HIV and Cardiovascular Disease

Running Title: Cardiovascular disease in HIV patients

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Abstract: HIV has transitioned from a progressive fatal disease to a chronic condition with an increased risk for comorbid conditions including cardiovascular diseases. Despite viral suppression with effective antiretroviral therapy, people living with HIV have a high rate of myocardial infarction, heart failure, stroke, pulmonary hypertension, cardiomyopathy, and other cardiovascular disease manifestations when compared to those without HIV. The elevated risk can be explained by chronic inflammation and immune dysregulation in HIV. Understanding the risk factors and pathogenesis of cardiovascular diseases can help to formulate strategies for the prevention and treatment of cardiovascular conditions in people living with HIV. We summarize the epidemiology, risk factors, demographic characteristics, pathophysiology, and immunological alterations associated with the risk of cardiovascular diseases in patients with HIV. In addition, we present the approach to prevention, identification, and treatment of cardiovascular diseases in people with HIV and the possible challenges in management strategies.

Keywords: HIV, cardiovascular disease, antiretroviral therapy, risk factors, inflammation

Abbreviations [Abbreviations in text are in this table; abbreviations in figure are in footer of figure]

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>AMI</td>
<td>Acute myocardial infarction</td>
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<tr>
<td>ART</td>
<td>Antiretroviral therapy</td>
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<td>BMI</td>
<td>Body mass index</td>
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<td>CMV</td>
<td>Cytomegalovirus</td>
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<td>CVD</td>
<td>Cardiovascular disease</td>
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<td>GDF-15</td>
<td>Growth differentiation factor 15</td>
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<td>hs-CRP</td>
<td>High-sensitivity C-reactive protein</td>
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<td>IL-6</td>
<td>Interleukin-6</td>
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<td>INSTIs</td>
<td>Integrate strand transfer inhibitors</td>
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<td>MACS</td>
<td>Multicenter AIDS Cohort Study</td>
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<td>MI</td>
<td>Myocardial infarction</td>
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<td>NNRTIs</td>
<td>Non-nucleoside reverse transcriptase inhibitors</td>
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<td>NT-proBNP</td>
<td>N-terminal pro-B-type natriuretic peptide</td>
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<td>PI</td>
<td>Protease inhibitors</td>
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<td>PLWH</td>
<td>People living with HIV</td>
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<td>RR</td>
<td>Relative risk</td>
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<tr>
<td>SMART</td>
<td>Strategies for Management of Anti-Retroviral Therapy</td>
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<td>WIHS</td>
<td>Women’s Interagency HIV Study</td>
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</tbody>
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1. Introduction

People living with HIV (PLWH) are twice as likely to develop cardiovascular disease (CVD) when compared to those without HIV.¹ The phenotype of CVD in PLWH includes a plethora of conditions like dyslipidaemia, hypertension, atherosclerosis, thrombosis, myocardial infarction (MI), stroke, peripheral artery disease, pulmonary hypertension, pericardial effusion, dilated cardiomyopathy, heart failure, and sudden cardiac death.²,³,4,5, ⁶

With improved treatment and prolonged life expectancy, the risk and manifestation of CVD in PLWH have evolved. When compared to those without HIV, PLWH are at a much higher risk of developing CVD and the risk continues to be sustained after adjustment for conventional cardiovascular risk factors.⁷,⁸ The risk of CVD in PLWH is known to reduce with the use of antiretroviral therapy (ART) though some ARTs may induce metabolic abnormalities that compound the risk of CVD. Prevention and screening for CVD risk factors and pharmacological and non-pharmacological interventions can help to reduce the burden of CVD and improve morbidity in PLWH. This review summarises the epidemiology and pathophysiology of CVD risk factors and the management strategies for reducing the risk of CVD in PLWH.

