Cardiovascular Opportunistic Infections in HIV Disease.

F. Buba

Department of Medicine (38), King Khalid University Hospital, King Saud University, P. O. Box 7805, Riyadh 11472, Saudi Arabia
ubfaruk@hotmail.com

Abstract

Cardiovascular opportunistic infections are fairly encountered in patients with HIV disease. The search on this topic was carried out electronically via peer-reviewed articles in PubMed sources, Cochrane reviews and other medically-oriented search engines. Most opportunistic infections occur when the CD4 counts fall below 200/mL. The spectrum of presentations includes pericarditis, pericardial effusion, myocarditis, dilated cardiomyopathy, endocarditis, pulmonary arterial hypertension and aneurysmal disease. The incidence of these complications showed significant difference between the periods prior and after the introduction of the highly active antiretroviral therapy (HAART). In addition, some complications are peculiar to certain region of the world notably tuberculous pericarditis in areas of endemic tuberculosis. The management of these conditions requires meticulous diagnosis, supportive therapies, prompt detection and treatment of opportunistic infections. Furthermore, the early institution of highly active antiretroviral therapy had altered the course of most of the HIV-related cardiac complications. The physicians managing these patients should also be aware of complications of treatment and potential drug-drug interactions.

Key Words: Human immunodeficiency virus, cardiovascular infections, highly active antiretroviral drug therapy, Supportive measures.

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Introduction

HIV/AIDS continues to exert considerable burden to the healthcare delivery systems especially in resource-limited countries since its discovery over two decades ago. The UNAIDS epidemic update of 2010 revealed an estimate of 2.6 newly diagnosed HIV infection with 1.8 million estimated deaths secondary to AIDS-related illnesses worldwide [1]. The epidemic seems to have remained quiescent in most regions of the world except increase in Eastern Europe and central Asia due mainly to high rate of new HIV infection from networks of people who inject themselves and their sexual partners. There is also evidence of increase in resurgence in several high-income countries mainly because of male homosexuals. Seventy-one per cent of new cases were however recorded in sub-Saharan Africa [1]. HIV is an enveloped RNA retrovirus. It has numerous ways of transmission [2]. Significantly, the chance of transmission heterosexually is linked to the viral load of the source [3]. The virus has predilection of infecting CD4+ cells. Further investigations had demonstrated the facilitation of the process of viral entry via CCR5 and CXCR4 receptors [4]. Recently, some publications had drawn an important role for viral infectivity factor, Vif, in supporting viral replication by counteracting the anti-retroviral cellular factor, APOBEC3G and the evidence of the lack of replication of HIV-1 in Vif deficient cells [5, 6]. The consequence of depletion of CD4+ cells leads to cellular and subsequently humoral deficiencies. HIV-related opportunistic infections (OIs) usually occur when the CD4+ T-cell count falls below 200/mm$^3$. For instance, dilated cardiomyopathy was strongly correlated with a CD4 count of less than 100/mm$^3$ [7].

Generally, the prevalence and presentation of cardiac complications of HIV were significantly different between pre-HAART (Highly active antiretroviral therapy) and post-HAART periods. For example, the prevalence of HIV-related cardiomyopathy due to opportunistic infections and myocarditis had reduced by 30% in developed countries where HAART is readily available. In contrast, non-availability of HAART and nutritional factors in developing countries had led to an increase by 32 per cent [8]. Opportunistic infections in HIV-related cardiac complications affect the pericardium, myocardium, endocardium and arteries.
**Pericardial diseases**

