Am J Cardiovasc Dis 2023;13(2):101-121
www.AJCD.us /ISSN:2160-200X/AJCD0147156

Review Article

The epidemiology, mechanisms, diagnosis and treatment of cardiovascular disease in adult patients with HIV

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Received October 21, 2022; Accepted March 22, 2023; Epub April 15, 2023; Published April 30, 2023

Abstract: More than 1.2 million people in the United States have Human Immunodeficiency Virus (HIV) infections but 13% of these people are unaware of their HIV infection. Current combination antiretroviral therapy (ART) does not cure HIV infection but rather suppresses the infection with the virus persisting indefinitely in latent reservoirs in the body. As a consequence of ART, HIV infection has changed from a fatal disease in the past to a chronic disease today. Currently in the United States, more than 45% of HIV+ individuals are greater than 50 years of age and 25% will be greater than 65 years of age by 2030. Atherosclerotic cardiovascular disease (CVD), including myocardial infarction, stroke, and cardiomyopathy, is now the major cause of death in HIV+ individuals. Novel risk factors, including chronic immune activation and inflammation in the body, antiretroviral therapy, and traditional CVD risk factors, such as tobacco and illicit drug use, hyperlipidemia, the metabolic syndrome, diabetes mellitus, hypertension, and chronic renal disease, contribute to cardiovascular atherosclerosis. This article discusses the complex interactions involving HIV infection, the novel and traditional risk factors for CVD, and the antiretroviral HIV therapies which can contribute to CVD in HIV-infected people. In addition, the treatment of HIV+ patients with acute myocardial infarction, stroke, and cardiomyopathy/heart failure are discussed. Current recommended ART and their major side effects are summarized in table format. All medical personnel must be aware of the increasing incidence of CVD on the morbidity and mortality in HIV infected patients and must be watchful for the presence of CVD in their patients with HIV.

Keywords: HIV cardiovascular complications, HIV novel risk factors, acute myocardial infarction, cardiomyopathy, heart failure, stroke, antiretroviral therapy, antiretroviral side effects

Introduction and epidemiology

The Human immunodeficiency virus was first isolated and identified in 1983 [1, 2]. Since 1983, human immunodeficiency virus 1 (HIV) has infected 84.2 million people and has contributed to the death of more than 40.1 million people in the world [3]. Currently, an estimated 1.2 million people in the United States have HIV infections but more than 13% of these people are unaware of their HIV infection [4]. People living with HIV who are unaware of their HIV infection constitute a hidden epidemic and are most responsible for new infections. Currently, 35,000 new HIV infections occur each year. Twenty-nine percent of newly diagnosed individuals with HIV have advanced infections with CD4 cell counts <200 cells/mm^3 [5]. If the infection is not treated, the HIV can cause an acquired immunodeficiency syndrome (AIDS), in which progressive failure of the body's immune system allows life-threatening opportunistic infections and cancers to occur and flourish.

The discovery and widespread utilization of combination antiretroviral therapy (ART) has transformed HIV infection from a progressively fatal disease in the 1980s into a chronic disease today. Currently, the life expectancy of a 20-year-old HIV+ adult on ART is 70 years [6]. To date, more than 40 antiretroviral drugs are approved by the U.S. Food and Drug Administration for HIV treatment.

At the end of 2021, 28.7 million people worldwide with known HIV had access to ART [7]. An

increased awareness of HIV and wide-spread administration of ART has led to a significant decrease throughout the world in AIDS and the number of adults dying from HIV-related causes. In 2021, 650,000 people died throughout the world of HIV-related illnesses which represents a 68% decrease in mortality from the peak of HIV mortality in 2004 [8]. However, ART does not cure HIV but rather suppresses the HIV infection in patients. The HIV persists indefinitely in latent viral reservoirs in lymphoid tissue in the body and can reemerge in the circulation with interruption of ART.

While many people living with HIV today are young people, the percentage of patients with HIV who are more than 50 years in the U.S. has risen to more than 45% due to ART [9]. The median age of HIV+ patients treated with ART in the United States will increase to 53 years in 2030 and 25% will be greater than 65 years [9]. Many of these individuals will have atherosclerotic cardiovascular disease (CVD) due to HIV, ART, and CVD traditional risk factors. In this regard, in patients with HIV, the incidence of CVD morbidity and mortality has significantly increased [10-13]. In a meta-analysis of 793,635 people living with HIV with a total of 3.5 million person-years of follow-up, the global burden of HIV-associated CVD has almost tripled during the past 20 years and has accounted for 2.6 million disability-adjusted life-years per year [12]. Unfortunately, subclinical cardiac dysfunction in patients living with HIV is often present but not diagnosed and therefore not treated. By the year 2030, an estimated 78% of individuals living with HIV will have subclinical or clinical CVD [14]. Atherosclerotic cardiovascular disease, including acute myocardial infarction, cardiomyopathy and heart failure, stroke and sudden cardiac death, are currently the major causes of death and will continue to be the major causes of death in individuals with HIV in the future [11-13, 15].

The etiology of the increased prevalence of cardiovascular disease in HIV+ people is the result of complex interactions among HIV-specific factors (i.e. chronic infection, immune activation and chronic inflammation), traditional CVD risk factors (i.e. tobacco or illicit drug use, obesity and dyslipidemia, diabetes mellitus, and hypertension), treatment with ART, and disparities in access to healthcare. HIV+ black women and men have the largest multi-morbidity burden including cardiovascular disease, obesity, hypertension, diabetes, and renal disease [16].

This articles discusses the epidemiology, the mechanisms, the diagnosis, and the treatment of cardiovascular disease in adult patients with HIV. All medical personnel must be aware of the increasing incidence of CVD on the morbidity and mortality in HIV infected patients and watchful for the presence of CVD in their patients with HIV.

HIV infection

The transmission of HIV occurs with the actions listed in **Table 1**. **Table 1** is adapted in part from [3, 4].

HIV replication cycle

The stages of the HIV life cycle are: 1) Cell Fusion, 2) Reverse Transcription, 3) Integration, 4) Replication, 5) Assembly, and 6) Budding. **Figure 1** represents a basic illustration of the HIV replication cycle and is courtesy of www.niaid.nih.gov/diseases-conditions/hiv-replication-cycle [17] and NIAID Flickr site.

The HIV replication cycle begins when HIV directly fuses with the surface of the host CD4 cell, macrophage or dendritic cell or undergoes clathrin-mediated endocytosis and enters the cell. See 1 in **Figure 1**. A capsid containing the virus's genome and the proteins reverse transcriptase, integrase, ribonuclease, and protease then enter the cell. See 2 in **Figure 1**.

Within the infected cell, the shell of the HIV capsid disintegrates and the HIV protein reverse transcriptase transcribes the HIV RNA into DNA [17, 18]. See 3 in **Figure 1**. However, the process of reverse transcription is prone to errors and results in transcription mutations that ultimately allow the virus to evade the body's immune system and also cause drug resistance. The viral DNA is transported into the cell nucleus, where the HIV protein integrase integrates the HIV DNA into the host's DNA. See 4 in **Figure 1**. The virus can become latent, allowing HIV and its host cell to avoid detection by the immune system for a variable time and viral latency is a significant barrier to the eradication of the HIV [17]. Alternatively, the cell's normal transcription machinery can transcribe the HIV

Table 1. Causes of HIV transmission

Causes of HIV transmission
● Unprotected oral, vaginal or anal sex with an individual who has an active HIV infection and transfers blood, semen, or vaginal fluids during sexual intercourse. Within these bodily fluids, HIV is present as both free virus protein particles and virus within infected immune cells.
● The sharing of hypodermic needles, syringes, rinse water, or other equipment used to prepare and inject illicit drugs into the body.
● The transfer of HIV from an infected mother to a child during pregnancy, birth, or breast-feeding.