Epidemiology

Prevalence of cardiovascular disease in HIV patients

CVD presents a huge burden in PLWH. In a systematic review of 11 articles published prior to 2019, a prevalence of 10-28% has been reported for subclinical CVD in patients with HIV in the Asia-Pacific region.⁹ It is estimated that 78% of PLWH will have CVD by the year 2030.¹⁰

In a combined analysis of the Women’s Interagency HIV Study (WHIS) and the Multicenter AIDS Cohort Study (MACS) cohorts, the prevalence of hypertension in HIV-infected patients increased with increasing age. Patients <40 years of age had a prevalence of 12% to 20% and this increased to about 35% in those ≥41 years of age.¹¹

Risk factors and demographics

HIV infection is an independent risk factor for CVD.¹²,¹³ Highest burden of CVD due to HIV is reported in sub-Saharan Africa and Asia-Pacific.¹ The profile of CVD varies between high-income and low-income countries.⁵ In the Asia-Pacific region, traditional risk factors for CVD such as diabetes, hypertension, and smoking are reported in 5% to 45% of the HIV and non-HIV populations. In PLWH, the risk for CVD was nearly doubled by the presence of HIV-specific risk factors and lower CD4+ counts and was increased by about 20 times due to synergistic interaction.
among the traditional risk factors.\textsuperscript{9}

When compared to people without HIV, those with HIV have a higher prevalence of subclinical CVD. Young adults with HIV generally have early onset of CVD.\textsuperscript{9} Risk for HIV-related CVD is 1.5 to 2 times higher in women than in men.\textsuperscript{14}

Pathophysiology
The onset and evolution of CVD in PLWH is influenced by viremia, degree of injury from HIV, and the underlying cardiometabolic factors. Unique pathophysiological features of CVD include an unusual plaque morphology, expansive vascular remodelling, aortic inflammation and abnormalities like aneurysms, and HIV cerebrovasculopathy (Figure 1).\textsuperscript{15}

![Figure 1: Risk factors and pathophysiology of cardiovascular disease in people with HIV infection](image)

Inflammatory effects of HIV proteins, CD4+ T-cell depletion, microbial translocation, altered cholesterol metabolism, monocyte activation, and altered coagulation account for a higher risk and rate of CVD in PLWH.\textsuperscript{3}

Epigenetic factors like DNA methylation may potentially predispose PLWH to CVD.\textsuperscript{12} Chemical mediators and peptides that have been linked to structural and functional cardiopulmonary abnormalities include ST2, N-terminal pro-B-type natriuretic peptide (NT-proBNP), high-sensitivity C-reactive protein (hsCRP), growth differentiation factor 15 (GDF-15), cystatin C, interleukin-6 (IL-6), D-dimer, and troponin.\textsuperscript{16}

Conventional risk factors like diabetes, hypertension, smoking, and dyslipidaemia amplify the risk of CVD in PLWH. Other factors like regional distribution and female gender are associated with CVD in PLWH.\textsuperscript{5}

Impact on cardiovascular system
When compared to the general population, PLWH show significantly increased rates of CVD, such as MI, stroke, and two to ten-fold increased risk of venous thromboembolism.\textsuperscript{17} The significantly high rates of CVD in PLWH persist even in the settings of adequate viral suppression with ART.\textsuperscript{6}

Independent of known risk factors, HIV infection is associated with a 50% increased risk of acute myocardial infarction (AMI). In a cohort study (October 1996 to June 2004) in 189 HIV and 26,142 non-HIV patients, those with HIV had a relative risk (RR) of 1.75 (95% CI 1.51-2.02) for AMI after adjusting for common risk factors. When compared to those without HIV, PLWH have a 20% to 100% increase in relative risk of MI.

Dilated cardiomyopathy in PLWH can be attributed to the underlying viral infection. In the lesser developed countries like Africa, malnutrition is a key cause for dilated cardiomyopathy in the HIV-infected populations.

