**VILNIUS UNIVERSITY**
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# HIV and Cardiovascular Disease

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**ABBREVIATIONS**

| | |
|---|---|
| ABI | Ankle brachial index |
| ACS | Acute coronary syndromes |
| AF | Atrial fibrillation |
| AIDS | Acquired immune deficiency syndrome |
| AMI | acute myocardial infarction |
| ART | Antiretroviral therapy |
| ASCVD | Atherosclerotic cardiovascular disease |
| BNP | B-type natriuretic peptide |
| CAD | Coronary artery disease |
| CA-IMT | Carotid artery intima media thickness |
| cART | Current antiretroviral therapy |
| CHD | Coronary heart disease |
| CHF | Congestive heart failure |
| CNS | Central nervous system |
| CRP | C-reactive protein |
| CT | Computer tomography |
| CVD | Cardiovascular disease |
| EC | Endothelial cell |
| GH | Growth hormone |
| HAART | Highly active antiretroviral therapy |
| HDL | High density lipoprotein |
| HF | Heart failure |
| HFpEF | Heart failure with preserved ejection fraction |
| HFrEF | Heart failure with reduced ejection fraction |
| HIV | Human immunodeficiency virus |
| IL | Interleukin |
| LDL | Low density lipoprotein |
| LV | Left ventricle |
| MI | Myocardial infarction |
| MRI | Magnetic resonance imaging |
| NRTI | Nucleoside reverse transcriptase inhibitor |

| | |
|---|---|
| OX-LDL | Oxidized low-density lipoprotein |
| PAD | Peripheral artery disease |
| PAH | Pulmonary arterial hypertension |
| PCSK9 | Proprotein convertase subtilisin/kexin type 9 |
| PLWH | People living with HIV |
| RAAS | Renin-angiotensin aldosterone system |
| ROS | Reactive oxygen species |
| SCD | Sudden cardiac death |
| TIA | Transient ischemic attack |
| TNF | Tumor necrosis factor |
| VAT | Visceral adipose tissue |
| VTE | Venous thromboembolism |

**SUMMARY**

Cardiovascular disease is a leading cause of morbidity and mortality among people living with Human immunodeficiency virus (HIV). This is due to various factors, such as chronic inflammation and immune activation associated with HIV infection, as well as traditional risk factors for cardiovascular disease, such as smoking, hypertension, and diabetes.

To provide an up-to-date overview of cardiovascular disease in HIV, a literature review was conducted using scientific research articles gathered from the PubMed online database.

Studies have shown that HIV-positive individuals have a higher risk of cardiovascular disease, with dyslipidemia being a significant contributing factor. While newer antiretroviral therapy regimens may have fewer negative cardiovascular effects, lifestyle interventions and medications such as aspirin, statins, and Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors can also reduce cardiovascular disease risk in people living with HIV. However, assessing cardiovascular risk in people living with HIV is challenging due to limited data and unique risk factors associated with HIV infection.

Multicomponent interventions that include physical activity and healthy dieting are effective in preventing cardiovascular disease in people living with HIV. Despite national HIV programs and risk reduction strategies, utilization of preventive medication and achievement of cholesterol and blood pressure targets are suboptimal in both HIV-positive and HIV-negative individuals.

**KEYWORDS:** Cardiovascular disease, HIV, Antiretroviral therapy, Chronic inflammation, Immune activation, Cardiovascular risk factors, Healthy lifestyle, Preventive treatment.

## 1. INTRODUCTION

Antiretroviral therapy has transformed HIV infection into a chronic disease, making it crucial for physicians and healthcare providers to be aware of the nuances of how HIV infection increases the risk of cardiovascular diseases, including acute myocardial infarction, stroke, peripheral artery disease, heart failure, and sudden cardiac death. People living with HIV have an excess risk of cardiovascular disease, which is driven by HIV-specific, traditional, and non-traditional cardiovascular disease risk factors (1,2).

Even though antiretroviral therapy (ART) can control HIV infection, it does not cure the disease. Individuals with HIV must continue taking ART indefinitely, and as a result, chronic inflammation and immune activation persist. This in combination with HIV population ageing being one of the major risk factors leads to development of cardiovascular disease (3).

The data linking HIV and clinical cardiovascular disease, risk factors, and risk assessment primarily come from Europe and North America. However, less is known about the incidence of cardiovascular disease and the burden of risk factors driving cardiovascular disease in sub-Saharan Africa, where 25.6 million of the estimated 37.9 million people living with HIV worldwide reside (1,2).

There is a limited amount data on long-term cardiovascular disease (CVD) outcomes in individuals with HIV due to its recent epidemiological transition to a chronic disease. Consequently, our understanding of CVD pathogenesis, prevention, and treatment in HIV is primarily based on studies that have more focus on HIV itself rather than cardiovascular aspect (3).

The aim of this literature review is to provide an up-to-date overview on cardiovascular diseases in relation to HIV. To review its epidemiology, disease mechanisms, risk factors and clinical manifestation as well as look into treatment guidelines, future approaches, and practical implications by using recent scientific medical research information.

## 2. LITERATURE SEARCH STRATEGY

To make this literature review meet the objectives a custom search strategy was established. Main source of the information was set to be scientific research articles since those provide best insight into up-to-date progression regarding the main topic. For gathering the source scientific research publications, the PubMed online database was picked due to sheer amount of material and advanced filtering methods. The terms that were used for searching the material consisted of the following: “HIV”, “Cardiovascular Disease”, “HIV and Cardiovascular

Disease". Some filters were applied to search results to make them more precise and exclude irrelevant material. First, publication date was set to 6 years ranging from 2017 to 2023 to pick most recent information within reasonable timeframe. In the field for species which publications are related to "humans" was picked. For article language English was selected. In addition some data was taken from the guidelines of American Heart Association and European Society for Cardiology. The final selection of the material was based according to relevancy for the structure of this review.

## 3. LITERATURE REVIEW

Before proceeding with the review, it is important to define what HIV and acquired immune deficiency syndrome (AIDS) is. According to World Health Organization HIV/AIDS is an infection. It targets the immune system and weakens it so that person's organism becomes vulnerable to opportunistic diseases such as infections or cancers (4).

### 3.1 Epidemiology

People living with HIV (PLWH) who have access to antiretroviral therapy are living longer but are at an increased risk for aging related diseases, such as cardiovascular disease. The median age of people with HIV on antiretroviral therapy is expected to increase from 43.9 years in 2010 to 56.5 years in 2030, with 78% of people with HIV being diagnosed with cardiovascular disease. A recent meta-analysis found that people living with HIV had more than twice the risk of cardiovascular disease overall, but the distribution of cardiovascular disease risk factors varies by geographical location and by HIV prevalence as shown in figure 1 below (1).