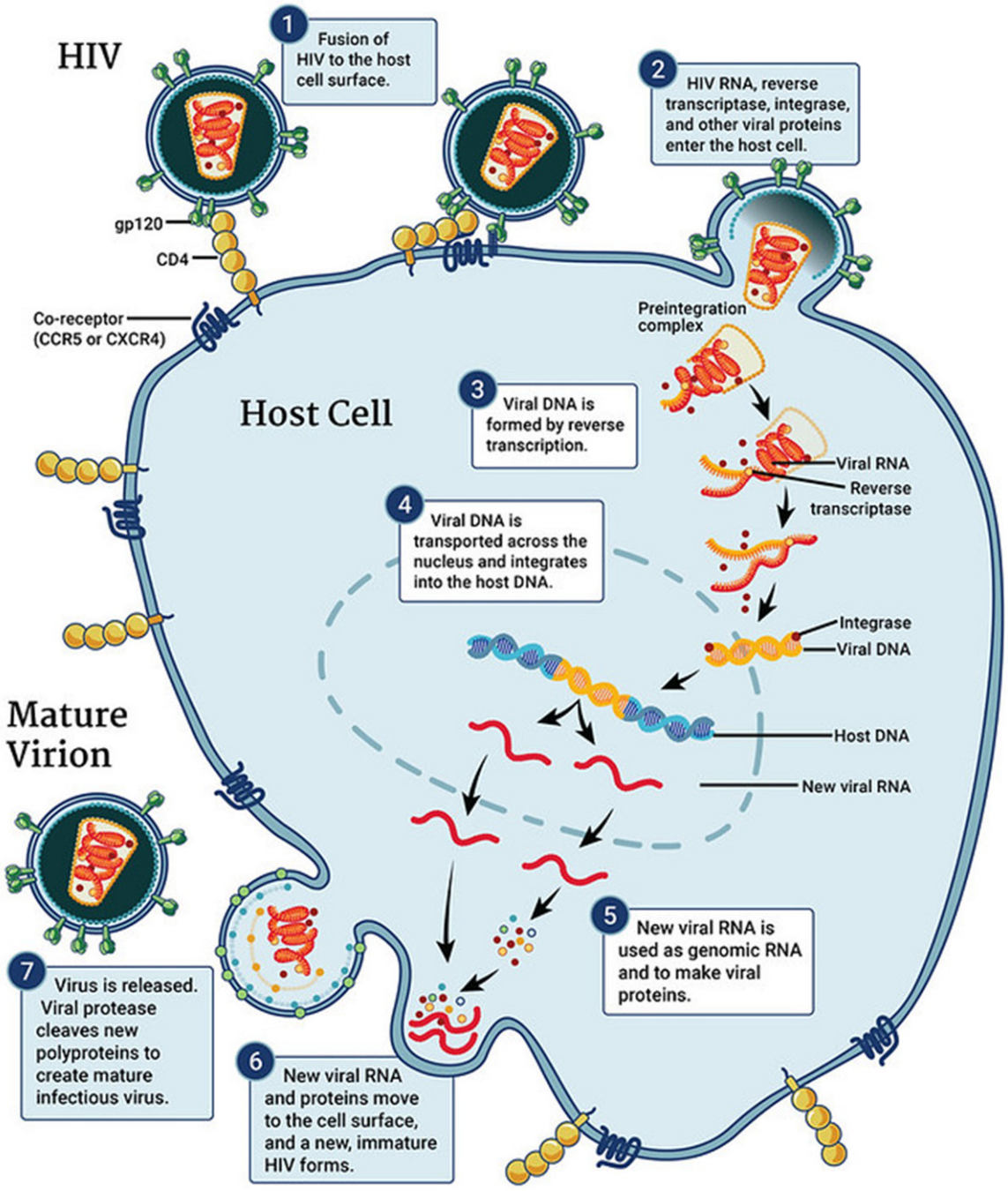

Figure 1. HIV replication cycle.

DNA into multiple copies of new HIV RNA. Some of this RNA becomes the genome of a new virus, while the cell uses other copies of the RNA to make new HIV proteins, such as reverse transcriptase, integrase, ribonuclease, and protease. See 5 in **Figure 1**. The new viral RNA and HIV proteins move to the surface of the cell, where a new HIV is encapsulated. See 6 in **Figure 1**. Finally, the HIV protein protease cleaves the newly synthesized structure to create an infectious virus that is released from the cell into the circulation to begin a new replication cycle in another cell. See 7 in **Figure 1**. HIV can also disseminate by direct transmission from one cell to another cell by a process of cell-to-cell spread, involving an infected CD4 cell to a CD4 cell, or an infected macrophage or an infected dendritic cell to a CD4 cell.

The HIV regeneration cycle generates approximately 10^{10} virions/day [18]. HIV infection is diagnosed by blood specimens from an infected individual that are repeatedly reactive by enzyme-linked immunosorbent assay for HIV antibody and positive by immunofluorescence assay (IFA) for HIV antibody, or polymerase chain reaction (PCR) for HIV RNA or reactive by western blot for HIV antibody protein.

The HIV causes a reduction in the numbers of $CD4^+$ cells through pyroptosis of infected T cells, direct killing of infected cells, killing of infected $CD4^+$ cells by $CD8^+$ cytotoxic lymphocytes, and apoptosis of uninfected bystander cells [14]. When $CD4^+$ cell numbers decrease to less than 400 cell/mm^3, cell-mediated immunity is decreased then lost, and the body becomes progressively more susceptible to opportunistic infections and cancer with the development of AIDS.

HIV mechanisms contributing to cardiovascular disease: novel and traditional risk factors

The etiology of the increased prevalence of CVD in HIV-infected people is the result of complex interactions among the viral infection, novel and traditional risk factors, and ART for HIV.

Novel HIV risk factors contributing to cardiovascular disease

Viral infection per se and ART are contributors to vascular endothelial dysfunction and subsequent CVD as evidence by the fact that the prevalence of CVD is 50% higher in people with HIV after adjustment for blood lipids, blood pressure, and tobacco use [19]. HIV infection is accompanied by chronic immune activation and chronic inflammation due to persistent virus in the body even in ART treated patients and is also due to opportunistic infections. HIV+ individuals often have co-infection with cytomegalic virus (CMV) and high CMV antibody, herpes simplex virus and varicella-zoster virus titers that are also associated with chronic inflammation [14].

The constant activation of monocytes, macrophages and CD8 T cells due to immune activation in HIV+ individuals results in circulating proinflammatory and profibrotic cytokines such as Interleukin (IL)-1β, IL-6, soluble Tumor Necrosis Factor α Receptor 1 (sTNF-αR1), sTNF-αR2, monocyte chemotactic factor (CCL2), soluble cluster of differentiation (CD) 163, soluble CD14, and intercellular adhesion molecule-1 (ICAM-1) which cause chronic inflammation [20]. These proteins contribute to vascular endothelial dysfunction, hypercoagulation, vascular thrombosis, excessive collagen production, fibrotic left ventricular (LV) remodeling and hyperlipidemia which ultimately results in CVD. In addition, circulating macrophages activate caspases, tumor necrosis factor- (TNF-) alpha, and Fas ligand expression which contribute to myocyte apoptosis and CVD [21].

HIV infection and/or treatment with ART can cause visceral obesity, or lipohypertrophy, which is a source of chronic inflammatory adipokines and a contributor to CVD. The adipokines leptin and resistin, as well as cytokines IL-6, and monocyte chemoattractant protein (CCL2) chemoattract monocytes/macrophages and contribute to free oxygen radical formation, systemic tissue inflammation, abnormal lipid metabolism, insulin resistance, endothelial dysfunction, and hypercoagulability.

The gastrointestinal tract also plays an important role in the pathophysiology of HIV infection and CVD. HIV preferentially infects CD4 T cells, many of which are located in gut mucosa. The loss of these CD4 T cells increases the gastrointestinal intestinal permeability to bacteria and lipopolysaccarides (LPS). The bacteria and lipopolysaccharides promote an inflammatory cascade that activates the sympathetic ner-

vous system and the renin-angiotensin-aldosterone system through production of free oxygen radicals, vascular endothelial damage, and the peripheral increase of endothelial angiotensin receptors [13]. As a consequence, there is vascular inflammation, vasospasm and increased vascular permeability, which are precursors and major contributors to CVD. Intestinal damage and bacterial translocation persist even when HIV infection is suppressed by ART.

