CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.1174317

Available online at: http://www.iajps.com *Review Article*

IS THE RISK OF CARDIOVASCULAR DISEASE DUE TO HUMAN IMMUNODEFICIENCY VIRUS INFECTION OR ITS THERAPY?

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Abstract:
Cardiovascular disease is a class of diseases which involve the heart or blood vessels. Among Human immunodeficiency virus (HIV) infected population, cardio-vascular disease (CVD) has been found to be the second leading cause of death. There is an increased incidence rate and prevalence of heart diseases among HIV infected population when compare to general population. Usually, the goal of anti-retroviral therapy (ART) is to suppress the virus growth which in turn reduces morbidity and mortality rate by immune reconstitution but this has been affected due to augmenting metabolic changes such as insulin resistance, dyslipidemia, inflammation, impaired fibrinolysis or combinations of these factors etc., which occurs simultaneously with HIV infection resulting in an increased risk of cardiovascular disease. Therefore, while making a therapeutic decision in HIV patients, individualized therapy for each patient should be based on presence of CVD risk factors. Understanding the disease severity and treatment will lead to successful management of CVD in AIDS patients.

Key words: *HIV, Dyslipidemia, Cardiovascular disease, Anti-retroviral therapy.*

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Please cite this article in press as K. Dhivya et al., ***Is The Risk of Cardiovascular Disease Due to Human Immunodeficiency Virus Infection or Its Therapy?****, Indo Am. J. P. Sci, 2018; 05(02).*

INTRODUCTION:

Acquired immunodeficiency syndrome (AIDS) is a disease caused by Human immunodeficiency virus (HIV) which affects the immune system by destructing the white blood cells (WBC's), making people more prone to get infections[1,2].Among HIV infected population, cardio-vascular disease(CVD) has been found to be the second leading cause of death [3]. 36.7 million People are living with HIV worldwide. The prevalence of HIV is 0.8% among adults aged 15-49 years whereas in India it is 2.1million with the prevalence of 0.3% at the end of 2016. The occurrence is more common in female than male [4, 5]. Apart from CVD, the other disease conditions which are common in HIV infected people are kidney disease, liver disease and non-AIDS defining malignancies [6].Cardiovascular disease is a class of diseases which involve the heart or blood vessels. CVD involving blood vessels are known as vascular diseases which includes coronary artery diseases (CAD) such as angina, myocardial infarction whereas CVDs that involve heart include stroke, heart failure, hypertensive heart disease, rheumatic heart disease, pulmonary heart disease, cardiomyopathy, cardiac dysrhythmias, congenital heart disease, valvular heart disease, endocarditis, myocarditis, aortic aneurysms, peripheral artery disease, thromboembolic disease and venous thrombosis[7].The various risk factors for heart diseases are age, gender, tobacco use, physical inactivity, excessive alcohol consumption, unhealthy diet, obesity, genetic predisposition and family history of cardiovascular disease, hypertension, diabetes mellitus, hyperlipidemia, psychosocial factors, poverty, low educational status and air pollution, whereas the individual contribution of each risk factor varies between different ethnic groups or communities [8-10].There is an increased incidence rate and prevalence of heart diseases among HIV infected population when compare to general population [11]. The atherosclerotic burden in HIV infected patients is very common which is not only due to traditional cardiovascular risk factor (smoking) but also due to other mechanisms like chronic inflammation, effects of combined antiretroviral therapy(cART) or immune activation after initiation of cART [12]. The goal of ART is to suppress the virus growth which in turn reduces morbidity and mortality rate by immune reconstitution but this has been affected due to augmenting metabolic changes such as insulin resistance, dyslipidemia, inflammation, impaired fibrinolysis or combinations of these factors etc., occurs simultaneously with HIV infection resulting in an increased risk of cardiovascular disease [13, 14]. Highly active antiretroviral therapy (HAART) will significantly modify the course of HIV disease, length of survival and improve the quality of life of HIV-infected patients. Apart from that earlier data have raised concerns that HAART is associated with an increased risk of both peripheral and coronary arterial diseases [15]. In addition, the morbidity and mortality rate of CVD in HIV patients will be increased due to some health care problems such as availability of health care services and facilities, rate of disease occurrence, socioeconomic status etc., [16]. Endothelial dysfunction occurs with both HIV infection and ART. HIV interacts with endothelial cell membrane then initiates inflammatory and biochemical intracellular reactions. Viral entry into the endothelial cells is favored through CD_4 antigen, galactosyl-ceramide receptors or chemokine receptors [17].ART causes endothelial dysfunction by directly damaging the cells or by indirect mechanisms like making synergy with HIV virus on endothelial cells which affects lipid and glucose metabolism [18].Endothelial dysfunction leads to activation and adhesion of platelets, leukocytes as well as activation of cytokines results in arterial wall structural damage and atherosclerotic plaque formation. Atherosclerosis is a consequence of infection-triggered endothelial damage in HIV infected patients. [19].This review article provides comprehensive and evidence based information about the risk of CVD developed by AIDS and AIDS therapy.