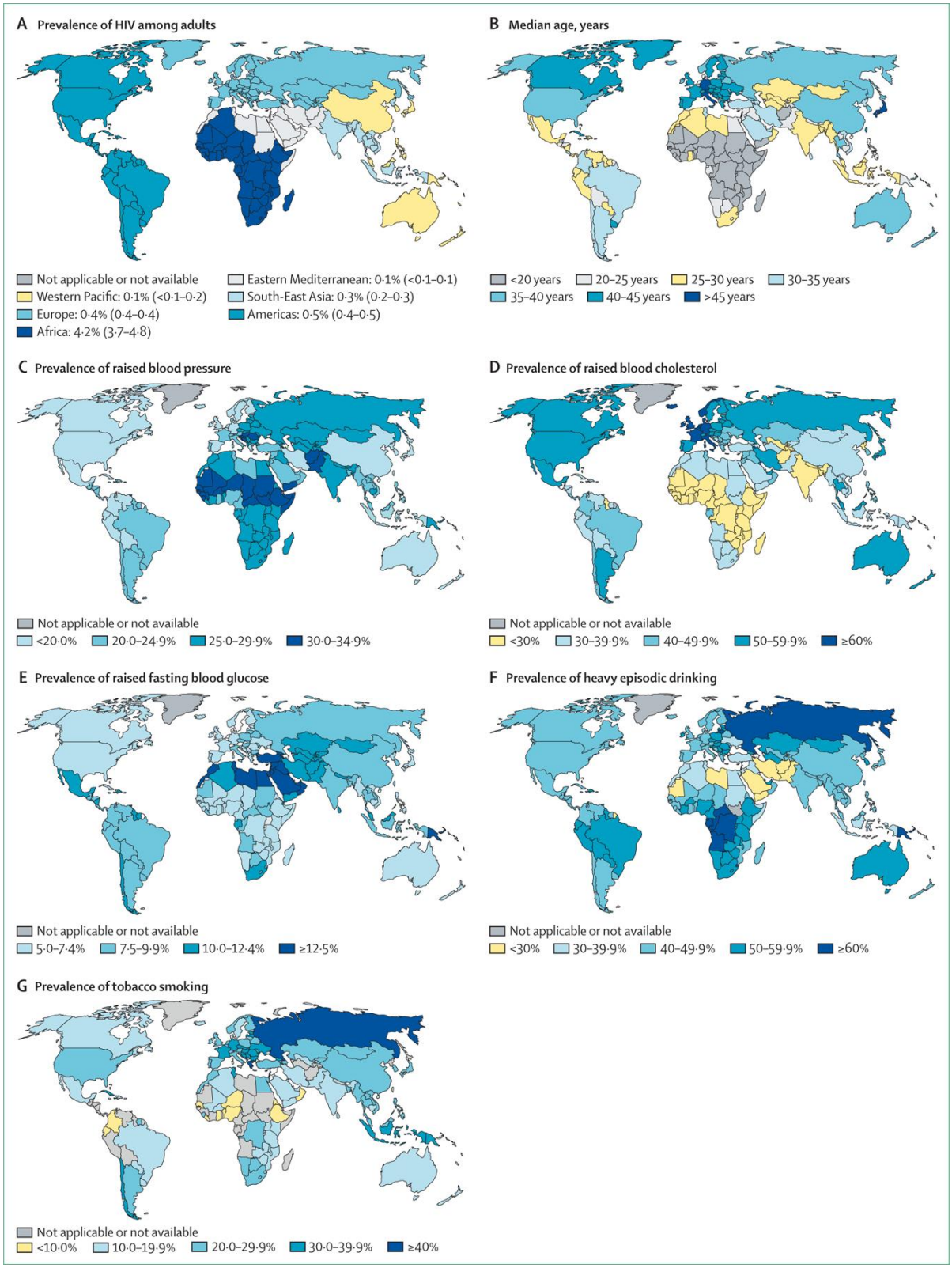


Figure 1. "Prevalence distribution of HIV and risk factors for cardiovascular disease" (1)

The proportion of PLWH over 50 years old has gradually increased since the 1980s, with approximately 47% of PLWH in the US being over 50 years old and 16% being over 65 years old. Older PLWH tend to have more advanced HIV disease and a less robust immune response

to anti-retroviral therapy. They also accumulate age-related diseases at a younger age, and these conditions account for the majority of deaths in this population (5).

PLWH also develop acute coronary syndromes (ACS) a decade earlier than people without HIV and have a higher risk of ACS recurrence. The risk of acute myocardial infarction (AMI) is also 1.4 to 2.2 times higher among PLWH on ART compared to matched controls (6).

While prolonged exposure to antiretroviral therapy was initially thought to contribute to CVD risk, recent data suggests that the effects of ART on CVD are relatively small and that HIV viremia and lower CD4+ cell counts are strongly associated with CVD risk (7).

So-Armah et al. reviewed recent knowledge regarding CVD in HIV populations in low- and middle-income countries, with a focus on sub-Saharan Africa, where HIV prevalence is the highest. Highly active antiretroviral therapy (HAART) is a multiple drug combination therapy. CVD in the absence of HAART is primarily driven by infective etiologies, while with HAART, PLWH can develop coronary artery disease and acute coronary syndromes and suffer from subsequent heart failure. Many studies indicate a high prevalence of CVD risk factors such as dyslipidemia, hypertension, obesity, tobacco use, and malnutrition in these populations, with low knowledge and awareness of these risk factors and their relationship with CVD (8).

More studies done in Sub-Saharan Africa expand on the epidemiological findings. One study found a variable relationship between HIV and cardiovascular disease in Sub-Saharan Africa on a country-by-country basis. The study suggests that HIV did not serve as a risk factor for self-reported cardiovascular disease in Sub-Saharan Africa during the years of the study. However, given the growing prevalence of diabetes and hypertension in the region and the high prevalence of undiagnosed cardiovascular disease, it will be important to continue monitoring cardiovascular disease at the population level and in individuals with and without HIV (9).

Another study found that conventional cardiovascular disease risk factors were the main drivers of carotid artery intima media thickness (CA-IMT) in both rural and urban settings. However, longer duration of antiretroviral therapy use was associated with higher CA-IMT in rural participants aged over 50 years with suboptimal virological control. The study also found that the effect of conventional CVD risk factors on CA-IMT increased with age. The study suggests that immune-related mechanisms may contribute to the increased risk of CVD in PLWH, in addition to conventional risk factors (10).

The duration of HIV infection is also associated with an increasing prevalence of health conditions, including CVD, dyslipidemia, chronic kidney disease, and type 2 diabetes. The issue of polypharmacy is emphasized in this older population, with the number of comorbidities and medications increasing with the duration of HIV infection (5).

PLWH had lower levels of conventional CVD risk factors compared to HIV-negative participants, which contradicts studies conducted in high-income countries. However, PLWH on ART had higher common CA-IMT compared to HIV-negative controls, and this effect increased with age. The age dependency of the influence of HIV and ART on CA-IMT was also described in other studies. Studies conducted in high-income countries reported higher CA-IMT in PLWH on ART compared to HIV-negative controls, while studies conducted in sub-Saharan Africa found equal or lower CA-IMT values in PLWH compared to HIV-negative participants. The findings suggest that CA-IMT is mainly driven by ART and not by HIV. In addition, differences in sex distribution and lifestyle between the HIV-positive population in high-income countries compared with sub-Saharan Africa may explain the contradictory findings (11).

While smoking is a known risk factor for atherosclerosis in PLWH, multisubstance use is common and may also impact cardiovascular disease risk. Studies have looked at the association between heavy alcohol use and cardiovascular events among PLWH, with mixed results. Some studies found an association while others did not. Heavy marijuana use has been linked to incident cardiovascular disease events, and cocaine use has been linked to acute coronary events in the general population (8).

**3.2 Pathophysiology**

There are different mechanisms responsible for an increased risk of cardiovascular diseases in PLWH. Before going into details these mechanisms are briefly summarized in figure 2 below.