The HIV viral proteins, trans-activator of transcription (Tat), glycoprotein-120 (gp120), and Negative regulatory factor (Nef) also cause immune activation and contribute to inflammation and CVD. See **Figure 1**. Extracellular Tat forms a cell entry complex that increases the virus infectivity of cells and the HIV reproduction number [22-24]. Tat activates vascular endothelial cell receptors to increase endothelial cell adhesion, cell permeability, cytokine production, and apoptosis [23, 24]. In addition, Tat upregulates BCL2 in infected macrophages and renders these cells resistant to cytotoxic lymphocyte killing [22]. Tat protein also induces the expression of CCL2, which attracts monocytes to injured vascular endothelium and the secretion of proinflammatory tumor necrosis factor alpha (TNF-α), nuclear factor kappa-B (NF-κB) and interleukin-6 (IL-6) and IL-1β which produce oxidative stress in the vascular endothelium and vascular damage. Moreover, Tat attenuates the expression of the mitochondrial superoxide scavenger manganese-superoxide dismutase. IL-1β can induce macrophage and foam cell apoptosis with the release of their lipid content into the intima of the artery and, in this manner, contribute to the lipid core in atherosclerotic plaques [24]. Tat also promotes endothelial cell senescence and dysregulation of senescence-associated microRNAs [24].

Gp120 is essential for HIV entry into cells and plays a vital role in attachment to specific cell surface receptors. In addition, gp120 accumulates in lymphoid tissues where the protein can induce apoptosis and severely decrease the immune response to the virus by dampening the antiviral cytotoxic lymphocyte response. In this manner, gp120 impedes the clearance of HIV. In the cardiovascular system, gp120 protein induces macrophage activation, increases the synthesis of TNF-α and oxidative stress, and stimulates endothelin 1 production with resultant vascular spasm [13, 23].

Negative factor (Nef) is involved in modulation of protein trafficking and cell signaling pathways, the attenuation of HIV antibody maturation in B cells, and an increase in HIV infectivity [24]. Nef enhances viral replication and promotes immune escape of HIV-infected cells by reducing the surface MHC-I A and B molecules of infected cells, thereby allowing infected cells to escape detection by cytotoxic T cells. In addition, Nef expressing T cells exhibit increased adherence to endothelial cells and can cause endothelial cell apoptosis. Nef proteins also facilitate the transformation of macrophages into foam cells, which contribute to vascular atherosclerotic plaque formation [23, 25]. In addition, Nef alters endothelial cell cholesterol homeostasis through phosphorylation of Caveolin-1 (Cav-1), leading to Cav-1 redistribution and impairment of HDL-mediated cholesterol efflux in endothelial cells [25, 26]. The interactions of the foam cells with endothelial cells contribute to endothelial dysfunction and facilitate the development of atherosclerosis. Consequently, HIV viral proteins Tat, gp120, and Nef can significantly contribute to vascular endothelial and ventricular dysfunction, myocardial infarction, cardiomyopathy, heart failure, and stroke.

Figure 2 summarizes the important pathways by which HIV can cause CVD. **Figure 2** is adapted in part from [27, 28].

Specific information on the contribution of ART to CVD in HIV+ patients is not entirely consistent due, in part, to the heterogeneity of the HIV patient population, observations made during first generation ART versus later generation ART, and the fact that two to as many as four ART drugs are now given simultaneously to HIV+ patients. Nevertheless, support exists for the contribution of ART to CVD [19, 21, 29]. The three major classes of ART, which include protease inhibitors (PIs), nucleoside reverse transcriptase inhibitors (NRTIs), and nonnucleoside reverse transcriptase inhibitors (NNRTIs), can be associated with hyperlipidemia. Protease inhibitors can increase LDL-C concentration primarily due to increased cholesterol absorption from the intestinal tract [30, 31]. The protease inhibitors, ritonavir, atazanavir and darunavir, and the NRTIs, stavudine and zidovudine

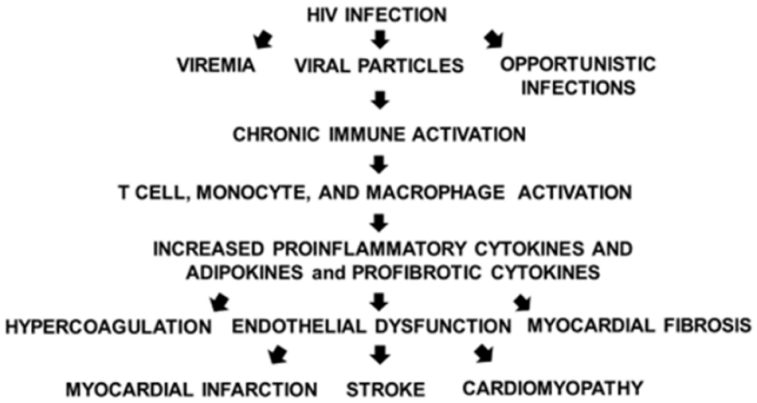

Figure 2. HIV pathways that contribute to cardiovascular disease.

can increase plasma lipid concentrations and cause insulin resistance, and in this manner contribute to the development of CVD [14, 21, 32]. The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study also reports an increased risk of atherosclerotic coronary artery disease and myocardial infarction in patients treated with the NRTIs abacavir and didanosine [21]. In addition, ARTs can increase carotid intima-media thickness, carotid and coronary vascular stenosis, and decrease flow mediated vascular dilation and blood flow [19, 32-35]. Furthermore, ART regimens containing the NRTi zidovudine have been implicated in HIV-associated cardiomyopathy [34]. Consequently, all medical personnel who treat HIV+ patients with ART must be vigilant for the development of hyperlipidemia, vascular endothelial dysfunction, and CVD in their patients.

The presence of novel risk factors accounts for approximately 50% of the increased risk for CVD in HIV+ people while the remaining 50% of the CVD risk is due to traditional risk factors [19, 36, 37].

Traditional risk factors contributing to cardiovascular disease

Individuals with HIV have an increased incidence of traditional cardiovascular risk factors including tobacco and illicit drug use, hyperlipidemia, the metabolic syndrome, diabetes mellitus, hypertension, and chronic renal disease [38]. These traditional risk factors often occur in clusters and significantly contribute to the increased risk for CVD. In a meta-analysis of studies of HIV positive patients, 46% used tobacco products, 22% had hyperlipidemia, and 19% had hypertension [39]. In a separate study of HIV+ US Veterans, 73% had one or more traditional CVD risk factors and only 2% had optimal cardiac risk profiles [37]. In this study, the incidence of acute myocardial infarction (AMI) increased significantly with each additional major CVD risk factor [37]. Hypertension is present in as many as 35% of HIV+ people on ART and in 50% of HIV+ individuals older than 50 years [13]. Moreover, a prospective study of 21,338 HIV+ United States military veterans found that HIV+ adults with hypertension have a greater than twofold risk of acute myocardial infarction in comparison with HIV– adults with hypertension [40, 41]. Furthermore, HIV+ patients with moderate visceral obesity have a fourfold increase in hypertension compared with patients without visceral obesity [42]. The mechanisms that contribute to hypertension and ultimately CVD in obese individuals include activation of the renin-angiotensin-aldosterone system by circulating adipokines/cytokines [28]. Obese HIV+ patients also have an increased incidence of diabetes mellitus. In this regard, one in ten HIV+ adults has diabetes mellitus and the prevalence of diabetes is 3.8% higher than the prevalence in the general population [43].

