of HIV into myocardial cells, the fact that these cells do not possess CD4+ receptors makes the pathophysiology of this process unclear. Evidence has suggested other causes, such as dendritic cells or cytokine mediated tissue injury, may play a role. It has also been hypothesized that Epstein-Barr virus (EBV) may facilitate the entrance and replication of HIV into myocytes. One of the most studied causes of cardiomyopathy in HIV-infected patients is the direct invasion of HIV into myocardial cells, the fact that these cells do not possess CD4+ receptors makes the pathophysiology of this process unclear. Evidence has suggested other causes, such as dendritic cells or cytokine mediated tissue injury, may play a role. It has also been hypothesized that Epstein-Barr virus (EBV) may facilitate the entrance and replication of HIV into myocytes.
patients may progress to develop chronic Chagas’ cardiomyopathy and may present with cardiac arrhythmias, heart failure, or stroke. Given the similarities in presentation and low levels of awareness, clinicians should assess patients living in or returning from endemic areas.

Infiltrative myocardial disease may be the result of a neoplasm including KS or high-grade HIV-associated lymphoma, which is described below.

HIV-induced immunosuppression has also been theorized to contribute to myocardial dysfunction. HIV-infected T-cells produce cytokines, including tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-2, endothelin-1 (ET-1), and alpha interferon, and activate inducible nitric oxide synthase (iNOS) that increases production of nitric oxide, which in turn is cytotoxic to myocardial cells [47]. Previous studies have found enhanced expression of iNOS in HIV-infected patients with more advanced stages of immunosuppression [48]. TNF alters intracellular calcium homeostasis leading to a negative inotropic effect, which may increase nitric oxide synthesis and cause decreased myocyte contractility [47, 49].

Alternatively, hypersensitivity reactions and cardiac-related autoimmunity have previously been described in the pathogenesis of myocarditis and cardiomyopathy [50]. Hypergammaglobulinemia and increased concentrations of serum immune complexes due to abnormalities of T-helper cells may result in inflammatory lesions in all bodily organs, including the cardiac muscle. A damaging autoimmune reaction secondary to circulating cardiac autoantibodies as a result of HIV-induced formation of cardiac cell-surface immunogenic proteins have been identified previously in HIV-infected patients with cardiomyopathy.

Drug-induced cardiotoxicity in HIV-infected patients may be the result of treatment with therapeutic medications or recreational use of illicit substances. Zidovudine-induced cardiomyopathy is thought to be the result of ultrastructural damages and inhibition of mitochondrial DNA replication, leading to lactic acidosis that ultimately damages the myocardium [12, 51]. Treatment with interferons, antineoplastic agents, and antivirals have been reported to cause cardiomyopathy and congestive heart failure that may be reversible following discontinuation of the cardiotoxic drug. Doxorubicin, an anthracycline antineoplastic used to treat KS and non-Hodgkin’s lymphoma (NHL), as well as foscarinet, an antiviral used to treat CMV, have been found to cause cardiomyopathy in a dose-related manner [52, 53]. Amphotericin B, a polycycl anomufilal, may cause reversible dilated cardiomyopathy [54].

Substance abuse, including alcohol, cocaine, methamphetamine, and intravenous drugs, occurs commonly within the HIV-infected patient population [55]. Previous studies have observed abnormal diastolic dysfunction in HIV-infected patients who use illicit drugs [56]. Methamphetamine use, in the setting of HIV-infection, has been shown to further suppress the immune system, increase the activity of HIV reverse transcriptase in monocyte-derived macrophages, and increase the risk of cardiac complications [57, 58].

While no direct evidence has been published, previous reports have described nutritional deficiencies, particularly of selenium, that are commonly observed in HIV-infected patients and may lead to cardiomyopathy [59, 60].

Endocardial fibrosis and mural thrombus are common findings of HIV-related dilated cardiomyopathy upon gross examination [61]. Histologic findings include myocyte hypertrophy and degeneration. Increased interstitial and endocardial fibrillar collagen deposition may also be present, and is often related to previous myocarditis. Myocarditis should be suspected in patients presenting with fever, atypical chest pain, and an upper respiratory tract infection. An echocardiogram, which is the most sensitive and specific test for diagnosis of dilated cardiomyopathy, should be performed [37]. Compared to HIV-infected patients with a similar stage of HIV-infection and a normal heart, those diagnosed with left ventricular dysfunction had a much shorter median survival (472 days versus 101 days, respectively) [62].