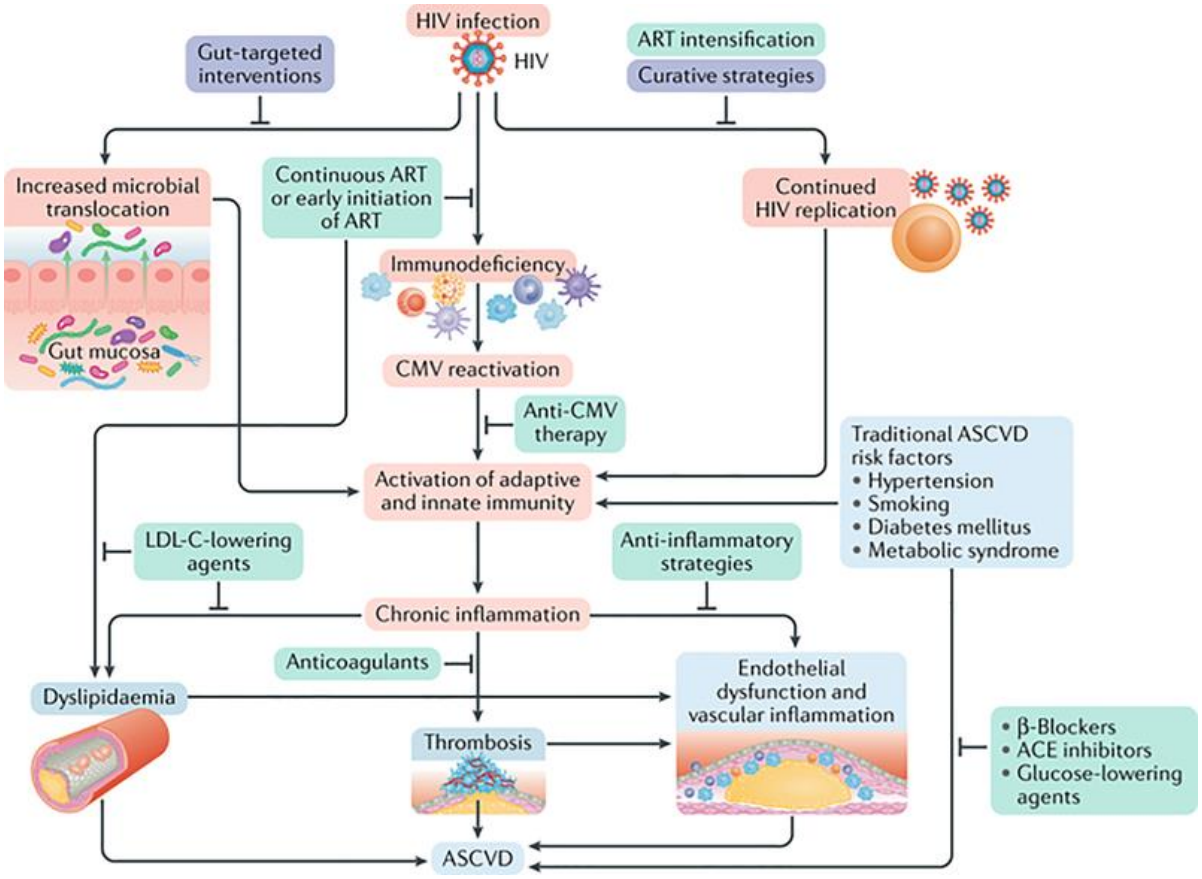


Figure 2. "Mechanisms of Atherosclerotic Cardiovascular Disease among People Living with HIV" (6)

### 3.2.1 Virus-related mechanism and chronic inflammation

The HIV virus can cause chronic inflammation, which can lead to atherosclerotic cardiovascular disease. CD4+ T-cell depletion, caused by HIV infection, is associated with higher rates of various cardiovascular diseases. HIV can cause cardiomyopathy, damage to the gut lining, and increase in microbial translocation, leading to chronic immune activation and inflammation. HIV can also infect the brain and alter the blood-brain barrier through monocytes, leading to inflammatory mediators and vessel wall remodelling (1).

The chronic inflammation and immune activation associated with treated HIV infection are strongly predictive of various health outcomes, including mortality, non-AIDS events, and cardiovascular disease. Inflammatory markers such as interleukin-6 (IL-6) and tumor necrosis factor (TNF) receptors are associated with coronary atherosclerosis in HIV, and arterial inflammation is higher in HIV patients compared to uninfected individuals. While treatment with antiretroviral therapy can reduce inflammation markers, many markers remain elevated in PLWH, even with viral suppression (3). The immune system response, even when the virus is suppressed, continues to produce inflammation, endothelial dysfunction, and atherogenesis.

Co-infections such as cytomegalovirus and gut microbial translocation may also play a role in atherosclerosis among PLWH (6).

PLWH also have increased levels of D-dimer, a biomarker of coagulation system activation, which correlates with CVD and mortality. Other elevated biomarkers in PLWH associated with CVD risk and mortality include von Willebrand factor (VWF), intercellular adhesion molecule 1 (ICAM-1), soluble vascular cell adhesion protein 1 (sVCAM-1), monocyte activation biomarkers (sCD14, sCD163), soluble tumor necrosis factor receptors 1 and 2 (TNFR-1, TNFR-2), and serum amyloid A. While many of these biomarkers decrease following ART initiation and viral suppression, they do not return to levels observed in uninfected individuals, suggesting that long-term HIV infection is associated with chronic inflammation and a prothrombotic state. The relative contribution of direct and indirect effects of HIV infection on chronic inflammation and the development of a prothrombotic state is unclear, but it is evident that HIV infection contributes to chronic inflammation and immune dysregulation through direct and indirect mechanisms.

The three HIV proteins, Tat, Nef, and Env, may contribute to chronic inflammation and endothelial cell dysfunction. Tat can activate transcription of the HIV genome and induce the expression of inflammatory mediators by macrophages and monocytes, as well as increase endothelial permeability and induce senescence in cultured endothelial cells (ECs). Nef downregulates surface expression of various molecules and induces apoptosis in bystander T cells, and can induce altered states in uninfected cells, including EC dysfunction. Env, in addition to serving as the viral envelope protein, can induce expression of ICAM-1, eNOS reduction, senescence, and apoptosis in ECs. Exposure to these viral proteins may impact uninfected bystander CD4+ T cells and cells such as ECs that are not normally permissive to HIV infection, contributing to chronic inflammation and apoptosis even in people on ART with undetectable levels of HIV RNA in their plasma. However, it is difficult to establish a direct role of individual HIV proteins in cardiovascular disease in patients due to the chronic and progressive nature of the disease and the ensuing time delay between initiating insult and final pathology.

Gastrointestinal tract inflammation is a defining feature of chronic HIV infection, with HIV preferentially depleting activated CD4+ T-helper 17 cells that are most common in the gastrointestinal tract. This depletion occurs soon after infection in both patients and nonhuman primate models, and if left untreated, it persists. The loss of CD4+ T cells and macrophages results in a decreased production of interleukins (IL-17 and IL-22) and increased local proinflammatory cytokine production, which disrupts the gut epithelium barrier function.

Damage to the epithelial barrier combined with depletion of host immune defences allows for microbial translocation, which is the passage of microbes or microbial products from the intestinal lumen into the circulation, resulting in systemic inflammation. Monocytes amplify this inflammation by secreting proinflammatory cytokines and releasing soluble forms of receptors that detect lipopolysaccharide, an indirect marker of microbial translocation. Chronic inflammation, like that in HIV infection, leads to endothelial cell dysfunction, promoting atherosclerosis (12).

HIV-related inflammation and viral proteins can elicit reactive oxygen species (ROS) production, further fuelling immune dysfunction and tissue injury. Innate immune activation plays an essential role in HIV pathogenesis and may contribute to the onset of atherosclerosis. Atherosclerosis is initiated by the infiltration of oxidized low-density lipoprotein (OX-LDL) through arterial walls, leading to an aberrant immune cell response. Activated monocytes take up OX-LDL by scavenger receptors, resulting in macrophages forming early fatty plaque streaks (foam cells). Changes in monocyte subsets and the differentiation of macrophages into M1 and M2 subtypes play an important role in the development of atherosclerosis and in promoting systemic and chronic inflammation during HIV infection (13).

### 3.2.2 ART-related mechanisms

Antiretroviral therapy has life-saving benefits, however, certain older regimens such as abacavir, lopinavir, and ritonavir may have side effects detrimental to cardiovascular health, including altered glucose and lipid metabolism, mitochondrial toxicity, and cardiac myopathy. Some newer regimens like dolutegravir or atazanavir may have less negative cardiovascular effects. Weight gain after starting ART can also increase the risk of diabetes, a cardiovascular disease risk factor. People with HIV often have multiple chronic comorbidities requiring polypharmacy, which increases the potential for drug interactions and QT interval prolongation, a risk factor for sudden cardiac death (1).

However, the use of antiretroviral therapy is crucial in preventing cardiovascular disease in people living with HIV as treatment interruption and uncontrolled HIV viremia are associated with a higher risk of heart attacks. Protease inhibitors (PIs) have been linked to heart attacks, with the exception of atazanavir, which has been associated with slower progression of carotid intima-media thickness. Abacavir, a nucleoside reverse transcriptase inhibitor (NRTI), has been associated with an increased risk of heart attacks, especially in individuals at high cardiovascular risk, despite some controversial findings from shorter-duration clinical trials (3). High adherence to ART is associated with the partial normalization of biomarkers of inflammation and immune activation. The impact of integrase inhibitors, which have been

linked to weight gain, on atherosclerotic cardiovascular disease (ASCVD) risk is not yet known (6).