Tobacco use is highly prevalent among HIV+ individuals and more than 40% of HIV+ individuals use tobacco. In these individuals, nicotine mediates local and systemic catecholamine release and, in this manner, increases blood pressure, heart rate, and CVD. Consequently, there is an almost threefold increase in risk of myocardial infarction in current HIV-infected smokers as compared with HIV-infected nonsmokers [44]. In addition, HIV-infected individuals who smoke tobacco live eight years less than HIV-nonsmokers [44]. Both tobacco users and nontobacco users with HIV also consume large quantities of alcohol which is associated with hypertension as well as decreased host immunity, malnutrition, increased HIV disease progression and transmission, and decreased ART efficacy [14, 28]. In people with HIV, the presence of traditional and novel risk factors

significantly contributes to accelerated atherosclerosis and CVD.

HIV & cardiovascular disease

HIV-associated atherosclerotic CVD: vascular atheroscerosis, myocardial infarction, and stroke

HIV+ men in comparison with HIV– men demonstrate an increased incidence of coronary atherosclerosis (59% vs. 34%), higher coronary plaque volume (55.9 µl vs. 0 µl), greater number of coronary segments with plaque formation (1 vs. 0 segments), and higher Agatston coronary calcium scores greater than 0 (46% vs. 25%), despite similar Framingham 10-year risk for myocardial infarction and family history of coronary artery disease [45]. In addition, the duration of the HIV infection is significantly associated with coronary plaque volume and the number of segments with coronary plaque. These relationships remain significant after adjustment for the individual age and traditional risk factors [45]. Moreover, the antiretroviral drugs indinavir, lopinavir-ritonavir, abacavir, and didanosine are associated with an increased risk of myocardial infarction [21, 46].

In HIV+ individuals, the incidence of acute coronary syndromes (ACS) is 3.88 per 1000 patient-years in comparison with 2.21 per 1000 patient-years in HIV– patients [47]. Moreover, the ACS in people with HIV often occur ten years earlier than in people without HIV. In people who do experience a MI, the one-month mortality can be as high as 20% [48]. Furthermore, the recurrence of an ACS within 12 months of the initial event is 6 or more times more frequent among HIV+ people [49]. The excess recurrence rates of ACS are predominantly driven by episodes of unstable angina due to new coronary artery obstructive lesions from accelerated coronary atherosclerosis [49].

Women with HIV have twice the risk of MI compared with HIV-infected men [50, 51]. Pathological mechanisms in HIV+ women that are responsible for this disparity include greater tobacco use, possible reduced ART effectiveness, persistent increased immune activation and systemic inflammation, larger numbers of nonwhites, poorer economic status, and limited access to health care [19]. Immune activation in HIV+ women is associated with a greater increase in inflammatory chemokine CXCL10, CD163 macrophages, and CD14+ CD16+ monocytes in comparison with HIV+ men [51]. In addition, HIV+ women have a greater incidence of coronary artery non-calcified plaques that are susceptible to rupture or erosion. In 60 HIV+ women, whose ages ranged from 18 to 60 years and who were without symptoms or history of CVD, 75% of their coronary artery segments had non-calcified plaque. In comparison, 102 HIV+ men had 50% of the coronary segments with non-calcified plaque and 41 HIV negative males had 33% of the coronary segments with non-calcified plaque [51]. Consequently, the risk of CVD complications is high in HIV+ women and men due to plaque rupture or erosion and artery thrombosis. In addition, HIV+ women and men with ≥500 HIV RNA copies per ml blood, $CD4^+$ T cell counts <200/mm^3, and low CD4/CD8 ratios that are persistent have an increased risk for CVD complications [3, 4].

In HIV infected women and men, Type 2 myocardial infarctions (T2MI) are more frequent than Type 1 MIs (T1MI) [20, 52-54]. T2MI in these patients result from increased myocardial oxygen demand or decreased myocardial oxygen supply which is often due to opportunistic infections with bacteremia (35%), illicit drug use (14%), hypertensive urgencies or emergencies (10%) and respiratory distress and failure (9%) [52]. Patients with T2MI are more commonly black and are less likely to consistently take ART than patients with T1MI [52]. Type 1 MIs result from atherosclerotic plaque rupture or erosion and occur in older HIV+ patients who are often white males with comorbidities such as hypertension and/or renal disease. Patients with AIDS and MIs have longer hospitalizations, higher rates of respiratory failure and requirements for mechanical ventilation, and greater mortality rates in comparison with MI patients with HIV but without AIDS [55].

During hospitalization for MIs, HIV+ patients have lower rates of AHA/ACC and ESC guideline directed MI care, longer lengths of hospitalization, and higher hospital costs [55, 56]. HIV+ patients with T1MI are less likely to undergo early percutaneous coronary intervention and less likely to receive drug-eluting stents after a MI compared with HIV negative patients [56].

Moreover, HIV+ individuals are less likely to be treated with anti-platelet, antihypertensive or lipid lowering medications after a first MI than are HIV negative patients [48, 52].

During the first year after an acute coronary syndrome, HIV+ patients experience a high rate of recurrent ACS, predominantly due to accelerated coronary atherosclerosis and new coronary artery obstructive lesions, and have an increased rate of heart failure requiring hospitalization [49]. The recurrent ischemic events are predominantly due to unstable angina and often require urgent percutaneous coronary angioplasty for relief of symptoms.

In HIV+ patients with MI, mortality rates after T2MI are significantly greater with 1-, 3-, and 5-year mortality rates of 39%, 52%, and 62% in comparison with patients with T1MI with mortality rates of 1-, 3-, and 5-year rates of 15%, 22%, and 30%, respectively [52]. Patients with T2MI and T1MI who do die during follow-up often have high HIV viral loads and renal dysfunction [52]. Moreover, among HIV+ people, the incidence of sudden death is twice that in the normal population with 53.3 deaths per 100,000 person-years versus 23.7 deaths per 100,000 person-years among persons without HIV [44, 53]. Forty-six percent of the sudden deaths in the HIV+ individuals are due to myocardial fibrosis and cardiac arrhythmias [53].

Cerebral vascular events: stroke

Stroke is an important cause of functional impairment and is a leading cause of death among individuals with HIV [23]. Between 1% and 5% of patients with HIV develop clinical symptoms and signs of stroke but 4% to as many as 34% of patients who die from complications of HIV have cerebral ischemic infarcts at autopsy examination [57, 58].

In the pre-ART era, the risk of stroke was nine times greater in HIV+ individuals compared to HIV– individuals [23]. The strokes occurred primarily in individuals with advanced AIDS, complicated by tuberculous meningitis, toxoplasmosis encephalitis, fungal meningitis, and neurosyphilis or in those individuals with coagulopathies or vasculitis due to HIV penetrating the blood brain barrier [23, 57, 58].

In the ART era, the incidence of stroke is approximately three times higher in HIV+ individuals than in uninfected individuals [59, 60]. The etiologies of stroke in HIV+ patients on ART include: extracranial or intracranial atherosclerosis in approximately 50%, opportunistic infection in 13 to 28%, coagulopathies in 19 to 49%, vasculopathy in 20 to 32%, and cerebral embolism in 5 to 15% [23, 61]. The etiologies of stroke are dependent on the stage of the HIV infection, the duration of ART, and whether or not ART is actually being taken by the patient.

In patients with HIV, ischemic stroke occurs more frequently than stroke due to cerebral hemorrhage [57]. In 64 HIV+ patients with stroke, partial anterior cerebral circulation occlusion occurred in 33, lacunar strokes in 13, total cerebral circulation occlusions occurred in 11, and posterior cerebral circulation occlusions in 7 [62]. Hemorrhagic stroke occurs in HIV+ patients with AIDS-associated vasculopathy or CNS lymphoma, toxoplasmosis, or tuberculosis [62, 63].

Chronic high circulating HIV numbers and CD4 counts <200 cells/mm^3 significantly increase the risk of stroke, especially in HIV+ women and men in their 30 s and 40 s [23, 64]. In older people with HIV, traditional as well as novel risk factors are common causes of stenotic or dolichoectatic arteries and cerebral artery thrombosis or hemorrhage [28, 60, 65].

