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The Effect of HIV on the Heart and HAART on the Heart

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ABSTRACT

HIV/AIDS is a disease characterized by immune dysfunction with superimposed severe opportunistic liability. The past few years has seen a significant rise to 75% of HIV patients compliant on ART. Delving into specific complications reveal significant associations between HIV and HAART in the heart. The purpose of this article is to throw more light on the key role players in cardiac dysfunction among HIV patients on HAART. In this article, we discuss the effects of HIV-associated chronic inflammation, immune dysfunction, high-risk medications, and their effects on the cardiovascular, and metabolic systems which further hastens the progression of cardiac dysfunction in individuals. Complications such as heart failure, coronary artery disease, pericardial effusion, and pulmonary hypertension are also discussed to appreciate the pathophysiology and outcomes. We believe that if more studies into cardiac complications of HIV patients on HAART are conducted, many patients will benefit from the evidenced-based outcomes which will influence clinical decision-making.

Keywords: HIV/AIDS; immune dysfunction; HAART; heart

INTRODUCTION

In recent times, the management of HIV (Human immunodeficiency virus) has experienced a gradual shift in focus. Thanks to the introduction of HAART (Highly active antiretroviral therapy), the infectious complications are becoming more controlled, especially in the developed world. However, non-infectious complications are becoming a major cause of concern; if ignored by a clinician, results are often disastrous. A common non-infectious complications of HIV/AIDS (Human immunodeficiency virus/ Acquired immunodeficiency syndrome) is cardiovascular compromise, and its management in people living with HIV may warrant a different approach compared to non-infected individuals. Perhaps, this shift in focus may prompt more researchers to find more detailed information on the pathogenesis of these complications, with the endpoint being better management and interventions to improve patient outcomes [1]. This paper aims to talk mainly on the common cardiovascular consequences of HIV, one of the major non-infectious complications.

We look to demystify the core and central mechanisms behind some of these cardiovascular manifestations, especially the role of inflammation and immune system dysfunction. It would also throw more insight on the need for rapid diagnosis, and likely improve disease outcomes from early intervention [2]. It is now quite evident that HIV-related viremia, immune dysregulation, and acute or chronic inflammation are the key drivers of HIV-associated cardiac complications. However, the role of traditional risk factors such as obesity and smoking also account for a significant portion of disease progression.

ETIOLOGY

The relationship between myocardial dysfunction in HIV and some ART (Antiretroviral therapy) has long been established. Nonetheless, HIV involves a pathological process that significantly increases the risk of cardiovascular problems as the disease progresses [3].

It would interest you to know that untreated HIV-positive patients have an increased risk for endothelial dysfunction [4,5], this often corrects only after a prolonged period of compliance with HAART [6]. Cardiotoxicity associated with some ART can worsen patient prognosis and rate of recovery therefore regular monitoring of BMI, serum lipids, serum glucose, echocardiography, etc. should be inculcated into management plan of patients on high-risk medications such as first-generation ART, efavirenz, or Protease Inhibitors [7]. Today, more than 75% of HIV-positive patients receive ART globally [8]. This has significantly improved the life expectancy of HIV patients as they now live near-normal lives. The most common cardiotoxic effects of ART include heart failure, metabolic changes, and carotid intimal thickness.

It is exceedingly difficult to unravel the exact effects of HIV and different types of ART on CVD (Cardiovascular disease) risk. Also, these side effects differ by ART class and sometimes effects of an individual drug differ from its class effect [9]. In general, ART toxicity can trigger new CVD risk factors or potentiate the negative impact of existing CVD risk factors like hypertension, diabetes mellitus, insulin resistance, obesity, and lipid disturbances [10]. Recent studies show that Abacavir is associated with an increased risk of myocardial infarction, independent of traditional CVD risk factors [11]. Of all NRTIs (Nucleoside reverse transcriptase inhibitors), abacavir has demonstrated great notoriety for its CVD risk profile. This risk profile was shown to be low in younger patients with low CVD risk [12]. This may be a pointer to the potentiation of already existing CVD risk factors in older patients. The exact mechanism for increasing the risk factors remains unclear but may be related to abacavir-induced changes in platelet-collagen interaction linked to platelet activation [13].

Tenofovir alafenamide use has been linked with weight gain and obesity [14] but the pro-inflammatory changes observed with abacavir were not seen, implying these changes are specific to abacavir.