### 3.2.3 Metabolism-related mechanisms

HIV infection can cause metabolic complications such as dyslipidemia, insulin resistance, and body composition changes, which can lead to cardiovascular disease. Dyslipidemia in HIV was initially linked to increased triglyceride levels, but it has since been found to be associated with inflammation and other factors that contribute to an atherogenic dyslipidemia. Insulin resistance and diabetes mellitus are also seen more frequently in HIV, with diabetes mellitus linked to a higher risk of coronary heart disease events. Body composition changes, including loss of subcutaneous fat and gain in abdominal visceral fat, were common in the past, but in the modern ART era, gains in both subcutaneous and visceral fat are often seen with the initiation of ART, regardless of regimen, and rates of generalized obesity are increasing among PLWH. Changes in body composition, including excess visceral adipose tissue, have been linked to overall mortality and increased coronary atherosclerosis (3).

The prevalence of hyperlipidemia among PLWH ranges from 28% to 80%, with hypertriglyceridemia being the most common. Hypertriglyceridemia does not independently predict ASCVD events among PLWH, so the treatment of hypertriglyceridemia remains uncertain. Additionally, chronic kidney disease is highly associated with cardiovascular risk (6).

The inflammatory environment in HIV infection may also lead to lipid abnormalities, and there is a complex relationship between inflammation and the lipid profile. Chronic inflammatory diseases such as rheumatoid arthritis, systemic lupus erythematosus, and psoriasis have also been linked to atherogenic lipid profiles. Certain markers such as IL-6, C-reactive protein (CRP), and D-dimer predict cardiovascular events and mortality in HIV+ individuals. Lower HDL concentrations were associated with a higher risk for CVD in HIV+ individuals, and HDL concentration increased in patients initiating ART, but the degree of improvement was dependent on levels of inflammation present at baseline. In ART-treated HIV+ individuals, metabolic factors such as LDL and ApoA1 correlated even more strongly with CVD risk than did inflammatory biomarkers (14).

### 3.2.4 Other factors

Traditional cardiovascular disease risk factors such as smoking, diabetes, dyslipidaemia, hypertension, and biological sex, as well as non-traditional risk factors such as unhealthy

alcohol consumption, depression, hepatitis C, and cytomegalovirus co-infection, contribute to this increased risk (1). Smoking is highly prevalent among PLWH and is strongly associated with formation of coronary plaque and myocardial infarction (MI). Heavy alcohol use and mood and anxiety disorders may also contribute to elevated CVD risk in PLWH. Low levels of physical and cardiorespiratory fitness are also associated with increased risk for CVD and all-cause mortality in patients with HIV (3).

The initiation of ART is also associated with the risk of hypertension. PLWH with hypertension have a 2-fold risk of acute myocardial infarction (AMI) and a higher death rate compared to those with only HIV or hypertension. The mechanisms of hypertension specific to HIV include ART-associated lipodystrophy and renal disease, direct ART effects, immune suppression or reconstitution, gut microbial translocation, chronic inflammation, and activation of the renin-angiotensin aldosterone system (RAAS) (6).

### 3.3 Clinical picture

Individuals with HIV are at a heightened risk for vascular diseases such as MI and stroke due to atherosclerosis and thrombosis. Different types of cardiomyopathies and heart failure are seen in individuals with HIV. Individuals with persistent HIV viremia and immune progression may experience severe systolic dysfunction, while less overt cardiomyopathy and heart failure are associated with diastolic dysfunction. Several studies have demonstrated that individuals with HIV have more subclinical changes in cardiac tissues, including myocardial inflammation, fibrosis, and steatosis, which are known to be associated with myocardial injury and dysfunction. There is less research on the connection between HIV infection and atrial fibrillation, sudden cardiac death, and peripheral artery disease. HIV-related pulmonary arterial hypertension is well-documented and has a higher prevalence than pulmonary arterial hypertension in the general population. Elevated pulmonary artery systolic pressure is also common among PLWH (3,7).

#### 3.3.1 Myocardial infarction and stroke

Studies from around the world over the past decade have reported an increased risk of MI and stroke among PLWH compared to uninfected individuals. HIV-related viremia and immune dysfunction are associated with higher MI and stroke risks, and lower CD4 count is a significant factor in both. Even PLWH who achieve sustained HIV viral suppression or have few cardiovascular risk factors have a higher MI risk than uninfected individuals. Women with HIV may be at an even greater risk for MI and stroke than men. In Sub-Saharan Africa, HIV is

the leading risk factor for stroke in young cohorts. Coinfection with HIV and hepatitis C may further increase stroke risk (3).

The risk of ischemic stroke among HIV-infected individuals is approximately 30% higher than in uninfected individuals, according to several longitudinal cohort studies. A recent systematic review and meta-analysis found consistently elevated stroke risk in PLWH compared to uninfected people, and stroke risk was found to be predominantly due to large artery atherosclerosis and stroke of undetermined etiology among PLWH. Some mechanisms that are thought to contribute to the higher prevalence of ischemic stroke in PLWH include HIV-associated vasculopathy, coagulopathy, opportunistic infection, and cardioembolism (15).

Several studies have provided insights into why PLWH are at higher risk for MI and what happens after the first event. The studies suggest that HIV is associated with accentuated aging (higher comorbidity risk at all ages) rather than accelerated aging (comorbidities occurring at younger ages) and that PLWH are at a greater risk of type 1 myocardial infarction (due to atherosclerotic plaque rupture). Studies have also focused on the morbidity and mortality of MI in PLWH, showing that improvements in CVD risk factors management have led to short-term survival improvements. However, well-controlled HIV infection is still associated with increased risk of death a year after an incident MI (8).

### 3.3.2 Heart failure

The risk of heart failure (HF) is also elevated among people living with HIV, with estimates ranging from 1.5 to 2 times greater than uninfected individuals, even after adjusting for relevant factors. This elevated risk is not solely due to MI, and PLWH have a higher hazard for HF with preserved ejection fraction (HFpEF) and HF with reduced ejection fraction (HFrEF). Similar to MI risks, unsuppressed HIV viral load and lower CD4 count are associated with higher HF risks in PLWH (3).

However, with the use of HAART, the proportion of heart failure caused by infective myocarditis has reduced. Nonetheless, recent studies show that HIV infection remains a risk factor for heart failure. Settings with limited access to HAART have a higher risk of heart failure. The changing epidemiology of heart failure in the HAART era includes a shift from a mainly dilated cardiomyopathy phenotype to include both HFrEF and HFpEF (8).

HIV-infected patients have higher rates of traditional risk factors for congestive heart failure (CHF), drug abuse, and coronary artery disease (CAD), as well as higher levels of autonomic

dysfunction and inflammation, which are considered novel risk factors for HF in the general population. Studies have also shown increased subclinical cardiac mechanical dysfunction and presence of myocardial abnormalities in HIV+ patients on ART. The sustained increased HF risk in HIV+ patients can be attributed to these mechanisms involved in pathogenesis of HF (15).

### 3.3.3 Peripheral artery disease

Peripheral Artery Disease (PAD) is as an understudied comorbidity in the HAART era. PAD is the third leading cause of atherosclerotic cardiovascular disease and is often asymptomatic but may lead to pain and increasing disability. Many conditions that co-occur with PAD, such as smoking and diabetes, are prevalent in HIV-infected populations. Studies have used the ankle brachial index (ABI) to determine the existence of PAD in HIV-infected people, and the prevalence of PAD ranged from 2 to 27%. The veterans aging cohort study reported a 30% increased risk of PAD associated with HIV status (8). Studies evaluating PAD in PLWH have shown inconsistent results regarding the prevalence of PAD in this population. Recent studies suggest that the prevalence of PAD in PLWH is similar to that of the general population, and ABI is not correlated with CA-IMT or traditional risk factors for cardiovascular disease in HIV+ patients (15).

### 3.3.4 Arterial and venous thrombosis

PLWH also have more noncalcified plaques, which increases their risk of cardiovascular events as these plaques are more prone to rupture. Platelets play a central role in arterial thrombosis, and activation of platelets by HIV may increase the risk of thrombosis in PLWH. Some specific antiretroviral therapy regimens have been linked to platelet activation and MI in PLWH, including older PIs and nucleoside reverse transcriptase inhibitors.