ASSOCIATION BETWEEN HIV AND CVD:

HIV is responsible for chronic inflammation in AIDS patients which leads to blockade in the blood vessels by arterial deposition of plaque. Markers of increased viral activity such as high viral loads, low CD4 counts and elevations in markers like C-reactive protein, D-dimer, interleukin-6 and cystatin-C have been associated with an increased risk of developing cardiovascular diseases in HIV infected patients [20].In addition, Hepatitis-C virus co-infection is common among HIV infected patients which further increases the risk of CVD [21]. Though there is many disease conditions under CVD, mechanisms of HIV induced various CVD conditions are almost similar. The individual mechanism of various CVD's induced by HIV and inflammatory mechanisms associated with development of CVD will be discussed below.

HIV associated Cardiomyopathy

HIV virions infect myocardial cells in a random distribution with indirect association between the presence of the virus and myocyte dysfunction. Myocardial dendritic cells plays a significant role in development of HIV associated cardiomyopathy by

activating specific cytokines like TNF-α, IL-1, IL-6, IL-10 and the inducible form of nitric oxide synthase(iNOS) that contribute to progressive and late myocardial tissue damage[22]. Co infection with other viruses also plays an important role. The interaction between cytotoxic T lymphocytes and the receptoral complex Fas/Fas ligand located on the surface of the target cell may cause mitochondrial damage leading to the impairment of the autonomic system which enhances the functional damage to myocardial cells because of down regulation of adrenergic receptors and increased adrenergic activity [23].

HIV-associated pulmonary hypertension

The pathogenesis of HIV-associated primary pulmonary hypertension is may be due to endothelial damage caused by the HIV-1 envelope glycoprotein 120 and vasoconstriction by stimulating the release of endothelin, IL-6 and TNF-Æ in the pulmonary arteries .Macrophages release TNF-Æ, oxide anions, and proteolytic enzymes in response to infection. Lymphokines promote leukocyte adhesion to the endothelium which play a role in the endothelial proliferation seen in pulmonary hypertension .Other proposed contributors include activated Æ1-receptors and genetic factors such as HLA DR6 and HLA DR52 [24].

HIV-associated stroke

HIV increases the risk of both ischemic and hemorrhagic stroke. The exact mechanism is unknown but some evidence suggested that opportunistic infections like meningitis, vasculitis, altered coagulation, vasculopathy and cardio embolic events are associated in developing CVD among HIV infected people [25].

HIV-associated myocardial infarction

The risk of myocardial infarction [MI] is more in HIV infected people compared to general population. MI may be the eventuality of traditional risk factors and viral replication [26].

HIV-associated venous thrombosis

The incidence of venous thrombosis is ten folds greater in HIV infected people compared to general population which ranges from 0.19% to 7.63% per year. The pathogenic mechanism underlying is complex and multifactorial which may be due to increased plasminogen activator inhibitor (PAI) - type 1 and heparin cofactor II as well as deficiency of protein S and protein C [27].

HIV-associated right ventricular dysfunction

Right ventricular hypertrophy is usually uncommon in HIV-infected people. Due to the immunologic effects of HIV disease, multiple bronchopulmonary infections and pulmonary arteritis will develop which increases pulmonary vascular resistance resulting in pulmonary disease that leads to right ventricular dysfunction [28].