Efavirenz, a commonly used NNRTI (Non-nucleoside reverse transcriptase inhibitors) is known to increase LDLs (low-density lipoprotein) and triglycerides, as well as promote insulin resistance. Rilpivirine, another NNRTI, was less likely to cause hyperlipidemia but it was associated with greater weight gain [14]. Nevirapine, a popular NNRTI, was noted to be lipid friendly as it increased HDL to a larger extent than LDL, and it did not promote insulin resistance [15]. Protease inhibitors (PI) are known to interfere with lipid metabolism, this partly contributes to their CVD risk factors [16]. PI use has been linked with increased CVD mortality and 30-day hospital readmission for heart failure [17]. Atazanavir is an exception in the PI class side effects profile as it was not associated with an increased risk of CVD in several studies [18]. Atazanavir combinations had the slowest rate of carotid intima-media thickness, an intermediate marker for CVD risk. Patients taking Atazanavir had higher bilirubin levels, an antioxidant, and it was hypothesized to slow the progression of atherosclerosis in such patients [19]. The lipid profile of patients taking Integrase Strand Transfer Inhibitors (INSTIs), a newer class, was significantly better than in using ritonavir-boosted PI or efavirenz [20]. However, INSTIs were associated with excessive weight gain, especially in black women [14]. The use of newer drugs like Maraviroc, a virus-entry inhibitor (CCR5), has minimal to no CVD risks compared to the older ART regimens. A significant decline in triglycerides and fewer comorbidities were noted with Maraviroc use compared to older regimens but this was not statistically significant, probably due to a low number of events [21].

COMPLICATIONS

Cardiomyopathy and Heart Failure

In a cardiac magnetic resonance imaging study about a decade ago, cardiac steatosis and fibrosis were identified as associated with the use of the old ART regimen. Older ART regimens cause mitochondrial toxicity which significantly resulted in diastolic impairment. Myocardial lipid levels had almost doubled in people living with HIV when compared to non-HIV individuals; in addition, about 75% of all patients with HIV had some degree of myocardial fibrosis [22]. A study conducted in 2019 revealed that intramyocardial triglyceride content was threefold higher [1.2 (0.4, 3.1) vs 0.4 (0.1, 0.5) %, P = 0.01] in women living with HIV compared to non-HIV-infected women; subsequently, a strong inverse relationship was established between intramyocardial triglyceride content and diastolic function (ρ = -0.62, P = 0.004) [23]. Since people with HIV on ART live longer, they are now more prone to developing chronic diseases like heart failure despite effective HIV therapy. With the use of current ART, the prevalence of heart failure is still high in HIV patients on ART; however, no specific ART or drug class is seen to be responsible for this [7].

The relationship between HIVAC (HIV-associated cardiomyopathy) and human immunodeficiency virus (HIV) has been long established, with myocarditis often being a preceding event and heart failure a sequela. The pathogenesis involves many mechanisms, one of which is "direct infection" of the myocytes by HIV-1 [24]. HIV-1 enters the myocytes via micropinocytosis and causes expression of gp-120. Activation of macrophages and inflammatory cytokines further exacerbate damage. Co-infection with other organisms that are known to cause myocyte damage is also an important mechanism here. These organisms include coxsackie B3, EBV, and CMV. Also, nutritional deficiencies have been shown to play a role in the progression of DCM; selenium being the frequently implicated [24,25].

The advent of highly active antiretroviral therapy has been helpful in reducing the incidence of HIV-related dilated cardiomyopathy in the developed world. However, once the diagnosis is made, the efficacy of HAART cannot be guaranteed. The developing world is likely to benefit from lower incidence of cases with increased availability of HAART. A known fact is that drugs are not without side effects, regardless of how beneficial they may be. It has been proposed that HAART may in fact cause dilated cardiomyopathy and resultant heart failure. Zidovudine may cause a dose-dependent cardiomyopathy. The mechanism behind HAART induced dilated cardiomyopathy is thought to be due to mitochondrial dysfunction. [24,26]

Coronary artery disease

Improvements in life expectancy in HIV patients on HAART has seen a significant rise in myocardial infarction among HIV infected elderly patients compared to the general population [27]. A distressing fact is that even younger patients aren't spared. Advances in medicine have tried to increase the life span of HIV-infected individuals; long enough for coronary artery disease to become an emerging area of concern [28].. What could be the reason why these set of people are more at risk when compared to the general population, why are traditional coronary artery disease risk factors more common in them; as several mechanisms have been reported. People living with HIV are at increased risk of coronary artery disease due to the direct effects of the virus and metabolic effects of HAART such as dyslipidemia and glucose intolerance.