Venous thrombosis (VTE) is a condition that can present as deep vein thrombosis or pulmonary embolism and is collectively referred to as venous thromboembolism. The incidence of VTE is significantly increased in people living with HIV. Intravenous drug users with HIV are at the highest risk of developing VTE. The research suggests that hypercoagulability and EC dysfunction are the major factors contributing to increased VTE in people living with HIV. In addition, there is deficiency of anticoagulant proteins in people living with HIV, such as protein S, protein C, heparin cofactor II, and antithrombin (12).

### 3.3.5 Sudden cardiac death

Sudden cardiac death (SCD) is suggested to be more common in HIV+ patients due to their higher risk of common causes of SCD such as CAD, cardiomyopathy, heart failure, pulmonary hypertension, and arrhythmias. While few studies have evaluated the risk of SCD in HIV+ patients, a retrospective cohort study found that the SCD rate was 4.5 times higher in HIV+ patients than in the general population. Further research is needed to determine the relative contribution of each cause of SCD and other HIV-specific factors. Left ventricle (LV) systolic and diastolic dysfunction were found to be strongly associated with a higher risk of SCD (15).

### 3.3.6 Dyslipidemia

The increased risk of cardiovascular disease in HIV-infected patients is largely attributed to dyslipidemia, particularly low levels of HDL cholesterol. HIV infection and antiretroviral therapy can both affect the quantity and function of HDL. Dysfunctional HDL in HIV-infected individuals may promote atherosclerosis and has been associated with decreased paraoxonase activity, as well as shifts in HDL subclass distribution. HIV infection has also been associated with the expression of microRNAs involved in lipid metabolism. Further research into HDL subclass and function in HIV patients treated with and without ART is needed to better understand the impact of HIV and ART as cardiovascular risk factors (16).

### 3.3.7 Other associated diseases

The relationship between HIV infection and atrial fibrillation (AF) is poorly understood. Studies have shown that rates of AF in HIV+ people are higher than in the general population, particularly in younger age groups, and that traditional risk factors such as older age, CAD, HF, and renal dysfunction are also associated with an increased risk of AF in HIV+ patients. Anticoagulation is an important consideration in managing HIV+ patients with AF, but recent analyses suggest that CHA2DS2-Vasc score is not a strong predictor of thromboembolic events in this subgroup and that warfarin therapy may be associated with more thromboembolic events (15).

Pulmonary arterial hypertension in HIV (HIV-PAH) has similar clinical presentation and histology to idiopathic PAH, and the prevalence was estimated to be about 0.5% among PLWH before the widespread use of ART. Individuals with HIV-PAH have a high risk of right ventricular failure and premature death. The most common symptom is dyspnea, and common findings from ancillary tests are cardiomegaly, pulmonary arterial enlargement, right ventricular hypertrophy, dilated right atrium and ventricle, and tricuspid regurgitation. Recent

studies have shown that HIV-PAH is underdiagnosed and that screening guidelines should be implemented (15).

The study also found that HIV-positive patients undergoing combination ART had a higher rate of patchy myocardial fibrosis, steatosis and scars in the basal septum compared to uninfected controls with no history of cardiovascular disease. The burden of patchy fibrosis was also twice as high in HIV patients compared to controls (15).

Both systolic and diastolic dysfunctions are common problems in symptomatic HIV+ patients. Studies have suggested that longer duration of HIV infection, higher body mass index, and exposure to zidovudine were also associated with higher rates of diastolic dysfunction. PLWH have higher LV mass, which has been associated with lower nadir CD4 counts. In addition to global LV dysfunction, there is a higher rate of regional LV dysfunction in HIV+ patients (15).

Before the advent of ART, pericardial effusion was a common cardiovascular complication in HIV patients, and it was associated with increased mortality. However, with the use of ART, mortality due to pericardial effusion has dramatically decreased. A recent study using cardiac magnetic resonance imaging (MRI) found that small pericardial effusions were found in 57% of HIV+ patients on ART, compared to 21% of controls, indicating the presence of low-grade inflammation even in patients on ART (15).

Sleep disorders, particularly obstructive sleep apnea, are associated with CVD and may be underdiagnosed among PLWH, who are also at risk for sleep impairment (3).

There are also other non-stroke processes that can present with acute focal neurologic deficits and have been referred to as stroke-like syndromes or stroke mimics. These syndromes are frequently associated with opportunistic infections that cause focal central nervous system (CNS) lesions such as tuberculosis, fungal infections, progressive multifocal leukoencephalopathy, and/or HIV-associated lymphoma (15).

### 3.3.8 Imaging insights

PLWH show more subclinical atherosclerosis than uninfected individuals, as measured by different imaging modalities. Studies have found that PLWH have more carotid plaque and higher CA-IMT compared to uninfected individuals. Imaging with noncontrast computer tomography (CT) has shown that coronary artery calcium progresses more rapidly in PLWH. HIV is associated with a greater prevalence and extent of noncalcified plaque and with coronary artery remodelling, both of which may represent a phenotype of elevated risk associated with

HIV infection. Treatment with statin therapy has reduced noncalcified plaque volume and high-risk plaque features relative to placebo. PLWH also have greater aortic arterial inflammation than uninfected individuals with similar cardiovascular risk factors. PLWH also exhibit distinctive arterial phenotypes in extracranial and intracranial arteries, with differing responses to vascular risk factors and inflammation. Intracranial arterial disease is an important component of cardiovascular disease in PLWH, accounting for more than one-third of ischemic stroke cases. Emerging data suggest that intracranial vessel wall remodelling occurs through neuroinflammation, which may be independent of atherosclerosis (3).

### 3.3.9 Lipid profiling

Lipidomic profiling has been shown to outperform traditional lipid panels in predicting cardiovascular disease risk, with specific lipid species, such as triacyl glyceride (TAG 54:2), cholesterol esters (CE 16:1), and phosphatidylethanolamine (PE 36:5), being highly predictive of CVD. Elevated TAG levels have been linked previously to insulin resistance, increased diabetes risk, and poor control of HIV infection. Lipid profiling can also accurately characterize stable and unstable CAD, with specific ceramides having even more predictive potential than LDL levels. The lipidome profile of HIV+ individuals is characterized by changes in 7 lipid classes and 83 individual lipid species, which are also linked to CVD and diabetes risk in HIV-populations. Lipidome changes induced by HIV replication during acute or chronic infection may differ from the lipidome within that individual following viral suppression by ART. A study on longitudinal samples from treatment naïve HIV+ individuals initiating a Raltegravir-based ART regimen showed broad alterations in the lipidome composition after 48 weeks of ART compared to HIV+ individuals at baseline, and when compared to levels in cross-sectional samples obtained from age and sex matched HIV- individuals (14).

### 3.3.10 Biomarkers

Immune markers as predictive indicators for cardiovascular disease in HIV-positive patients were investigated. Although markers such as CRP, IL-6, and sVCAM-1 were commonly assessed, no clear relationship between any of the immune markers and surrogate markers of CVD was found. This lack of association could be due to weak associations, methodological constraints, or heterogeneity in patient populations, antiretroviral therapy, and other factors that influence the inflammatory response and risk of CVD. While CRP and IL-6 have been linked to CVD in the general population and HIV-infected patients, the review did not indicate any consistent relation with surrogate CVD outcomes. In addition to inflammation, the autonomic

system and neurohormones, such as B-type natriuretic peptide (BNP), are important in the pathogenesis of LV dysfunction and HF. NT-proBNP has been associated with CVD in the general population and is a potential biomarker for CVD in HIV-infected patients (15,17).

### 3.4 Clinical guidelines and treatment recommendations

American Heart Association and European Society for Cardiology provide guidance on adjusting risk estimation and treating high-risk individuals with a combination of lifestyle optimization and pharmacotherapy. Guidelines for stroke risk prediction and heart failure prevention and treatment are also discussed, with recommendations to follow general population guidelines due to the lack of specific HIV-related guidelines. Experts suggest following guidelines for peripheral artery disease and sudden cardiac death. Overall, there is an emphasis on the importance of considering traditional and non-traditional cardiovascular disease risk factors and individualized treatment for people living with HIV (1,3,18).