Management of symptomatic cardiomyopathy in HIV-infected patients is similar to that in HIV-negative patients, and includes the treatment of heart failure with a combination of diuretics, angiotensin-converting enzyme (ACE) inhibitors, β-blockers, aldosterone antagonists, and digoxin [50]. However, treatment should be aimed at the underlying cause in cases where it can be identified. Surgical procedures, including coronary artery bypass graft and valve replacement, should be performed in a similar fashion as in the general population [63]. Although no data have confirmed the benefit of ARV therapy on cardiomyopathy, the prevalence of HIV-associated cardiomyopathy has been reduced by approximately 30% due to increasing use of ARV therapy and decreasing rates of opportunistic infections and myocarditis in resource-rich settings [50, 64]. Drug interactions between ARV and commonly used CV medications can be found in a previously published review article [65].
PULMONARY ARTERIAL HYPERTENSION

First described in 1987 by Kim and Factor, the incidence of PAH in HIV-infected patients is 1 in 200 as compared to 1 in 200,000 in the general population [61, 66, 67]. It is more common in male and younger patients with risk factors including pulmonary infections, intravenous drug use, homosexual contacts, and hemophilia. The most common microscopic finding in HIV-infected patients with PAH is plexogenic pulmonary arteriopathy [61]. Although multifactorial and poorly understood, the pathologic mechanism has been described to be the result of endothelial damage and vasoconstriction due to HIV-induced release of endothelin-1, IL-6, and TNF-α, as well as secretion of TNF-α, oxide anions, and proteolytic enzymes by alveolar macrophages in response to an infection. PAH carries a poor prognosis in HIV-infected patients, with the probability of survival at one, two, and three years to be 73%, 60%, and 47%, respectively [68]. In a prospective comparison, although HIV-infected patients with PAH were younger and had a lower disease severity than their non-infected counterparts, investigators found similar rates of mortality between groups [69].

Treatment with ARV therapy significantly reduced both pulmonary artery pressure and mortality in patients with PAH [70]. Available data have failed to show the efficacy of calcium channel blockers (CCB) in HIV-infected patients [67]. Furthermore, the use of CCB in this patient population may lead to the development of serious adverse effects, including hypotension as a result of systemic vasodilation and decreased right ventricle filling. Iloprost, an inhaled prostacyclin analogue, significantly increased cardiac index, in addition to significantly decreasing pulmonary arterial pressure and vascular resistance in 8 patients with HIV-associated severe PAH concomitantly treated with ARV therapy [71]. No significant drug interactions or adverse events were reported. Continuous infusion epoprostenol, in addition to ARV therapy, increased the six-minute walk test by 183 meters from baseline and improved the NYHA Class in 19 of 20 patients with NYHA Class III-IV HIV-associated PAH [72]. The use of bosentan, an oral nonselective endothelin receptor antagonist, in HIV-infected patients with PAH resulted in improvements in six-minute walk distance, NYHA functional class, hemodynamic parameters, and quality of life after 16 weeks [73]. Sildenafil, a cyclic GMP phosphodiesterase type 5 inhibitor, has been shown to improve symptoms and hemodynamic parameters in HIV-infected patients with PAH [74]. Sildenafil should be used cautiously as concomitant use in patients treated with PI-containing ARV regimens may result in significantly increased concentrations of sildenafil, whereas sildenafil may also significantly decrease concentrations of PIs.

No specific guidelines are available for the treatment of PAH in HIV-infected patients. Treatment regimens should therefore include ARV therapy, but focus on PAH-specific therapy, excluding CCBs.

MALIGNANCIES

First described in 1983, KS or high-grade HIV-associated lymphoma may lead to involvement of the heart in HIV-infected patients and is usually fatal [10, 50]. Retrospective autopsy studies identified KS involving the heart in 12% to 28% of HIV-infected patients [61, 75]. Metastatic KS may involve the visceral layer of serous pericardium or subepicardial adipose tissue. Fatal cardiac tamponade was identified to be the result of KS of the epicardium and pericardium in a report of 5 HIV-infected patients by Vijay et al. [76]. A transient improvement in vital signs was observed following pericardiocenteses; however, patients were noted to survive for only a few hours to days with diagnosis of KS of the pericardium occurring at autopsy. The pericardial sac was found to be tense and filled with dark bloody fluid, supporting the possibility that the KS lesions were penetrated with the pericardiocentesis needle. Thus, the authors recommend a pericardial window to be performed for decompression and establishing a diagnosis, as pericardiocentesis represents a high-risk procedure in these patients and will not yield a diagnosis.