Immune activation and Inflammation

In people with HIV, depletion of CD4+ T-cells and increase in HIV-proteins like Tat, Nef, Env, and glycoprotein 120 induce a state of chronic inflammation, immune dysregulation, and endothelial dysfunction. This leads to high levels of mediators such as IL-6 and C-reactive protein which promote endothelial cell dysfunction, platelet activation, and atherosclerosis in patients with long-term HIV infection. Activation of monocytes and the expression and release of the pro-coagulant tissue factor activate the coagulation system leading to an increased risk for arterial and venous thrombosis. HIV patients treated in 10 HIV specialty clinics in the USA (2002 to 2009) with peripheral CD4+ T cell count of <350 cells/µL were 58% more likely to experience CVD compared to those with a CD4+ T cell count of >500 cells/µL. Despite ongoing treatment with ART, HIV infection induces T cell activation. Elevated counts of CD8+ T cells are associated with an increased risk of carotid artery stiffness and plaques. HIV- RNA, even at low replication in patients being treated with ART, contributes to an increased risk of CVD.

Treatment

Treatment of CVD in PLWH is centred on disease modifying anti-inflammatory strategies. These include reduction of HIV reservoirs and modulation of immune responses to augment the control of chronic inflammation. HIV disease is treated with continuous ART for persistent viral suppression and immune recuperation. Key factors in management of risk of CVD in PLWH include the timing for initiation and duration of ART and the type of ART to be selected according to disease profiles.

Antiretroviral therapy and cardiovascular health

ART has improved survival outcomes for PLWH and influenced the natural history of HIV disease. Sustained viral suppression with ART is associated with reduced risk for non-HIV complications like MI and heart failure. Early initiation of ART during the course of the HIV infection is associated with lesser inflammation. An epidemiological transition in PLWH is the survival to older age that brings in challenges of increased morbidity due to chronic health conditions including CVD. ART is associated with dyslipidaemia including triglyceridemia and increase in low-density lipoproteins and total cholesterol. Inflammation and immune activation increase the atherogenicity of lipids via several mechanisms. When compared to the general population, PLWH who receive ART are at an increased risk of ischemic heart disease. A Danish National Hospital Registry reported an increased risk of first hospitalization (adjusted relative risk: 2.12; 95% CI: 1.62-2.76) for ischemic heart disease in PLWH after ART initiation (n=3953) when compared to population controls (n=373856). However, this risk did not increase further in the initial 8 years of ART.

Risk for CVD is influenced by the class of ART. When compared to the protease inhibitors (PIs) or non-nucleoside reverse transcriptase inhibitors (NNRTIs), integrase strand transfer inhibitors (INSTIs) have less atherogenic potential with a more favourable lipid profile and may be associated with lower levels of inflammatory markers.

ART has some disadvantages for the risk of CVD in PLWH. The detrimental effects include altered glucose and lipid metabolism, mitochondrial toxicity, cardiac myopathy, and impaired left ventricular function. These effects are more pronounced with older ARTs, e.g. abacavir, lopinavir, and ritonavir when compared to the newer ARTs, e.g. dolutegravir or atazanavir. Exposure to abacavir in 2952 HIV-infected Danish patients increased the risk of MI. This risk was particularly pronounced in patients who initiated abacavir within 2 years of starting highly active ART and in those who initiated abacavir as part of NRTI regimen. In the Strategies for Management of Anti-Retroviral Therapy (SMART) study, patients receiving abacavir or didanosine were more likely to be using antihypertensive and antilipemic medications. An increased risk of MI was seen in HIV patients exposed to abacavir and didanosine in within preceding six months and the excess risk mitigated beyond six months after drug cessation in the D:A:D study.

ART-induced lipid abnormalities usually occur within 3 months of initiation of therapy. PI- based regimens are commonly associated with dyslipidaemia which is seen in up to 50% of PLWH who receive a PI. The degree of lipid abnormalities varies with individual PIs and the duration of treatment. PIs are also associated with increased rates of coronary artery disease and the risk of MI shows a positive correlation with the duration of therapy.