#### 3.4.1 Pharmacotherapy

Currently there are 7 major groups of antiretroviral therapy drugs in use. Common examples are listed in table 1 (19).

Table 1. "Classification of antiretroviral drugs for HIV" (19)

| | |
|---|---|
| Nucleotide/Nucleoside Reverse Transcriptase Inhibitors (NRTI) | Abacavir (ABC), Tenofovir disoproxil fumarate (TNF), Lamivudine (3TC), Emtricitabine (FTC), Zidovudine (AZT), Stavudine |
| Non-Nucleotide Reverse Transcriptase Inhibitors (NNRTI) | Efavirenz (EFV), Nevirapine (NVP), Delavirdine (DLV), Etravirine (ETR), Rilpivirine (RPV), Doravirine |
| Integrase Inhibitors (II) | Raltegravir (RAL), Dolutegravir (DTG), Bictegravir |
| Protease Inhibitors (PI) | Ritonavir (RTV), Nelfinavir (NFV), Atazanavir (ATZ), Darunavir (TMC114), Saquinavir (SQV) |
| Fusion Inhibitors (FI) | Enfuvirtide |
| Pharmacokinetic Enhancers (PE) | Cobicistat |
| CCR5 Antagonist | Maraviroc |

There are potential benefits of switching from current antiretroviral therapy (cART) to a more lipid-friendly regimen in people living with HIV with dyslipidemia to reduce cardiovascular

risk. The principles of cART switching are to maintain virologic suppression, improve adherence and tolerability. The decision should be based on several factors including those contributing to dyslipidemia, previous cART regimens, virologic responses, genotypic resistance test, adherence history, and toxicities. Different antiretroviral classes have varying effects on lipid values, with ritonavir having the most significant effect. In the nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) class, stavudine, zidovudine, and abacavir have been associated with dyslipidemia, while tenofovir disoproxil fumarate (TNF) has a favorable effect on lipid profile. Efavirenz has been associated with increases in total cholesterol and triglycerides, while rilpivirine has less effect on lipid parameters. The integrase inhibitors (INIs) have little effect on lipid profile, and the C-C chemokine receptor type 5 (CCR5) inhibitor maraviroc has no effect. There are potential options for appropriately switching cART agents to improve lipid parameters, such as switching from abacavir/lamivudine to TNF/emtricitabine. However, each cART switching has a potential virologic failure risk, and it is recommended to prefer regimens supported by clinical trials, switch studies, or observational cohort studies (20).

Statins have been shown to significantly reduce cardiovascular events in patients without HIV. Observational cohorts have shown that most statins (excluding simvastatin and lovastatin) can be safely prescribed for PLWH, with lipid-lowering effects like those for people without HIV. However, there is limited data on the net benefits of statins in people over 75 years old. PLWH are less frequently prescribed high-intensity statins after acute coronary syndrome, and LDL reduction 6 months after the event is lower (3). Statin usage has been studied extensively in HIV+ individuals and has been shown to improve lipid profiles, inflammatory markers, and CVD risk. The Stopping Atherosclerosis and Treating Unhealthy Bone with Rosuvastatin in HIV (SATURNHIV) trial showed that statin treatment reduced T cell and monocyte activation markers, reduced vascular inflammation, and improved renal function in ART-treated HIV+ individuals with normal LDL levels but increased biomarkers of immune activation. Atorvastatin treatment also resulted in reduced non-calcified plaque volumes in HIV+ individuals. The Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE) study is currently evaluating the efficacy of statin use in preventing CVD events in low-risk HIV+ individuals (14,21,22). However, the American Heart Association multispecialty guideline includes HIV infection as a risk enhancer and recommends the use of statin therapy in PLWH with borderline to intermediate risk of CVD. Rosuvastatin, atorvastatin, and pitavastatin are the best choices for PLWH (3,5). The combination of fibrates and statins has also shown higher

efficacy in HIV-associated dyslipidemia. Studies have shown significant reductions in triglyceride levels with fenofibrate, ranging from 18% to 58%. However, there is an increased risk of renal toxicity associated with the use of fibrates and statins that should be considered. The use ezetimibe, a lipid-lowering drug has also been studied. When added to a stable statin therapy, ezetimibe shows a significant reduction in total cholesterol and LDL-C with mixed results about HDL and triglycerides. Ezetimibe is a good option to intensify statin therapy and is affordable for statin-intolerant patients, with a very low toxicity profile (17).

In addition to statin therapy, antithrombotic agents may also be beneficial in reducing CVD risk in HIV. Risk stratification tools, such as CHA2DS2-VASc and HAS-BLED scores, can help estimate stroke and bleeding risk and guide antithrombotic therapy. However, the reliability of these scores in PLWH is unclear (3). Aspirin is a low-risk and low-cost platelet inhibitor that has immunomodulatory properties, but its role in primary prevention of CVD in those at risk remains controversial (5). Several small studies have analysed the effect of different antithrombotic agents on platelet activation, coagulation, inflammation, and innate immune cell activation in people living with HIV on combination antiretroviral therapy. These studies suggest that different antithrombotic agents have varying effects on biomarkers of inflammation and coagulation in PLWH on ART (12).

While current treatments, such as ART and lipid-lowering therapies, can help to some extent, there is still a need for alternative and adjunctive approaches. One promising approach is the use of PCSK9 inhibitors, which have been shown to significantly reduce LDL-C levels and cardiovascular events in uninfected people. However, PCSK9 levels are higher in people living with HIV, particularly those who are ART naïve, and further research is needed to evaluate the impact of PCSK9 inhibition on clinical events in this population. Another potential approach is the use of monoclonal antibodies targeting IL-1β, which has been shown to significantly reduce IL-6 and CRP levels and lower the rate of recurrent cardiovascular events in non-HIV populations. However, further study is needed to define the role of targeted therapies to reduce inflammation and CVD risk in HIV (3,20).

HIV-infected individuals may experience significant accumulation of visceral fat, which is associated with dyslipidemia and reductions in growth hormone (GH) secretion. Tesamorelin, a synthetic analog of human GH-releasing factor, reduces visceral adipose tissue (VAT) and concomitantly reduces triglycerides, total cholesterol concentration and non-HDL-C among HIV-infected subjects. Studies have shown that the use of tesamorelin decreases VAT, reduces

triglyceride levels, and improves the ratio of total cholesterol to HDL cholesterol. Tesamorelin is usually well tolerated with common adverse events including injection site erythema, pruritus, headache and arthralgia (20).

In addition, diabetes mellitus and hypertension should be managed as recommended for the general population because there are insufficient data to recommend a divergent approach in HIV. High-dose corticosteroids may be necessary in patients with immune reconstitution inflammatory syndrome with impending brain herniation and helpful in less severe cases with symptomatic central nervous system inflammation (3).

### 3.4.2 Lifestyle interventions

Quitting smoking is crucial due to its high prevalence among PLWH and its clear link to atherosclerosis and heart attack. Limiting alcohol consumption is also important, although the impact of light to moderate alcohol consumption on CVD is debatable. Regular physical activity is essential for improving inflammation and cardiometabolic health in HIV, and a lifestyle-focused behavioral intervention can reduce sweetened beverage consumption and weight. Adhering to ACC/AHA dietary guidelines, which emphasize fruits, vegetables, legumes, healthy protein sources, whole grains, and limited intake of sweets, sugar-sweetened and artificially sweetened beverages, and red meats, is recommended (3,23).

### 3.4.3 Supplements

Omega-3 fatty acids have been used in HIV-associated dyslipidemia with a good safety profile. They have shown a reduction in triglycerides ranging from 7% to 38% in HIV patients on PI-based regimens. Recent randomized trials with less than 50 patients per arm have also shown triglyceride reduction of 9-48%. When combined with statins, the combination results in a more favorable lipid profile with very low toxicity. The higher dose (2-4 g/day) needed to achieve efficacy can lead to side effects such as flatulence (20).