During the first 6 months of ART with recovery of the immune system in patients with HIV, thinning and erosion of intracranial arteries can occur and are associated with a high risk of stroke [8, 52, 66]. In addition, ART can increase the risk of stroke by directly contributing to hyperlipidemia and accelerating arterial atherosclerosis and also indirectly by increasing patient life expectancy and age-related morbidities [23]. Prolonged use of protease inhibitors (PIs) such as darunavir and the nucleoside reverse transcriptase inhibitor (NRTI) abacavir can induce cerebral vascular events [23]. Darunavir treatment for greater than 6 years increases the risk of stroke by 1.59 times, even after adjustment for hyperlipidemia and viral load [63]. In addition, darunavir treatment in 39 HIV+ patients for 12 months in the PREVALEAT II trial produced a significant increase in carotid intima-media thickness and the risk of carotid artery stenosis [19, 32]. Furthermore, the protease inhibitor atazanavir can cause cerebral arterial remodeling and the

Table 2. Etiologies, pathophysiology and mechanisms of stroke in HIV+ patients

Stroke Etiologies	Pathophysiology	Stroke Mechanisms
Atherosclerosis	Immune Activation, HIV protein activation, ↑Adhesion Molecules, Chemokines & Cytokines, Oxidative Stress, Endothelial Cell Dysfunction, Hyperlipidemia	Accelerated Atherosclerosis and Vascular Plaque Formation. Inflammation, Coagulopathy, Thrombus Formation, Aneurysm Formation
Infections: HIV, Tuberculosis, Cryptococcus, Toxoplasmosis, Varicella Zoster, Syphilis, Endocarditis Emboli	↑Cytokines, Chemokines, Adhesion Molecules, Chronic Inflammation, Inflammatory Cell Vascular Infiltration, Anticardiolipin, Antiphospholipid Antibodies, Antiprothrombin Antibodies, Coagulopathy	↑Blood Brain Permeability, Large and Small Vessel Disease, Vasculitis, Coagulopathy, HIV Large & Medium Vessel Occlusion, Thrombus Formation, Mycotic Aneurysm, Intracranial Hypertension, Endocarditis
Antiretroviral Therapy	Systemic Inflammation, Endothelial Toxicity and Dysfunction, Hyperlipidemia	Vascular Endothelial Cell Dysfunction, ↑Intima-media Vascular thickness, Plaque Formation, Cerebral Atherosclerosis
Traditional Risk Factors: Hypertension, Diabetes, Hyperlipidemia, Metabolic Syndrome, Tobacco Use, Atrial Fibrillation	Chronic Inflammation, Endothelial and Smooth Muscle Cell Dysfunction, Increased Intraluminal Pressure, Hyperlipidemia	Vascular Remodeling, Accelerated Arterial Atherosclerosis, Thrombosis, Atrial Fibrillation, CNS Emboli
Neoplasm	Lymphoma	CNS Mass Effect, Intracranial Hypertension

non-nucleoside reverse transcriptase inhibitor (NNRTI) efavirenz can increase the permeability of the blood brain barrier and increase stroke severity [23].

Table 2 lists the risk factors, pathophysiology and mechanisms of stroke in HIV+ patients and is adapted in part from [23, 29, 57, 65-67].

The sudden onset of a focal neurological deficit is a common presentation of HIV+ patients with stroke [57]. However atypical stroke presentations can occur and are manifested by migraine type headaches, acute confusion, visual disturbances, fever, paresthesias, acute loss of consciousness, and stepwise focal neurological deficits over hours to days [57]. The mortality rate in HIV patients with acute ischemic stroke is approximately 12% but can be as high as 35% in patients with hemorrhagic stroke [63].

Approximately 15% of HIV+ patients presenting with an acute focal neurologic deficit will have a "stroke mimic" that requires a cranial MRI for diagnosis. Infections that can lead to a stroke mimic include toxoplasmosis infection, progressive multifocal leukoencephalopathy, viral encephalitides due to HIV or to cytomegalovirus, cryptococcoma, lymphoma, tuberculoma, and HIV-associated tumefactive demyelination [61].

HIV-associated cardiomyopathy and heart failure: a multi-factorial process

Prior to the widespread availability of ART, cardiomyopathy and heart failure in HIV+ individuals were primarily due to myocarditis from the direct myocardial effects of HIV, opportunistic infections, autoimmunity, severe immunosuppression, and nutritional deficiencies [21, 68-70]. Opportunistic infections in the pre-ART era included Cytomegalovirus, Epstein-Barr virus, Coxsackie B virus, Toxoplasma gondii, Cryptococcus neoformans, and Mycobacterium avium-intracellulare. The myocarditis caused cardiac dilation, rapidly progressive LV systolic dysfunction and a median survival of approximately 100 days after the initial diagnosis [69-72]. With the development and general availability of ART, the etiologies of cardiomyopathy have changed to include chronic low-grade inflammation due to residual HIV infection with ongoing T cell activation, immune dysregulation with the development of cardiac alpha myosin antibodies, chronic vascular inflammation, accelerated coronary atherosclerosis, poorly controlled hypertension, and ART cardiotoxicity [69, 70]. Currently, HIV+ patients have twice the risk of developing cardiomyopathy with heart failure, either with preserved or reduced LV ejection fraction, compared to HIV– individuals [28]. Among patients with heart failure, approximately 40% have heart failure with reduced ejection fraction (HFrEF) and approximately 40 to 50% have heart failure with preserved ejection fraction (HFpEF) or borderline HFpEF [52].

Table 3 summarizes the common etiologies for cardiomyopathy in HIV and is adapted from [21, 69, 70].

Table 3. Common etiologies for cardiomyopathy in HIV

HIV Status	Cardiomyopathy Etiology	Cardiomhopathy Phenotype
UNTREATED, UNCONTROLLED or POORLY TREATED HIV	Myocarditis/Myopericarditis, HIV toxicity, Opportunistic Infections Macro- and Micronutritional Deficiencies: thiamine, carnitine, taurine, selenium, niacin, coenzyme Q10	Ventricular Enlargement, LV Systolic Dysfunction, ⬇LV Ejection Fraction and Global LV Myocardial Strain
ART TREATED HIV	Myocardial Inflammation, Atherosclerosis, Anti-Myosin Antibodies, ART	LV Diastolic Dysfunction, ⬇LV Relaxation and Compliance

The incidence of HIV– associated cardiomyopathy ranges from 9% to as much as 64% in HIV+ patients in low and middle income countries [28, 70, 73]. Moreover, HIV+ women develop cardiomyopathy and heart failure four times more often than HIV– women, have more frequent hospitalizations (42 vs. 9 per 100 person years), and have greater all-cause mortality (53 vs. 21% and cardiovascular mortality (83 vs. 33%) than HIV– women [74].

Once heart failure is established, there is a four-fold increased risk of being admitted to the hospital for decompensated heart failure and a three-fold increase in cardiovascular mortality [75, 76]. The incidence of sudden death in patients with cardiomyopathy and heart failure is four-fold greater than the expected rates in the general population and is often associated with CD4 counts of <200 cells/mm^3 and high viral loads [52, 75, 76].

The pathophysiology of cardiomyopathy and heart failure involves LV dysfunction with decreased LV global longitudinal strain due to inflammation, myocardial fibrosis, steatosis, and ART [75-77]. Despite ART treatment, HIV+ patients continue to have T cell activation, increased plasma β2-microglobulin, IL-8, tumor necrosis factor alpha (TNF-α), and soluble intercellular adhesion molecules that contribute to LV inflammation, vascular thrombosis, myocardial fibrosis, and cardiomyocyte apoptosis [69]. In addition, the HIV viral proteins decrease mitochondrial function and increase nitric oxide production which cause myocyte injury and decrease myocardial contractility [21, 69]. Increased TNF-α, IL-1, IL-6, and HIV glycoprotein 120 also lead to excess production of cardiac nitric oxide which decreases LV contractility and contributes to ventricular remodeling.