Inflammatory mechanisms associated with HIV induced CVD

Many data proposed that inflammation as a cause of cardiovascular disease in the general population which suggests HIV-associated inflammation may be the significant cause of cardiovascular disease in HIV-infected adults[29].This occurs through multiple pathways like persistent viral replication(The risk of CVD can be determined by the degree of HIV replication. Many studies stated that uncontrolled viral replication has been strongly associated with vascular dysfunction) [30], $CD4^+$ T-Cell depletion (Majority of the immunologic abnormalities observed in treated HIV disease are associated with lower $CD4^+$ T-cell counts and are thought to be the more unambiguous mediators of cardiovascular disease in people treated for HIV) [31], T-cell activation (Women's interagency HIV study (WIHS) cohort reported that the frequency of activated T cells was associated with increased risk of carotid plaques and carotid artery stiffness) [32],co-infections in HIV-infected individuals (Co-infections results in higher pathogen burden are independently associated with risk of atherosclerosis as well as myocardial infarction or death and elevated Cytomegalovirus-specific T-cell responses, particularly the inflammatory cytokine interferon γ response may contribute to atherosclerosis in HIV-infected individuals) [33,34] and monocyte activation (higher levels of lipopolysaccharides (LPS) in patients with HIV infection may lead to chronic inflammation which in turn results in endothelial dysfunction and accelerated atherosclerosis. LPS activate monocyte that lead to an elevated levels of soluble CD163 which is associated with non-calcified coronary plaque and accelerate the formation of an acute thrombus) [35, 36].All these pathways results in chronic activation of immune system as well as endothelium that lead to altered lipid metabolism, increased clotting, loss of mucosal integrity and immune senescence which ultimately results in cardiovascular disease [37].

ASSOCIATION BETWEEN HAART AND CVD

Metabolic changes associated with ART among HIV infected people is the main reason for developing CVD [38]. In spite of ART have both direct and indirect cardiovascular toxicity, the choice of drug and time of initiation of therapy plays a significant role in developing CVD [39]. Among various classes of ART, protease inhibitors (PI) are commonly induces CVD. The mechanism of ART induced CVD is discussed below based on various categories.

Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs)

NRTIs work by blocking the HIV reverse transcriptase enzyme which is responsible for the reverse transcription of viral RNA to DNA [40]. Abacavir interferes with purinergic signaling and induces platelet endothelium interaction leading to inflammation and thrombosis which results in CVD. Abacavir and Tenofovir disoproxil fumarate are commonly used NRTIs. Abacavir has a potential cardiovascular risk [41, 42].Several studies, demonstrated the increased MI risk associated with Abacavir use. Tenofovir Disproxil Fumarate needs special mention in that it is associated with decreased CVD risk as it has favorable effect on the lipid profile [43].

Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTIs)

NNRTIs works by blocking the HIV replication by interfering with HIV Gag-Pol polyprotein processing which is required to initiate the virus budding during replication [44].Of all NNRTIs, Efavirenz has been shown to increase LDL, HDL and triglyceride levels .This effect is a result of interaction of efavirenz with cholesterol ester transfer protein which controls the exchange of cholesterol and triglyceride esters. Due to this unique lipid altering effects of efavirenz, rilpivirine is used if NNRTIs are considered as treatment option for HIV-infected individuals with baseline dyslipidemia [45].

Protease Inhibitors

PI exerts their effect by competitively binding to active site of virus protease. PI increases lipid levels in the blood which is a potential risk factor for cardiovascular diseases, improper functioning of gall bladder and pancreas [46]. Two mechanisms of PI induced CVD development has been explained from murine model. First, PI up regulates CD-36 and thereby induces atherosclerosis. Second, PI inhibit proteins that are involved in lipid metabolism such as the LDL receptor-related protein (LRP) which suggests that PI-associated lipid abnormalities may be partly due to reduced clearance of LRP ligands [47]. The CVD risk increases with increased PI exposure. Evidences suggest that there is an increased risk of ischemic heart disease, dyslipidemia and myocardial infarction in HIV infected people treated with PI. The PI lead to dyslipidemia through the sterol regulatory element-binding protein (SREBP) pathway, particularly the SREBP-1c pathway which controls de novo lipid synthesis, up regulation of SREPB-1expression as well as inhibition of lipoprotein lipase, the main enzyme involved in lipid catabolism[48].

Integrase Inhibitors

Integrase inhibitors work by chelating the enzyme bound cations and prevents the viral DNA integration into host genome [49].Integrase inhibitors are largely considered to be lipid neutral and there is no significant risk of CVD with their use. The only exception of this class is elvitegravir, which causes lipid alterations similar to those of evafirenz [50].

CONCLUSION:

It is very clear from this review that both HIV and HAART are associated with the development of cardiovascular events among HIV infected population. It highlights the need for assessing and managing various risk factors of CVD when people are diagnosed with HIV infection to avoid further complication. Dyslipidemia is a well-known adverse effect of ART, especially with the use of PI. Hence, frequent monitoring of lipid levels and other metabolic changes following HAART as well as considering alternation for certain antiretroviral drugs helps in preventing cardiovascular events. Therefore, while making a therapeutic decision in HIV patients, individualized therapy for each patient should be based on presence of CVD risk factors, understanding the disease severity and treatment will lead to successful management.

ACKNOWLEDGEMENT:

The authors are thankful to the management of Sri Venkateswara College of Pharmacy for providing excellent research guidance and support.

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