However, a review aimed to evaluate the effects of increased intake of fish and plant-based omega-3 fatty acids on the risk of cardiovascular disease mortality and events was conducted. The review included randomized controlled trials lasting at least 12 months that investigated men and women aged 18 years and older who were at any risk of CVD and received dietary supplements and advice to promote omega-3 intake. Effectiveness of these interventions on primary, secondary, and tertiary outcomes was evaluated. The review concludes that short-chain fatty acids and long-chain omega-3 fatty acids have little or no effect on mortality or

cardiovascular health, but omega-3 alpha-linolenic acid slightly reduces the risk of CVD events and arrhythmias (24).

### 3.4.4 Interventional procedures

After percutaneous coronary intervention, PLWH have similar outcomes compared with uninfected individuals, but they are less likely to undergo the procedure and receive drug-eluting stents. In the nonacute setting, PLWH are more likely to receive percutaneous coronary intervention after an abnormal stress test. Inflammation and immune activation are important drivers of restenosis risk after stent placement. Coronary artery bypass graft surgery appears to be safe and effective for PLWH. However, rates of longer-term major adverse cardiac events after the surgery may be higher for PLWH compared with uninfected individuals. Endovascular treatment has shown success in patients with HIV-associated vasculopathy, although safety data is limited. It is also important to follow general population indications for implantable cardioverter-defibrillator therapy in PLWH with reduced left ventricular ejection fraction as it increases sudden cardiac death. For PLWH with end-stage HF, transplantation or left ventricular assist device implantation should not be considered a contraindication as life expectancy for PLWH is approaching that of uninfected individuals (3,15).

## 3.5 Risk assessment and reduction

There are some challenges when assessing cardiovascular disease risk in PLWH, due to the relatively recent emergence of HIV as a chronic disease and the lack of long-term data on CVD incidence in the modern antiretroviral therapy era. Traditional CVD risk factors such as age, diabetes, smoking, hypertension, and dyslipidemia are also associated with elevated CVD risk in PLWH. HIV infection itself is also a risk factor, especially for those with low CD4 counts or a history of untreated HIV (3).

### 3.5.1 Risk assessment

There is no consensus on the best CVD risk estimation model for PLWH, but the Data Collection on Adverse Effects of Antiretroviral Drugs (D:A:D) model, which incorporates traditional CVD risk factors as well as certain HIV-specific factors associated with CVD, is commonly used (3). The D:A:D model is an HIV-specific risk prediction model developed to predict 5-year CVD risk based on a large cohort of predominantly European PLWH, incorporating traditional CVD risk factors, CD4 count, and use of antiretroviral drugs. It was developed using data from people living with HIV and has been updated to be used in clinical

practice. The model's performance in validation studies has been modest, similar to other CVD risk prediction models such as FHS-CVD, PCE, and SCORE. These models are summarized in table 2 (25).

Table 2. "Summary of CVD Risk Prediction Models Commonly Used in PLWH" (25)

| Model | Source population | Risk factors | Predicted outcome |
|---|---|---|---|
| Framingham Heart Study (FHS) | US adults | Age, blood pressure, smoking, total cholesterol, HDL-C, diabetes | Composite coronary heart disease - CHD (coronary death, MI, coronary insufficiency, angina), cerebrovascular events (stroke, transient ischemic attack - TIA), PAD, heart failure |
| ACC/AHA Pooled Cohort equations (PCE) | US adults | Age, blood pressure, smoking, total cholesterol, HDL-C, diabetes | MI, fatal or nonfatal stroke, CHD death |
| Systematic Coronary Risk Evaluation (SCORE) | Adults from 12 European countries | Age, sex, blood pressure, smoking, total cholesterol | CHD death, fatal stroke |
| Data Collection on Adverse Effects of Antiretroviral Drugs (D: A:D) | Adults from U.S., Europe, Argentina, and Australia | Age, sex, blood pressure, smoking, total cholesterol, diabetes, smoking, family history of CVD, CD4 count, years of use of PIs and NRTIs, current abacavir use | Composite CVD (fatal or nonfatal MI including sudden death, stroke, TIA, invasive coronary artery procedures including CABG, angioplasty, death from other CHD) |

However, the inclusion of family history of CVD, a variable not available in many cohorts of PLWH, has limited its evaluation. Several HIV-specific risk scores were also developed from

the The Center for AIDS Research (CFAR) Network of Integrated Clinical Systems cohort (CNICS), incorporating ASCVD risk score variables and HIV-specific variables, and demonstrated adequate discrimination but worse calibration than PCE (25).

Certain factors identified as CVD risk enhancers in the 2018 ACC/AHA cholesterol clinical practice guidelines, such as early family history of MI or stroke, persistently elevated LDL-C, chronic kidney disease, subclinical atherosclerosis on imaging, and high levels of selected biomarkers, may also be relevant in PLWH. Elevated triglycerides, however, are not considered a significant CVD risk enhancer in HIV (3,26)

The presence and extent of subclinical atherosclerosis, measured using imaging techniques such as coronary artery calcification and CA-IMT, can help refine CVD risk assessment in PLWH, particularly those at intermediate risk. However, the value of these measurements for CVD risk stratification in HIV is unclear, and routine screening is not recommended at present (3).

The efforts were made over the past 20 years to identify new biomarkers and risk factors that can improve cardiovascular disease risk prediction. These efforts are aimed at more accurately identifying individuals who are predicted to have low or intermediate risk by traditional models but still develop CVD in the future. Some of the biomarkers of interest include coronary artery calcium scoring, high-sensitivity C reactive protein, ankle-brachial index, advanced lipoprotein testing, D-dimer and lipoprotein-a. However, currently, none of these biomarkers are routinely recommended for primary prevention of CVD (25).

Other factors that are often not accounted for in cardiovascular disease prediction models include healthcare and economic disparities, polypharmacy, and clinical cardiovascular guidelines that may not consider HIV status. Co-morbidities such as hepatitis C that further perturb lipid levels and independently contribute to cardiovascular disease risk are also relevant to the discussion of cardiovascular disease risk prediction in HIV (8,25).

### 3.5.2 Risk reduction

The efforts are being made to reduce coronary heart disease risk in low-income and middle-income countries through national HIV programs. Risk assessment and reduction strategies for cardiovascular diseases in people with HIV begin with HIV management, risk screening, referral, and risk factor management. Lessons learned include the importance of efficiently

testing new deployments of existing resources. Risk reduction strategies for coronary heart disease also apply to stroke and peripheral artery disease.

European study found that the risk factor burden for coronary heart disease is high but that modification of risk factors such as hypertension is improving over time. The incidence of cardiovascular disease mortality among people with HIV has decreased, but the relative contribution of cardiovascular disease to mortality is increasing due to the ageing population of people with HIV in high-income countries. Future research is needed to assess the effect of HIV control and risk factor management on peripheral artery disease risk, and to understand the interaction between heart failure risk factors and HIV-related cardiovascular disease risk factors. Given the scarce data on sudden cardiac death in HIV, more research is also necessary to assess the impact of approaches to reduce ischaemic heart disease on sudden cardiac death risk among people with HIV (1). A study that aimed to investigate the use of preventive cardiovascular medication and achievement of targets according to Dutch CVRM guidelines was conducted. The study found that a substantial proportion of those at high cardiovascular risk or with prior CVD had an indication for cardiovascular treatment, but the use of cardiovascular medication was poor, and achievement of cholesterol and blood pressure targets was suboptimal in both HIV-positive and HIV-negative individuals. The study's results are expected to be generalizable to other high-income settings with unrestricted access to ART (27,28).

While studies have shown that statins can reduce atherogenic lipid levels and some inflammatory markers in individuals with HIV, their effectiveness in preventing hard atherosclerotic coronary artery disease endpoints is still being evaluated through the REPRIEVE study. Other potential CVD preventive strategies being studied include PCSK9 inhibitors, antithrombotic therapy, and anti-inflammatory therapies that target the gut to reduce microbial translocation and gut inflammation. Current CVD risk estimation tools consistently underestimate CVD risk among individuals with HIV due to HIV-related CVD risk-enhancing factors such as prolonged HIV viremia, low CD4+ cell count, coinfection, and lipid distribution abnormalities. Therefore, the American Heart Association recommends adjusting predicted CVD risk upwards by 1.5-fold to 2-fold for individuals with HIV who have HIV-related risk enhancers (7,22,29).