INSTIs are associated with minimal changes in lipid profiles. Use of INSTIs is now widespread and the favourable safety profile is anticipated to positively influence the risk of CVD. Dolutegravir has a safer lipid profile and offers a preferred treatment option in older patients with HIV who may have other risk factors for CVD. However, the observed gain in weight with this class of ART mandates a careful assessment of patient profiles before initiation of therapy.

PLWH may develop cardiomyopathy with the extensive use of ART. Cardiomyopathy caused by the disease, i.e. due to viral infection and cytokine activity, mainly leads to systolic dysfunction. On the contrary that due to extensive use of ART predominantly causes diastolic dysfunction. Cardiomyopathy is reported with the use of zidovudine which is associated with myocardial cell dysfunction due to mitochondrial damage.
Hypertension management in HIV patients

Management of hypertension in PLWH includes a close monitoring of risk factors like age, body mass index (BMI), and the use of ART. Independent of age, BMI, and viral suppression, dolutegravir is associated with hypertension. Some studies have reported an association between low nadir CD4+ cell counts (<50 cells/µL) and hypertension after initiation of ART.56-59 There are no specific recommendations or guidelines for the management of hypertension in PLWH.51,52

It is important to monitor and optimize ART in PLWH who have risk factors for hypertension. Prolonged duration of ART is an independent risk factor for hypertension and the effect is pronounced in people with nadir CD4+ counts of <50 cells/µL.50 ART is associated with weight gain and increase in BMI which are risk factors for hypertension. Some studies suggest a modest increase in blood pressure with ART and others report a lower risk for development of hypertension with NNRTIs. However, these observations are not conclusive.11,53

Management strategies for cardiovascular complications in HIV patients

The focus of clinical management of CVD in PLWH is to lower the risk of CVD by promoting a healthy lifestyle with a balanced diet and adequate physical activity. Behavioural modifications should be targeted to avoid tobacco, alcohol, and substance use. Screening for conventional risk factors for CVD like diabetes, hypertension, dyslipidaemia, and others can enable an early diagnosis and intervention to prevent the onset and evolution of CVD.54 Based on benefits in general populations without HIV, these recommendations can influence the onset and progression of CVD in PLWH. Prevention of smoking, elevations in total cholesterol and hypertension can evade 37%, 44% and 42% of MIs, respectively in PLWH.55 When diagnosed with conditions such as diabetes or hypertension that predispone to CVD, PLWH should at least undergo an annual assessment both for the presence of risk factors as well as established CVD.56,57 This assessment and stratification of CVD and associated risk factors should also be adopted for those who are on ARTs.

Further, an early diagnosis of HIV and introduction of ART to control viral loads can reduce immune activation, immunosuppression, hypercoagulability, and systemic inflammation that cause or perpetuate CVD in PLWH. ART has a complex effect on the risk of CVD with reduction in inflammation but an increase in dyslipidaemia.2 Newer ARTs are more lipid friendly and may be preferred over the older ones. The common lipid lowering statins show drug-drug interactions with ART and should be used with caution.3

Component to atherosclerosis, chronic inflammation is an important therapeutic target in PLWH. Treatment should aim to curtail drivers of inflammation including HIV reactivation from latest foci of infection, microbial translocations, chronic coinfections, e.g. cytomegalovirus, and a hypercoagulable state.58

Any concomitant infections should be treated in PLWH. Cytomegalovirus (CMV) infections are common in PLWH.59,60 An ongoing phase II study (ELICIT, NCT04840199) is evaluating the anti-inflammatory effectiveness of leteimovir in PLWH and asymptomatic CMV infection who are on ART. Insights from this study can help to understand if leteimovir can reduce systemic inflammation and risk of CVD in PLWH.