NHL occurs 25 to 60 times more frequently in HIV-infected patients compared to the general population and is usually disseminated early in these patients [77, 78]. These lymphomas may present as a primary cardiac lymphoma, but will more commonly be the result of disseminated disease [79 - 82]. Cardiac lymphoma can form nodules and intracavitary masses, as well as result in heart failure, superior vena cava syndrome, arrhythmias, heart block, or blood flow obstruction due to cardiac masses.

Previously, the general prognosis of cardiac lymphoma in HIV-infected patients was considered to be poor; however, recent reports since the introduction of ARV therapy in combination with advanced chemotherapy has led to improved outcomes in these patients [78, 83]. Previous evidence suggests that concomitant use of ARV therapy and chemotherapy is tolerable, in most cases. ARV in combination with chemotherapy produces response and disease-free survival rates similar to those observed in patients with cancer without HIV [84, 85].
ENDOCARDITIS

The etiologies of endocardial disease seen in HIV-infected patients include marantic endocarditis (nonbacterial thrombotic endocarditis) and infectious endocarditis (IE). Marantic endocarditis is characterized by friable, sterile vegetations consisting of platelets and red blood cells that adhere to any cardiac valves. Marantic endocarditis has been reported to occur in 3-5% of HIV-infected patients, mostly commonly in those over 50 years of age [86]. Neoplastic, hypercoagulable, and chronic wasting diseases have been linked with marantic endocarditis, which may lead to valvular dysfunction, most commonly left-sided lesions [18, 87]. The majority of cases are clinically silent; however, systemic embolization can occur in up to 42% and may involve the brain, lung, spleen, kidney, and coronary arteries [88].

The prevalence of IE in HIV-infected patients is similar to that found in uninfected patients with comparable risk behaviors, usually occurring in intravenous drug abusers [89, 90]. Of the 108 episodes of IE among 105 HIV-infected patients, 94.3% were intravenous drug abusers with tricuspid valve involvement [90, 91]. A nested case-control analysis found that intravenous drug users and patients with advanced immunosuppression, defined as CD4+-cell count < 50 cells/ml or HIV-1 RNA > 100,000 copies/mL, had a much higher risk of IE, with those over 40 years of age having a higher mortality. A significant increase in mortality is observed only in patients with more advanced HIV.

Rates of IE have decreased with the advent of ARV therapy [92]. In both HIV-positive and –negative patients with IE, patient presentations are similar [91]. Presenting symptoms are most commonly fever, chills, and dyspnea, but can also include weight loss, concomitant pneumonia or meningitis [92, 93]. S. aureus was the most common etiologic organism, isolated in almost 70% of patients. One fourth of these were methicillin-resistant S. aureus. Fungal endocarditis has been previously reported to be caused by Aspergillus fumigatus, Cryptococcus spp. and Candida spp. [50].

HIV infection has not been shown to be a risk factor for IE, excluding intravenous drug users [41]. Treatment strategies for HIV-infected patients with IE are similar to those used for HIV-negative patients.

CORONARY ARTERY DISEASE

Immune dysfunction, proliferation of T-cells, inflammation, endothelial dysfunction, and lipid disorders associated with HIV-infection may lead to the development of atherosclerosis [94 - 96]. HIV promotes monocyte penetration of the vascular intima to promote secretion of cytokines and expression of endothelial cell adhesion molecules during atherogenesis [97]. Higher concentrations of IL-6, a proinflammatory cytokine, have been found in HIV-infected patients with ongoing viral replication or advanced immunosuppression [98]. Intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), E-selectin, P-selectin, and von Willebrand factor (vWF), biomarkers associated with endothelial activation, have been observed in previous studies in patients with advanced HIV-infection or opportunistic infections [99, 100].

HIV transcription (Tat) protein and negative factor (Nef) may induce endothelial dysfunction promoting the development of CVD in HIV-infected patients [101]. Tat protein serves as the principle transactivator of HIV replication and is secreted by infected cells [102]. Endothelium-dependent vasorelaxation was significantly impaired in porcine coronary arteries in the setting of low concentrations of Tat. Furthermore, Tat induces inflammation by activating human endothelial cells [103]. Previous evidence has also implicated Nef as one of the primary factors in HIV-induced endothelial activation [101]. Nef expression in macrophages promotes secretion of multiple inflammatory proteins [104].