Long term treatment with ART, especially protease inhibitors such as ritonavir and lopinavir, is a risk factor for hyperlipidemia and epicardial and myocardial steatosis, especially in HIV+ women [28, 78, 79]. In addition, ART regimens containing the NRTi zidovudine also have been implicated in HIV-associated hyperlipidemia and cardiomyopathy [36]. Epicardial steatosis is associated with increased coronary artery calcification and stenosis [78, 80]. Myocardial steatosis, including toxic triglyceride intermediates, contribute to myocyte apoptosis, cardiomyopathy and heart failure, and correlates inversely with LV diastolic function [27, 28, 79, 81].

Symptoms and signs of cardiomyopathy and heart failure commonly include fatigue/lethargy shortness of breath and orthopnea in patients with jugular venous distension, peripheral edema, and weight gain. Cardiac imaging plays an integral role in the assessment of HIV+ patients who present with cardiomyopathy and symptoms and signs of heart failure. On cardiac magnetic resonance (CMR) imaging and spectroscopy, HIV+ patients with cardiomyopathy and heart failure have increased myocardial fibrosis and LV remodeling, which is associated with increased adverse cardiovascular events and sudden death [52, 82, 83]. Late gadolinium enhancement on CMR, which is indicative of fibrosis, is most frequently visualized in the septum, posterior, and lateral segments of the base and mid-left ventricle [3]. In a CMR and spectroscopy study of 90 HIV+ patients on ART, 76% had myocardial fibrosis predominantly in the basal inferolateral wall and 47% had increased myocardial lipid concentrations [77]. The myocardial fibrosis and steatosis was associated with decreased peak myocardial strain. Similarly, in a separate CMR study that compared 28 HIV+ patients on ART for approximately 9.7 years with 27 HIV– individuals, the HIV+ patients showed lower LV ejection fractions and LV global strain values [84]. In addition, myocardial fibrosis was pres-

ent in 82.1% of HIV+ patients, but only in 27.3% of HIV– patients. Significantly, CMR parameters indicating myocardial inflammation were increased in HIV+ patients as measured by native T1 relaxation times, relative T2 signal intensity ratios, and early gadolinium enhancement ratios [84].

The use of echocardiography in the HIV Heart Study of 698 HIV+ patients demonstrated that 34% of the patients had systolic dysfunction and 48% had LV diastolic dysfunction that was associated with increased left atrial size, increased LV end-diastolic pressure, and decreased LV compliance [85]. In addition, the Multicenter AIDS Cohort (MACS) study demonstrated that men with HIV who underwent echocardiographic examinations had larger LV mass, RV size and higher rates of RV dysfunction compared to HIV– men [86]. Right ventricular dysfunction on multimodality imaging also occurs frequently in patients with dilated cardiomyopathy or in patients with HIV associated pulmonary hypertension and is associated with increased patient mortality [87]. However, RV dysfunction can also occur in HIV+ patents without LV dysfunction or pulmonary hypertension. These echocardiographic and CMR myocardial abnormalities help to explain the increased morbidity and mortality observed in patients with chronic HIV cardiomyopathy.

Treatment

Lifestyle management and risk factor modification

Adults with HIV should undergo a 10-year risk estimation for CVD at https://www.cvriskcalculator.com and should have a discussion with their medical provider regarding risk factor reduction. Smoking and illicit drug cessation and limitation of alcohol intake are important in CVD prevention and treatment. All HIV+ individuals should consume a diet that emphasizes the intake of vegetables, fruits, nuts, whole grains, and lean animal protein or fish. Overweight and obese adults require caloric restriction to less than 1200 to 1400 calories/day and greater than 150 minutes/week of moderate intensity physical exercise in order to achieve and maintain weight loss. The initiation and monitoring for side effects of pitavastatin or rosuvastatin is recommended in patients treated with LDL cholesterol ≥190 mg/dL, those with diabetes mellitus who are 40 to 75 years of age, in patients with a history of MI or stroke, and in patients with a 10-year risk of CVD >10% [52, 88, 89]. Pitavastatin and rosuvastatin are associated with a reduction in circulating inflammatory markers, T cell and monocyte activation, and cardiac fibrosis [69, 80]. Simvistatin and lovastatin should not be prescribed because of interactions with ART [52]. A useful reference website for medical personnel concerned about drug-drug interactions when treating HIV+ patients is https://www.hiv-druginteractions.org/checker.

A proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor such as evolocumab should be considered in patients who do not experience an LDL cholesterol reduction with a statin or statin plus ezetimibe therapy especially since PCSK9 concentrations are increased in the plasma in parallel with IL-6 in HIV+ individuals [90]. In this regard, evolocumab reduced the LDL concentration to <70 mg/dL in 73% of HIV+ patients over 24 weeks in the BEIJERINCK trial and the drug was well tolerated [90].

In patients with CVD, aspirin is recommended and has no specific drug interactions with ART [23]. However, the PIs and the NNRTIs efavirenz and etravirine can limit or inhibit the platelet P_2Y_{12} receptor blockers clopidogrel, prasugrel, and ticagrelor [48, 91]. Therefore, platelet activation assays are important in measuring the extent to which ART limits these drugs. For patients treated with warfarin and ART, therapeutic international normalized ratios (INR) are difficult to achieve. Consequently, serial INR monitoring is important when warfarin is coadministered with ART, and in the first weeks after stopping HIV drugs. Caution is also advised with HIV patients treated with elvitegravir-cobicistat because these drugs can cause significant increases in the plasma concentrations of the direct oral anticoagulants apixaban, betrixaban, or dabigatran and result in patient bleeding.

In adults with an estimated 10-year CVD risk >7.5% and a systolic blood pressure of >140 mmHg or a diastolic blood pressure of >90 mmHg, initiation and maintenance of an angiotensin converting enzyme (ACE) inhibitor or thiazide diuretics is recommended for blood pressure control. In individuals at high risk for CVD, a blood pressure target of <130/80 mmHg, is

reasonable if the blood pressure goal can be achieved without treatment-induced hypotension, near-syncope or syncope, or kidney injury [92].

With regard to treatment of HIV+ individuals with diabetes, the integrase inhibitor dolutegravir increases the plasma concentration of metformin and many PIs increase the plasma thiazolidinedione concentration. For patients on ritonavir or cobicistat, the dosage of saxagliptin should be decreased while the dose of canagliflozin should be increased [20, 52]. Metformin can be prescribed in the absence of renal or hepatic insufficiency, but patients must be monitored for the development of lactic acidosis. Sulphonylureas are safe in HIV+ patients but may not be effective in the presence of ritonavir or nelfinavir. In patients with refractory diabetes, insulin does not interact with ART, has an anabolic effect, reduces inflammatory TNFα, and is not contraindicated in patients with renal or hepatic dysfunction.

HIV+ patients are frequently treated with drugs that prolong the ECG QT interval, such as the azole antifungals, macrolide antibiotics, tricyclic antidepressants, and some protease inhibitors. These drugs can contribute to ventricular tachycardia or fibrillation and result in a nearly 2-fold increase in cardiovascular events [36].

Treatment of HIV+ patients with myocardial infarction and stroke

HIV+ patients with acute coronary syndromes often have proximal coronary artery obstructions even with low Thrombolysis in Myocardial Infarction risk scores for mortality [48]. Patients with symptoms and ST segment elevation MI (STEMI) of <12-hour duration with troponin elevation >99th percentile, and persistent ECG ST-T wave elevations in two contiguous ECG leads should be treated with aspirin, anti-platelet therapy, and with coronary primary percutaneous coronary angioplasty (PCI) and stent placement [52, 93, 94]. Patients who are more than 12 hours from the onset of symptoms and who have recurrent chest pain, hemodynamic instability, malignant cardiac dysrhythmias, or heart failure should also be evaluated for coronary angioplasty and stent placement. The incidence in HIV+ patients with MI of recurrent stenosis when treated with drug-eluting stents is 19% and is due to persistent coronary vascular inflammation [95].