2. Challenges and Emerging Approaches

Prolonged life expectancy in PLWH has led to an increased prevalence of CVD-associated morbidity and mortality.12 Prevention of CVD should be a key component in care guidelines for PLWH. HIV-specific risk scores may be formulated to target screening of risk factors for CVD in PLWH. The American Heart Association suggests the use of standard risk scores and adjustment of the calculated risk estimates by 1.5 to 2 times for PLWH particularly those with persistent viremia.6

A common clinical challenge is to balance the benefits and CVD risks with ART in PLWH. In a prospective observational study in 23,468 patients, combinations of PI and NRTI were independently associated with a 25% relative increase in the rate of MI per year of exposure in the initial 4 to 6 years of treatment though the absolute risk was low. The combination ART led to an increased incidence of MI over longer exposure to combination ART. Continuous monitoring for desired benefits with surveillance for anticipated CVD risk can help to optimize treatment strategies in PLWH.61

Mechanisms and immune mediators of HIV-specific CVD are not precisely understood and should be explored in clinical trials in future. Treatment options with broad immunomodulatory effects may potentially be useful in managing CVD in PLWH. In a pilot study, a single subcutaneous dose of 150 mg canakinumab significantly reduced circulating markers of inflammation in 10 treated and suppressed HIV-infected individuals (≥ 400 CD4+ T-cells/mm³) who had established CVD or one CVD risk factor. There was a 10% reduction in arterial inflammation and reductions in leukopoietic activity and monocyte cytokine production.62

3. Conclusions

The chronic inflammatory profile of HIV disease supports the onset and progression of CVD in PLWH. The clinical manifestations of CVD in PLWH largely depend upon the underlying risk factors for CVD. These are influenced by various biological and geographical factors as well as the opportunities of early diagnosis and timely and effective treatment of HIV infection.

Prevention, identification, and management of CVD is key to management of HIV. The use of ART has been associated with an increase in CVD risk factors including dyslipidaemia, fat redistribution, insulin resistance, weight gain, and diabetes. ART has remarkably changed the natural history of HIV disease with a notable extension in survival. With improved life expectancy, the risk for lipid and glucose metabolic abnormalities has significant effect on the long-term outcomes and prognosis of CVD in PLWH. Delayed
initiation of ART until advanced immunosuppression may exacerbate the risk of CVD associated with ART in PLWH.\textsuperscript{30-32} When compared to earlier years, there has been a decline in the anticipated risk of MI in PLWH in the year 2010-2011. This can potentially be explained by early initiation of ART, use of ART with favourable effects on lipid parameters, and the widespread deployment of risk reduction strategies.\textsuperscript{6} These encouraging effects can be evaluated for other CVD manifestations in well controlled studies in future. Primary prevention coupled with judicious early initiation of ART can preserve immune function in PLWH.

Ongoing research may focus on describing the prevalence and pathogenesis of specific CVD conditions in PLWH. Insights for the unique features of vascular remodelling, HIV-specific alterations in cerebrovascular vessels, risk factor profiles and clinical phenotypes of heart failure in ART-treated patients can help to develop and adopt immunomodulatory strategies to mitigate the risk of CVD in PLWH.

**Declarations**

**Conflict of interest:** The authors have declared that no competing interests exist.

**Authors’ contributions**

All authors have equally contributed to conception, design, proof reading and approving the final manuscript.

**References**


Changes in cardiovascular biomarkers in HIV individuals: a population heart disease in HIV


Belkin MN, Uriel N. Heart health in the age of highly antiretroviral therapy in patients with HIV

Starting Antiretroviral Therapy in Acute HIV

Albeit Reduced, Chronic Inflammation in Persons

Cohort Study.

Therapy Era: Results From the Veterans Aging

Heart Failure With Reduced Ejection Fraction and

treatment.

et al. CD4+ count (SMART) Study Group, El

Strategies for Management of Antiretroviral Therapy

guided interruption of antiretroviral

1631. doi:10.1086/518285

2001;98(18):10142-10147. doi:10.1073/pnas.181328798