It is a fairly common disease in HIV infected patients. Heidenreich et al. [9], found an annual incidence of 11 per cent of pericardial effusion in asymptomatic patients with AIDS. Further, even with matched CD4 counts, the mortality was twice as much with pericardial effusion. Various OIs have been documented to cause pericarditis and pericardial effusions comprising *Mycobacterium tuberculosis* [10] and lately documentation of multidrug resistant strains [11], *Mycobacterium avium-intracellulare* [12] *Streptococcus pneumoniae* [10] *Staphylococcus aureus* [13]. Other pathogens reported include *Nocardia* [14], *Cryptococcus neoformans* [15] *Aspergillus species* [16], cytomegalovirus and herpes simplex [17]. In sub-Saharan Africa and other endemic areas of the developing world, *Mycobacterium tuberculosis* is the main cause of pericardial diseases reaching 86-100 per cent [18, 19]. There are numerous patterns of presentation which comprise asymptomatic pericardial effusion, pericarditis, cardiac tamponade and constrictive pericarditis [20, 21]. However, presentation of tamponade requiring intervention is rare but may occur [22,23]. It is suggested that HIV should be considered as a differential if a young patient presents with unexplained pericardial effusion or cardiac tamponade [24,25]. Echocardiography remains the most important diagnostic tool in pericarditis with effusion [26]. Treatment should be tailored towards the infecting organism based on fluid analysis utilizing Gram stain, acid fast bacilli and cultures plus pericardial biopsy. Treatment of tuberculous pericarditis should be in accordance with established recommendations [27]. Other modalities such as steroids or percutaneous drainage in tuberculous pericarditis had produced conflicting outcomes. It is therefore recommended that randomized trials be conducted, especially with stratification of HIV status to analyze the impact of such therapies [28]. Despite this, steroids are useful in the management of immune reconstitution inflammatory syndrome (IRS) [29]. It is pertinent to note that delay in initiation of antiretroviral therapy with antituberculous treatment because of the concern of IRS did not confer any advantage as the randomized trial by Abdool Karim et al [30] recorded significant improvement in survival for patients with simultaneous treatment. Clinicians should also remain on the alert for potential drug-drug interactions between rifampicin and quinolones on one hand and antiretroviral and other drugs on the other hand. Recurrence of TB may happen in HIV positive as compared with non-HIV patients even with successful initial therapy [31].

**Myocardial diseases**

The main types of myocardial diseases in HIV patients are left ventricular dysfunction, dilated cardiomyopathy and myocarditis. They occur with increased frequency in AIDS patients [32]. Myocarditis is the most common cardiac pathological finding at autopsy of patients infected with HIV, with a prevalence of 50% or more [33]. Prevalence and annual incidence of HIV-associated cardiomyopathy in the pre-HAART period using postmortem and echocardiographic studies were 30 to 40 per cent and 15.9/1000 patients respectively [34]. In a prospective study among 416 HIV patients with documented heart disease, the frequency of cardiac dysfunction was 17.7 per cent [35]. Cardiomyopathy is usually seen when the CD4 counts falls below 400cells/mL [22]. There are multiple factors responsible for dilated cardiomyopathy; however studies have confirmed the link with co-infecting viral infections by myocardial biopsy [23, 36, 37, 38]. Viruses demonstrated as co-infectors were: coxsackievirus group B [39,40], cytomegalovirus, and Epstein Barr virus [40]. Other organisms implicated include *Toxoplasma gondii* [41], *Histoplasma capsulatum*, *Cryptococcus neoformans*, *Aspergillus species* [16], *Candida* [42] and *Mycobacterium avium intercellulare* [23,37]. Patients may be asymptomatic however they can present with dyspnoea, paroxysmal nocturnal dyspnoea and ankle oedema. Signs which may be present include tachycardia, raised jugular venous pressure and gallop rhythm. Electrocardiography, chest x-ray, echocardiography and serum b-type natriuretic peptide (BNP) are helpful in establishing diagnosis. Treatment should encompass lifestyle modifications and pharmacological therapy. The lifestyle modifications are moderate and regular exercises as tolerated [44]. There should also be combination of healthy diet and reduced fluid and salt intake [23]. Drugs established to improve quality of life include angiotensin converting enzyme inhibitors, diuretics, b-blockers and sponrolactone. OIs should be sought aggressively and managed to alleviate or resolve the cardiomyopathy. In the presence of ventricular arrhythmias, the placement of implantable cardioverter-defibrillator should be considered. Despite treatment, left ventricular systolic dysfunction and dilated cardiomyopathy are associated with significant mortality independent of age, gender and CD4 levels especially if ventricular dysfunction developed early in the disease [45]. Spontaneous recovery from cardiomyopathy however was previously described [46,47]. LV recovery had also been demonstrated following intravenous immunoglobulin treatment of refractory HIV-related cardiomyopathy [48]. Most patients will, however have accelerated left ventricular (LV) dysfunction [49]. Furthermore, it is still unknown whether HAART has a role in determination of outcome.