Lower CD4+ T-cell counts have been directly correlated with an increased risk of CVD in HIV-infected patients [105]. Increased rates of coronary artery plaque and carotid artery stiffness have been observed in relation to a higher number of activated CD8+ T-cells [106, 107]. In one study, an increased frequency of carotid artery plaques was observed in participants with CD4+ counts < 200 cells/ml [108]. Increased levels of high-sensitivity C reactive protein, IL-6, D-dimer, and cystatin C suggest that inflammatory and prothrombotic changes may lead to atherogenesis and subsequent plaque rupture [109]. In addition, these inflammatory changes may play a role in the endothelial dysfunction observed in this patient population [110].

Both total cholesterol (TC) and high-density lipoprotein-cholesterol (HDL-C) are reduced in the early stage of HIV infection [110]. Lower levels of apolipoprotein B and smaller low-density lipoprotein-cholesterol (LDL-C) have been observed in more advanced stages of HIV. Previous reports have suggested that HIV may alter normal lipid processing and delivery to vessel walls. Lower rates of LDL-C clearance have also been observed in HIV-infected patients [111]. HIV-infected macrophages accumulate significant amounts of lipids due to abnormal cholesterol efflux, similar to
macrophage foam cells, and have been identified in atherosclerotic plaques [112].

Monitoring and management of lipid values should follow the recommendations made in the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III), despite the recent publication of updated cholesterol treatment guidelines due to its lack of data regarding the management of dyslipidemia in HIV-infected patients [113 - 115]. Evidence suggests that some ARV medications may worsen serum lipid profiles, leading to a further increased risk of CAD [116 - 128]. Modification of ARV regimens is reasonable and may improve lipid profiles; however, caution is advised due to the risk of virologic failure [113 - 115]. Lipid-lowering medications, such as statins, fibrates, and cholesterol absorption inhibitors, as well as other medications targeting lipids, effectively lower TC, triglycerides, and LDL-C in HIV-infected patients.

CEREBROVASCULAR DISEASE

Cerebrovascular disease in HIV-infected patients may manifest as either ischemic or hemorrhagic. Etiologies of ischemic stroke in HIV-infected patients include HIV-associated vasculopathy, opportunistic infections, neoplasms, cardioembolism, or coagulopathy [129]. Hemorrhagic stroke may be the result of HIV-associated vasculopathy, HIV-induced thrombocytopenia, or mycotic aneurysm. ARV therapy has also been proposed as a mechanism of cerebrovascular disease and stroke in HIV-infected patients [130].

The pathogenesis of stroke in HIV-infected patients is primarily derived from both in vitro human and animal models, while in vivo models have focused on endothelial dysfunction and circulating biomarkers [131 - 133]. Endothelial dysfunction is a crucial process provoking the inflammatory process in the pathogenesis of stroke. As previously discussed in the above sections, endothelial dysfunction may result in similar complications in HIV-infected patients [134]. Minimal research exists examining the association between HIV and stroke risk [129].

Up to 5% of HIV-infected patients develop stroke, but an even higher percentage, up to 34%, have been noted to have cerebral ischemia at autopsy [129]. However in the United States, an increasing number of patients are admitted with concurrent diagnoses of stroke and HIV infection [129, 135]. Pharmacologic and non-pharmacologic management should target the acute stroke and its associated complications. Additionally clinicians should identify the etiology of the stroke, and treatment should be directed at treatable causes. Emphasis should be placed on identifying and reversing risk factors, initiating or modifying ARV therapy, as well as initiating medications for secondary prevention, including antiplatelet agents, statins, and antihypertensive medications.

CONCLUSION

CV complications directly related to HIV-infection are most commonly seen in patients with profound immunodeficiency as a result of opportunistic infections, malignancy, and multiple organ system dysfunction. Following the introduction of ARV therapy, the incidence of these complications has continued to decrease on a global scale. However, select patient populations such as women, African Americans, and Hispanics, particularly those living in rural areas of the United States, are often not linked to appropriate preventative or treatment services. In these medically underserved areas, clinicians must remain aware of the manifestations and treatment of CV complications observed in untreated HIV-infected patients.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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