A study characterizing the prevalence of cardiovascular disease, its risk, and the use of aspirin and statins for primary and secondary CVD prevention among people living with HIV was

conducted in South Florida. Results showed that the overall prevalence of CVD among PLWH is high, with myocardial infarction and cerebrovascular disease being higher than previous reports. Patients with CVD were found to be older, have higher median hemoglobin A1C levels, and were less likely to be on ART. The study showed that patients on ART therapy had a 63% reduction in the odds of having documented cardiovascular events, even when controlling for age, sex, diabetes, and smoking history. Results of this study demonstrate a suboptimal utilization of antiplatelet and lipid-lowering agents for primary and secondary prevention of CVD among PLWH (30).

Another review discusses the use of statins in PLWH. While several statins are approved by the FDA, their use in PLWH is complicated by complex interactions with antiretroviral therapy. Multiple studies have demonstrated the efficacy of statins in reducing cholesterol levels in PLWH, with a recent meta-analysis showing that statin treatment effectively reduced total cholesterol, LDL-C, and non-HDL-cholesterol. In addition to reducing cholesterol levels statins have immunomodulatory effects, decreasing monocyte and T-cell activation and reducing inflammation in people living with HIV. Statin therapy has also been shown to reduce key proteins associated with coagulation, oxidative stress, glucose metabolism, and redox signalling, all of which are involved in the development of CVD (31).

Regarding behavioral interventions for cardiovascular disease prevention a review of 18 studies was made. The interventions were grouped into three categories: physical activity, weight loss, and dietary interventions. Multicomponent interventions were the most common, combining physical activity and healthy dieting. Overall, the review found that multicomponent interventions were the most effective in preventing CVD. The authors suggest that incorporating AHA's Simple 7 metrics for sustained cardiovascular health into lifestyle, CVD incidence and premature deaths can be reduced. AHA's Simple 7 metrics includes four modifiable factors (smoking, weight control, healthy diet, and physical activity) and three measures (blood pressure, cholesterol and blood sugar). The authors call for larger scale behavioral clinical trials on CVD prevention in PLWH to inform effective strategies for behavioral prevention and management (32,33).

Use of injection drugs is important contributor to the risk of HIV. A study discusses on how inflammation in people who inject drugs contributes to comorbidities. The ACCESS study found that high intensity heroin use was a risk factor for HIV viral rebound, which could result in heightened risk for non-AIDS related events through enhanced systemic inflammation. The

rise in opioid-related deaths highlights the importance of targeted efforts to engage and empower people with opioid use disorders to seek treatment. Medication-assisted treatment is a viable option that involves harm reduction and the diminution of cravings and withdrawal symptoms (34).

### 3.6 Future approaches

There is a need for more research to identify optimal strategies to reduce the risk of thrombosis in HIV patients, especially in areas where the burden of both cardiovascular disease and HIV is high. Lifestyle modifications, such as smoking cessation, a healthy diet, and managing risk factors like diabetes, hypertension, and dyslipidemia, should also be emphasized. Guideline-based statin therapy is underutilized for PLWH, but efforts are underway to address treatment disparities. Anti-inflammatory strategies to decrease the risk of cardiovascular disease in HIV patients, particularly those with intestinal barrier dysfunction or co-infections, are worth investigating. Early initiation of ART and the cardiovascular risks associated with newer ART regimens also require further study. Additionally, there is a need for deeper clinical phenotyping of heart failure presentations and triggers, as well as a more complete estimation of the prevalence and severity of peripheral artery disease among people with HIV. Mechanistic studies could help evaluate mediators of peripheral artery disease and sudden cardiac death, beyond traditional risk factors for atherosclerosis. The disparity in heart failure outcomes for people with HIV and the importance of public education about the signs and symptoms of peripheral artery disease must be researched further to reduce avoidable amputations (1,35).

In addition to that further studies are needed to understand the underlying mechanisms and to evaluate whether immune changes occur as a consequence of persistent immune activation and chronic inflammation or whether early metabolic perturbations exacerbate chronic inflammation. Longitudinal studies may provide unique insights into these intriguing questions (13).

### 3.7 Practical implications

People living with HIV are a vulnerable population facing structural and socioeconomic barriers to optimal healthcare services. Understanding and addressing cardiovascular disease in PLWH requires recognizing the systematic barriers perpetuating disparities in care delivery, such as education level, residential location, healthcare literacy, disenfranchisement from the healthcare system, cognitive impairment, substance abuse, stigma, and social isolation. These factors can be intensified by disparities in care based on age, race, ethnicity, sex, and

transmission routes. PLWH have been found to have fewer clinic visits and receive less guideline-directed medical therapy for CVD. Disparities in CVD prevention and management for PLWH result in greater risk for MI and other cardiovascular complications.

The infrastructure and strategies developed for HIV care and research can be leveraged for better prevention and treatment of CVD in PLWH. There is a need for investment and attention in improving the quality of care, including longer visit times, care coordination, multidisciplinary team engagement, and targeted implementation research aimed at delivering integrated cardiovascular preventive and therapeutic care. Models of integration of primary care and HIV services have been shown to be effective. (3,6,15).

The underestimation of CVD risk in PLWH by established risk prediction models, can lead to delayed implementation of preventive measures. Even with suboptimal risk stratification strategies, implementation of CVD prevention is limited in HIV clinics worldwide. While awaiting data from the ongoing REPRIEVE trial, primary CVD prevention in PLWH should focus on identifying high-risk individuals, implementing interventions on dietary and lifestyle factors, and using lipid-lowering therapies when indicated (25).

Integrating health services for non-communicable diseases and HIV/AIDS has potential benefits. Review of studies that reported service integration for HIV/AIDS with coronary heart diseases, chronic CVD, cerebrovascular diseases (stroke), hypertension, or diabetes was conducted. The authors suggest that integration should build on existing protocols and use the community as a locus for advocacy and health services, while promoting multidisciplinary teams and greater involvement of pharmacists (36).

## 4. CONCLUSIONS

Cardiovascular disease is a major cause of morbidity and mortality among people living with HIV. While antiretroviral therapy has significantly improved the life expectancy, it has also contributed to an increased risk of cardiovascular disease due to various factors such as chronic inflammation and immune activation associated with HIV infection. Traditional risk factors for cardiovascular disease, such as smoking, hypertension, and diabetes, as well as metabolic complications such as dyslipidemia and insulin resistance, also increase the risk of cardiovascular disease in people living with HIV.

Studies have shown that HIV-positive individuals accumulate age-related diseases at a younger age and may develop acute coronary syndromes earlier than HIV-negative individuals. The risk

factors and prevalence of cardiovascular disease vary by geographical location and HIV prevalence. HIV-positive individuals also have higher rates of subclinical cardiac mechanical dysfunction and the presence of myocardial abnormalities.

While newer antiretroviral therapy regimens may have fewer negative cardiovascular effects, high adherence to antiretroviral therapy is still crucial in preventing cardiovascular disease. Lifestyle interventions such as smoking cessation, limiting alcohol consumption, regular physical activity, and a healthy diet can improve cardiometabolic health and reduce the risk of cardiovascular disease. Other potential pharmacological preventive strategies for cardiovascular disease in people living with HIV include statins, PCSK9 inhibitors, aspirin, antithrombotic therapy, and anti-inflammatory therapies. Regarding interventional procedures percutaneous coronary intervention and coronary artery bypass graft surgery are safe and effective for people living with HIV. Implantable cardioverter-defibrillator therapy and transplantation or left ventricular assist device implantation may be necessary.

Assessing cardiovascular disease risk in people living with HIV is challenging due to limited data and unique risk factors associated with HIV infection. New biomarkers and risk factors are being studied, but none are currently recommended for routine use. Despite national HIV programs and risk reduction strategies, utilization of preventive medication and achievement of cholesterol and blood pressure targets are suboptimal in both HIV-positive and HIV-negative individuals.

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