Chronic inflammation and activation of the immune system are central to the pathogenesis of coronary artery disease and its complications in people living with HIV. Aberrant monocyte/macrophage action is also an important factor [28,29]. These processes worsen atherosclerosis and endothelial dysfunction eventually impeding adequate blood flow within coronary vessels to heart parenchyma [28,29]. Some studies have shown that HAART has a minuscule effect in reducing HIV-associated inflammation and activation of the immune system. Therefore, prevention is thus aimed at controlling traditional coronary artery risk factors. The general management is aimed toward a modification of core disease mechanisms [27,29].

Pericardial effusion

Pericardial effusion is a documented finding in some cases of HIV. Its presence is often indicative of disease progression. It is mostly present without symptoms, however, some may have overt cardiac tamponade with the typical Beck's triad on examination. Sadly, when present, the prognosis is often grim. A cohort study reported in 1995 further buttresses the above point. In this study, 231 HIV-positive subjects were enlisted screened, and followed up using echocardiograms over time. From the results, 80% of effusions were noticed to be asymptomatic. Interestingly, 36% of HIV/AIDS patients with effusions expired within 6 months as compared to 93% survival rate of HIV/AIDS patients without pericardial effusion [30].

Possible causes of HIV related pericardial effusion include lymphoma, myocardial infarction, and endocarditis to name a few [31]. However, very often, the cause isn't known. A rare case of pericardial effusion secondary to Kaposi sarcoma in a HIV infected man was reported, and the diagnosis was only made post-mortem [32]. We however believe that apart from the opportunistic systemic infections associated with HIV, chronic inflammation and immune dysregulation may contribute to pericardial effusion in HIV patients. Depending on the severity of symptoms and etiology of pericardial effusion, therapeutic pericardiocentesis or pericardiotomy may be indicated.

Pulmonary hypertension

Considering that HIV causes multi systemic damage, it does not come as a surprise that cardiac vessels may not be spared. Often diagnosed late, HIV associated pulmonary arterial hypertension (HIV-PAH) is a dangerous and commonly overlooked complication of HIV infection. Unfortunately, it tends to affect younger patients, and little is currently known about the pathophysiology of pulmonary hypertension in HIV [33]. The coexistence of HIV and pulmonary hypertension isn't a mere coincidence, considering that people living with HIV are about a thousand times more likely to come up with it.

Current numbers are only reflective of true cases. The use of echocardiography as a screening tool has proven helpful, even though it has its shortcomings as regards diagnostic accuracy. Although not a screening tool, the gold standard investigation is cardiac catheterization. Dyspnea on exertion or at rest with exercise intolerance should be readily identified in people living with HIV as it may be a pointer to severe cardiorespiratory compromise [34]. The benefit and effect of HAART on the prevalence of pulmonary hypertension in HIV infected patients hasn't been substantiated. Medications like epoprostenol, phosphodiesterase-5 inhibitors and endothelin receptor antagonists may proffer some therapeutic benefit [33,34].

CONCLUSION

Medical advancement in recent times, through the modification of HAARTs and other non-pharmacological interventions, has improved the life expectancy among HIV/AIDS patients. Especially in relation to cardiovascular complications, this accomplishment of longer life expectancy enables individuals to later suffer from secondary effects of long-term drug use or acceleration of disease due to uncontrolled traditional risk factors. Several HIV-associated problems such as chronic viremia, long-term ART side effects, chronic inflammation, and immune system dysfunction worsen CVD risk. Unluckily, there is limited large-scale clinical data to support HIV-specific evidence-based interventions and choice of therapy. Studies should explore identifying demographics and clinical HIV groups at heightened risk, then further delineate CVD mechanisms along with the interplay of ARTs and traditional risk factors. Response to these challenges will provide a stepping stone to the long-term trajectory for evidence-based decision-making among HIV/AIDS clinicians or caregivers to alleviate the incidence of cardiovascular complications in HIV/AIDS patients.

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