Patients with non-ST segment elevation myocardial infarction (NSTEMI) with recurrent chest pain, hemodynamic instability, malignant cardiac dysrhythmias, or heart failure are at high risk for complications and require medical stabilization and coronary angiography with stent placement, if possible, within 24 hours of hospitalization. NSTEMI patients at low risk with an increase in blood troponin but no recurrent chest pain or evolving ECG changes should undergo coronary computed tomographic angiography for risk stratification. In low-risk patients, PCI and stent placement can be performed as an elective procedure. For patients with complex coronary artery disease who are on ART without advanced immunosuppression, coronary artery bypass graft surgery is safe and effective and is associated with similar inpatient mortality but slightly higher requirements for postoperative blood transfusions compared with HIV– patients [52]. After PCI or coronary artery bypass surgery, HIV+ patients require treatment with statin and antiplatelet medications and careful medical follow-up with laboratory monitoring of lipids and platelet activity, because of possible accelerated coronary atherosclerosis and coronary restenosis [49].

For HIV+ patients with stroke, the laboratory workup should include anticardiolipin antibodies, lupus anticoagulant, anti-b2-glycoprotein, hemoglobin electrophoresis for sickle cell disease, treponema immunoassay agglutination test, spinal fluid microscopy and biochemistry, India ink and acid-fast bacilli stains, blood culture, tuberculosis culture, unenhanced CT, ECG, echocardiogram and carotid/vertebral duplex ultrasound [57]. In selected patients with recurrent events or patients with autoimmune disorders, conventional cerebral angiography or brain biopsy should be considered [57]. HIV-induced vasculitis is associated with a high mortality.

In patients with stroke due to a large artery occlusion in the anterior circulation who can be treated within 6 hours of neurologic symptoms, mechanical thrombectomy is an effective treatment when performed by experienced operators. Alternatively, the intravenous administration of tissue plasminogen activator (TPA) within 6 hours of the onset of symptoms can be beneficial and is reported to not cause significant complications in HIV patients [23, 57].

For patients with HIV-associated multi-focal vasculitis with brain inflammation and coagulopathy, ART is important [57]. Zidovudine, emtricitabine, and nevirapine have high CNS penetration and can decrease the cerebral infract size and accelerate post-stroke recovery [96]. However, clinical neurological deterioration can occur after starting ART and suggests an immune reconstitution syndrome (IRIS) mediated by T cells [57]. In these patients, treatment with high-dose corticosteroids is useful. Treatment of stroke in patients due to an infectious etiology other than HIV should be based on the laboratory identification of the infectious agent and CSF examination and/or brain histopathology. Careful selection of ART is necessary for these patients as well as patients with CVD and diabetes.

Treatment of patients with HIV cardiomyopathy

Echocardiographic measurements of LV ejection fraction and global longitudinal strain are extremely useful in the evaluation of patients with cardiomyopathy and HFrEF. In patients with HFpEF, useful echocardiographic measurements include LV relaxation indices with measurement of mitral flow velocities in early and late diastole, mitral annular velocity restoring forces, diastolic compliance, and LV filling pressure [97]. In addition, CMR measurements of myocardial inflammation and fibrosis by T1 mapping and determinations of LV mass are independently predictive of cardiovascular events in patients with cardiomyopathy [82].

Patients with HIV cardiomyopathy and heart failure should be treated according to current AHA/ACC and ESC heart failure consensus guidelines, including tobacco and illicit drug cessation, weight loss in overweight and obese patients, management of diabetes and lipids, and control of hypertension and atrial fibrillation. In patients with HFrEF, early initiation of beta-adrenergic receptor antagonists and ACE inhibitors or angiotensin receptor/neprilysin inhibitor medications can be beneficial in preventing progression to severe systolic dysfunction through reduction in circulating catecholamines and LV afterload. Inhibition of the Renin-Angiotensin-Aldosterone System (RAAS) with a mineralocorticoid receptor antagonist, such as spironolactone or eplerenone, also reduces the progression of heart failure and is cardioprotective by limiting renin modulation of HIV replication and limiting production of renin by CD4 cells [69]. In patients with biopsy-proven autoimmune myocarditis with cardiomyopathy, corticosteroids can decrease LV remodeling and improve LV function [21]. In patients with HFpEF, thiazide or furosemide diuretics, a mineralocorticoid receptor antagonist, and a sodium-glucose cotransporter-2 (SGLT2) inhibitor, such as empaglifozin or dapaglifozin, can be useful in improving symptoms and signs of heart failure. Currently, the effects of Sacubitril/Valsartan on cardiomyopathy and heart failure are being investigated in the ENCHANTMENT HIV Study to determine the effects of this drug combination on cardiac inflammation, fibrosis, and cardiac function [97].

Successful ART is extremely important in the treatment of HIV+ patients with cardiomyopathy. A significant decrease in HIV RNA viral load and an increase in the CD4 cell count reduces the risk of heart fibrosis, cardiomyopathy and heart failure in patients with HIV [41, 52, 95].

ART treatment

In the Strategies for Management of Antiretroviral Therapy (SMART) study, the episodic treatment with ART, which was a drug conservation strategy, was compared with continuous ART treatment [98]. During 16 months of follow-up, the episodic use of ART was associated with an increased risk of CVD, opportunistic infections, and death [94]. Currently, all major treatment guidelines recommend ART for HIV+ individuals regardless of their CD4 cell count because the suppression of HIV replication controls disease progression and human transmission. This is known as the “test and treat strategy”. HIV is currently treated with two or more different medications, although those medications can be combined into one capsule. Treating HIV by drugs that inhibit multiple different viral metabolic pathways decreases the viral load quickly, prevents drug resistance, reduces HIV transmission and decreases AIDs development, hospitalization, and death.

Currently, there are nine categories of ART, including protease inhibitors (PI), nucleoside reverse transcriptase inhibitors (NRTIs), nucelotide reverse transcriptase inhibitors (NtRTIs), non-NRTIs non-nucleoside reverse transcriptase inhibitors (NNRTIs), integrase strand transfer inhibitors (INSTIs), CC-chemokine receptor 5 (CCR5) antagonists, fusion inhibitors, CD4-directed post attachment inhibitors and GP120 attachment inhibitors. Bictegravir, Abacavir, Tenofovir Alafenamide, or Boosted Darunavir

Table 4. NIH recommendations for HIV treatment (listed in alphabetical order)

HIV TREATMENT
● Bictegravir + Tenofovir Alafenamide + Emtricitabine
● Dolutegravir + Abacavir + Lamivudine for individuals who are HLA-B*5701 negative and without chronic hepatitis B virus
● Dolutegravir + Emtricitabine or Lamivudine + Tenofovir Alafenamide or Tenofovir Disoproxil Fumarate
● Boosted Darunavir plus Tenofovir Disoproxil Fumarate or Tenofovir Alafenamide plus Lamivudine (When ART is prescribed prior to the results of HIV genotypic resistance testing for reverse transcriptase or the results of hepatitis B virus tests)

should not begiven to women who are pregnant or wish to become pregnant.

Current guidelines for the use of drugs in adults with HIV from the Department of Health and Human Services recommend two NRTIs, which leads to termination of proviral DNA synthesis, administered in combination with a third active antiretroviral drug from one of three drug classes: (1) an INSTI, which inhibits the insertion of the proviral DNA into the host DNA, (2) a NNRTI, which impedes proviral DNA synthesis, or (3) a PI, which inhibits viral protease from releasing the viron from the host cell, with a pharmacokinetic enhancer [99]. Current National Institute of Health recommendations for specific initial HIV drug treatment are listed in **Table 4** in alphabetical order. **Table 4** is adapted in part from [99]. The exact combination of drugs is determined by the strain of HIV, the viral load, drug viral efficacy, the CD4 cell count, the severity of the infection, the drug toxicity, the patient comorbid conditions, drug-drug interactions, and the costs. Drug treatment for HIV is constantly evolving. The reader is advised to consult https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv. for updates and drug interactions.

Although some investigators have shown that there is no sex difference in response to ART treatment, other investigators report that women experience less ART-related decrease in markers of inflammation and immune activation than men, which is irrespective the type of the treatment regimen [19, 100]. This variance may explain the sex-based discrepancies in the prevalence of HIV-related CVD events.