**Endocardial diseases**

Valvular heart disease happens mainly as either bacterial or fungal endocarditis. HIV disease generally does not seem to predispose to increased incidence of endocarditis. Further, patients with HIV have averagely similar manifestations and outcome (85% vs 93%) as compared with HIV-negative patients [8]. However, salmonellal endocarditis is more prevalent as compared with immunocom-
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Patent individuals [50]. In addition intravenous drug users with advanced immunosuppression are more prone to develop IE. However, sustained valvular damage is less likely due to impaired immune response. Gebo et al [51] noted decreased rates of endocarditis in a review of periods of pre-HAART versus post-HAART eras. They found a decrease in incidence from 20.5 to 6.6 per 1000 person-years. Generally, mortality is higher in those with CD4 counts of below 200/mm³ [23, 34]. Right-sided valves are most commonly affected with the predominant organism being Staphylococcus aureus in up to three-quarter of cases [52]. Gram negative organisms and fungi also demonstrate higher incidence [53] with mortality higher than in non-HIV patients if left valve is affected and CD4 count is less than 200cells/mL [53,54]. Bacterial pathogens isolated include Salmonella species, [50] Streptococcus pneumoniae and Haemophilus influenzae. Organisms such as Aspergillus species [16], Candida species and Cryptococcus neoformans are fungal causes of endocarditis recorded in both IV and non-IV drug abusers in HIV patients [24]. Further, Losa et al [55] had also reported eight cases of infective endocarditis from Enterococcus faecalis, Staphylococci, Salmonella enteritidis and Coxiella burnetti in non-IV drug abusing HIV patients in a series over a period of twenty years. Symptoms and signs of infective endocarditis include fever, lethargy and heart murmurs which were documented in one-third of patients. Repeated blood cultures and transoesophageal echocardiography are essential in reaching diagnosis. Immediate and appropriate empirical therapy should be started promptly. Once sensitivity of the blood culture is available then therapy should be directed towards the result. Valve replacement surgery should be considered in patients with haemodynamic instability, antibiotic failure and profound valvular destruction. Prophylaxis for endocarditis in patients for dental surgery should be as per recommendation of established guidelines [56].

Pulmonary Hypertension

It has been shown that pulmonary hypertension (PH) is commoner in HIV patients as compared with the general population [57]. Further another study had shown similar incidences despite the access to antiretroviral therapy [58]. It is defined as a mean pulmonary artery pressure (mPAP) >25mmHg at rest with a mean pulmonary capillary wedge pressure ≤15 mmHg or an mPAP with exercise >30mmHg [59]. Causative factors implicated include lung infections, venous thromboembolism and left ventricular dysfunction [24]. Animal model had shown that immune response to Pneumocystis jirovicei may be disturbed and prolonged with potential development of chronic disorder like pulmonary hypertension [60]. This novel finding should be evaluated by designing prospective, cohort study on patients who survive Pneumocystis pneumonia in humans. HIV-related PH is mostly seen in young and male patients with major symptom being progressive shortness of breath, followed by non-productive cough, fatigue, syncope or near syncope and chest pain [57]. Diagnostic tools employed include chest x-ray, electrocardiography and echocardiography, however, cardiac catheterization is mandatory to definitively diagnose the disease and exclude any underlying cardiac shunt [61]. Modalities of treatment include individualized assessment for anticoagulation, vasodilator agents as tolerated, diuretics, oxygen as required and endothelin antagonists [24, 62]. A review of the HIV-PAH cases reported in the literature over a twenty-two year period showed a more favorable outcome in patients treated with PAH-specific therapy than in those treated with antiretroviral therapy only [63]. Nevertheless, HAART could delay the development of PAH in HIV-infected patients and is recommended independent of the CD4 counts [64].

Aneurysmal Disease

Patients with HIV/AIDS are more prone to develop aneurysmal disease as compared with the general population with aortic and cerebral arteries as the principal sites [65]. However, there were reports of infections involving other unusual sites such as inferior gluteal artery aneurysm by non-typii Salmonella [66] and common iliac artery by Streptococcus pneumoniae [67]. Other organisms associated with vasculopathy in series of patients include Staphylococcus aureus [68] and a rare report of invasive Aspergillus-associated pulmonary artery pseudoaneurysm [69]. Patients present with local pain of variable severity which may radiate. Other features include compressive symptoms and fever. Examination may reveal pulsatile and tender mass at clinically assessable arteries. Diagnostic tests employed include multiple sets of blood cultures and relevant imaging like ultrasound and computed tomography scans of involved arteries. The management comprises appropriate antimicrobials, resection and reconstruction of affected arteries.

Conclusion

Cardiovascular complication is fairly common. The prevalence and pattern of OIs related to pericarditis, myocarditis and endocarditis appear different between pre-HAART and post-HAART eras. In addition tuberculosis pericarditis is particularly prevalent in endemic areas of tuberculosis. HAART has significantly affected prevalence and improved the outcome of most cardiovascular-related complications of HIV. Prompt detection of OIs and treatment should be pursued meticulously to improve survival of patients.

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Correspondence:

F. Buba
Department of Medicine (38)
King Khalid University Hospital
King Saud University
P. O. Box 7805, Riyadh 11472.
Saudi Arabia
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