PRE-exposure prophylaxis and prevention of HIV

Daily Pre-exposure prophylaxis (PrEP) with oral emtricitabine/tenofovir disoproxil fumarate (Truvada® or generic equivalent) is taken to prevent HIV infection in sexually active men and transgender women at risk of HIV exposure and acquisition [101]. The most common side effects include headache, abdominal pain, and weight loss. Creatinine clearance should be measured every 12 months for patients under age 50 or patients whose estimated creatinine clearance was greater than 90 mL/min when they started oral PrEP and every 6 months for all other patients [101]. Follow-up medical visits should occur at least every 3 months to provide HIV antigen/antibody test and HIV-1 RNA assay, medication adherence and behavioral risk reduction support, and bacterial sexually transmitted disease screening for men having sex with men and transgender women who have sex with men. Acyclovir, valacyclovir, cidofovir, ganciclovir, valganciclovir, aminoglycosides, high-dose or multiple NSAIDS or other drugs that reduce renal function or compete for active renal tubular secretion increase the serum concentration of PrEP. Consequently, patients must be monitored for drug-induced renal toxicity. In addition, ledipasvir, sofosbuvir, velpatasvir, and voxilaprevir can increased the toxicities of PrEP and require patient monitoring.

When taken as prescribed, PrEP can reduce the risk of HIV infection during sex by approximately 99%. PrEP can also reduce the risk of HIV infection from injection drug use by <74% [101]. Since PrEP is designed to protect against HIV, condom use is important to help prevent HIV if PrEP is not taken as prescribed and for the protection against other STDs.

ART adverse effects

Table 5 lists the major side effects of ART. **Table 5** is adapted in part from [29, 44, 67, 102, 103].

Table 5. Major side effects of antiretroviral therapy

Antiretroviral Class	Mechanism of Action	Antiretroviral Drug	Adverse Effects
Protease Inhibitors	Inhibits cleavage of HIV polyprotein into active proteins including reverse transcriptase and integrase	Ritonavir (RTV)	Increased risk of myocardial infarction, PR and QT prolongation, Hypertriglyceridemia, Decrease in endothelial cell nitric oxide production, Pancreatitis
		Lopinavir (LPV)	Increased risk of myocardial infarction, PR and QT prolongation, Hypertriglyceridemia, Pancreatitis
		Idinavir (IDV)	Renal abnormalities, Increased creatinine concentrations, Glycosuria, Hypophosphatemia
		Nelfinavir (NFV)	Hyperlipidemia, Hyperglycemia, Hepatotoxicity
		Fosamprenavir (FPV)	Hyperlipidemia, Hyperglycemia, IRIS, Renal Abnormalities
		Tipranavir (TPV)	Lipodystrophy, Hyperlipidemia, Hyperglycemia, IRIS
		Darunavir (DRV	Hepatotoxicity Lipodystrophy, Hyperlipidemia, Hyperglycemia, Increased cardiac events
		Saquinavir (SQV)	Dysrhythmias, Lipodystrophy, Hyperlipidemia, IRIS, Hepatotoxicity Hyperglycemia, Downregulation of eNOS
Nucleoside reverse transcriptase inhibitors (NRTIs)	Incorporation of nucleoside analogues by the reverse transcriptase leads to termination of proviral DNA synthesis	Zidovudine (AZT)	Bone marrow suppression, Mitochondrial toxicity
		Abacavir (ABC)	Lactic acidosis, Hepatotoxicity, Hyperlipidemia, Pancreatitis, IRIS, Increased risk of MI
		Emtricitabine	Skin rash
		Lamivudine	Lactic acidosis, Hepatotoxicity, Hyperlipidemia, Peripheral neuropathy
Nucleotide reverse transcriptase inhibitors (NtRTIs)	Incorporation of nucleotide analogues by the reverse transcriptase leads to chain-termination of proviral DNA synthesis	Tenofovir disoproxil-fumarate (TDF)	Renal abnormalities, Increased creatinine concentration, Glycosuria, Hypophosphatemia
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	NNRTIs bind the substrate pocket of the reverse transcriptase, thereby reducing polymerase activity and impeding proviral DNA synthesis	Nevirapine (NVP)	Hepatotoxicity
		Efavirenz (EFV)	Hyperlipidemia, Hepatotoxicity, Insulin resistance, QT ECG prolongation
		Etravirine (ETV)	Skin rash
Integrase inhibitors (INSTIs)	Block the active site of viral integrase and inhibit insertion of the proviral DNA into host cell genome	Raltegravir (RAF)	Increased creatine kinase concentrations, Myopathy
		Dolutegravir (DTG)	Hepatotoxicity, Hypersensitivity reactions, Fat accumulation, Metabolic syndrome
		Bictegravir (BTG)	Lactic Acidosis, Hepatotoxicity, fat accumulation. Contraindicated in hepatic disease and renal disease with creatinine clearance <30 mL/min
CC-chemokine receptor 5 (CCR5) antagonists	Monoclonal antibody antagonizes the CCR5 receptor and inhibit viral entry into the cell	Leronlimab	Hypertension, Lymphadenopathy
		Aplaviroc	Hepatotoxicity
Fusion inhibitors (FI)	Binding to gp41-TM inhibits viral entry into the cell	Enfuvirtide (ENF)	Neutropenia, Increased bacterial infections, Hypersensitivity
Pharmacologic Enhancer	Boost effectiveness of certain HIV medicines by slowing breakdown of the HIV medicine	Cobicistat	Liver and kidney toxicity
CD4-Postattachment Inhibitor	Viral entry into the CD4 cell is prevented by binding to gp120-SU or by binding the CD4 receptor	Ibalizumab	Liver and kidney toxicity, IRIS

IRIS = Immune Reconstitution Inflammatory Syndrome, PR = Time interval from atrial depolarization to ventricular depolarization, QT = Time interval from ventricular depolarization to repolarization, eNOS = endothelial nitric oxide synthase, Gp41 = a transmembrane (TM) protein required for infection of host cells, gp120-SU = HIV Surface envelope glycoprotein 120 which is important in virus binding to target $CD4^+$ T-cells, MI = Myocardial infarction. For updates, the reader is advised to consult https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/adverse-effects-antiretroviral-agents-full.

Summary and future directions

More than 1.2 million people in the United States have HIV infections but 13% of these people are unaware of their HIV status. Current combination antiretroviral therapy (ART) does not cure HIV infection but rather suppresses the infection with the virus persisting indefinitely in latent reservoirs in the body. As a consequence, HIV infection has changed from a fatal disease in the past to a chronic disease today. Chronic low grade inflammation and immune activation, accelerated atherosclerosis, and ART toxicity contribute to the development of atherosclerosis with acute myocardial infarction, stroke and heart failure due to cardiomyopathy. These disorders are now the major causes of death in HIV+ individuals. Nevertheless, HIV+ patients have lower rates of acute and chronic AHA/ACC and ESC guideline directed care. All medical personnel must be aware of the increasing incidence of CVD on the morbidity and mortality in HIV infected patients and must aggressively treat these disorders in their patients with HIV. The management of novel and traditional risk factors must be improved and disparities in the availability of health care must be corrected. A useful reference website for medical personnel concerned about drug-drug interactions when treating HIV+ patients is https://www.hiv-druginteractions.org/checker.

Future research investigations must target the latent reservoirs of HIV infection, the chronic inflammation, the immune activation and the accelerated atherosclerosis in HIV+ patients. These investigations should include the development of therapeutic vaccines to selectively stimulate T and B lymphocytes to destroy the HIV and pharmacologic agents to deplete HIV reservoirs and block viral reproduction pathways without causing body toxicity. Clinical vigilance, early treatment and continued research are necessary in order to end the chronic disease due to HIV.

Acknowledgements

The author thanks Meg Blount, MLIS and all the librarians at the Moffitt Hospital/University of South Florida for their assistance in providing many of the articles cited in this manuscript. The Author's work in the cardiovascular research laboratory is supported by a grant from the Cardiomyopathy Foundation. Not all pertinent references could be included in the References due to space limitations.

Disclosure of conflict of interest

None.

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