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HIV infection and coronary heart disease: mechanisms and management

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Abstract

Antiretroviral therapy has largely transformed HIV infection into a chronic disease condition. As such, physicians and other providers caring for individuals living with HIV infection need to be aware of the potential cardiovascular complications of HIV infection and 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, as well as how to select available therapies to reduce this risk. In this Review, we discuss the epidemiology and clinical features of cardiovascular disease, with a focus on coronary heart disease, in the setting of HIV infection, which includes a substantially increased risk of myocardial infarction even when the HIV infection is well controlled. We also discuss the mechanisms underlying HIV-associated atherosclerotic cardiovascular disease, such as the high rates of traditional cardiovascular risk factors in patients with HIV infection and HIV-related factors, including the use of antiretroviral therapy and chronic inflammation in the setting of effectively treated HIV infection. Finally, we highlight available therapeutic strategies, as well as approaches under investigation, to reduce the risk of cardiovascular disease and lower inflammation in patients with HIV infection.

At the end of 2017, approximately 36.9 million people were living with HIV infection, with 1.8 million becoming newly infected during that year[1]. The WHO recommends that all people with HIV infection receive antiretroviral therapy (ART) (Table 1). ART has transformed HIV infection into a chronic disease. As a consequence, by the year 2030, a modelling study suggests that 73% of people with HIV infection will be aged ≥50 years and 78% of individuals living with HIV infection will have cardiovascular disease (CVD)[2]. As shown in Fig. 1, individuals infected with HIV have been shown to be at an increased risk of CVD, including sudden cardiac death[3], acute myocardial infarction (MI)[4], stroke[5], peripheral artery disease and heart failure with either reduced or preserved ejection fraction[6]. This Review focuses on coronary heart disease in the setting of HIV infection.

Although ART controls the HIV infection, the disease is not cured; individuals must continue taking ART indefinitely, and, in this setting, chronic inflammation and immune

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activation persist, leading to downstream consequences including the development of atherosclerotic CVD (ASCVD)[7]. The population living with HIV is ageing, and, although traditional CVD risk factors are crucial contributors to CVD, HIV-specific factors, including ART, chronic inflammation and immune activation, have a role in HIV-associated CVD, including atherosclerosis. The atherosclerosis associated with HIV infection differs in important ways from atherosclerosis in the non-HIV setting in terms of both aetiological factors and clinical presentation. The low-grade inflammation associated with HIV infection accelerates atherogenesis through a variety of mechanisms. For example, atherosclerotic plaques in patients with HIV infection are more likely to be non-calcified and more prone to rupture than atherosclerotic plaques in patients without HIV infection[8,9]. Around one-half of MI events among patients with HIV infection are related to an imbalance in cardiac oxygen demand and supply rather than to atherothrombotic disease[10]. Finally, individuals infected with HIV who develop acute coronary syndrome (ACS) are, on average, a decade younger than uninfected patients with ACS and are more likely to be men who smoke and have low levels of HDL cholesterol (HDL-C)[11].

In this Review, we address the epidemiology and clinical features of CVD in people living with HIV infection and discuss the mechanisms of HIV-associated ASCVD and the management of CVD risk factors in people with HIV infection. Although much of this information is similar to that in people with CVD without HIV infection, important differences exist, particularly on the potential future therapies for CVD in people living with HIV.

Epidemiology of CVD in HIV infection

Before the advent of ART in the late 1990s, HIV infection almost always progressed to AIDS, with frequent opportunistic infections leading to death. Cardiomyopathy with systolic dysfunction was common in patients with AIDS and was associated with high short-term mortality (Table 2). For example, in one small study from the pre-ART era, median survival was 101 days in patients with AIDS with dilated cardiomyopathy compared with 472 days in patients with AIDS with normal ventricular function[12]. Cardiomyopathy was attributed to direct HIV infection of the myocardium with or with-out myocarditis, co-infection with other viruses such as coxsackievirus B3 and *Cytomegalovirus* (CMV), opportunistic infections and nutritional disorders[13]. Pericardial effusions were also common and presaged a high short-term mortality[14].

The incidence of HIV-associated cardiomyopathy has decreased from the pre-ART era, from 25.6 to 3.9 cases per 1,000 person-years[15]. The phenotype of cardiomyopathy has also changed markedly, from symptomatic systolic dysfunction with left ventricular dilatation in the pre-ART era to asymptomatic systolic or diastolic dysfunction detected by echocardiography in ART-treated patients with HIV infection. Whereas older ARTs, such as nucleoside reverse-transcriptase inhibitors (NRTIs), were implicated in mitochondrial toxicity leading to dilated cardiomyopathy[16], more recent studies have suggested that protease inhibitor use is related to increased cardiovascular mortality and 30-day re-admission for heart failure[17].

A 2018 systematic review of 80 longitudinal studies of CVD in HIV cohorts, which included 793,635 individuals living with HIV, concluded that the risk of MI and stroke in patients with HIV infection was increased by 2.16 (95% CI 1.68–2.77) compared with uninfected individuals[18]. The magnitude of this increased risk is similar to that associated with major CVD risk factors, such as diabetes mellitus and hypertension[19].Given that the prevalence of HIV infection is much lower than the prevalence of these traditional CVD risk factors, the overall influence of HIV infection on the risk of CVD would, at first glance, seem to be low; however, the global burden of HIV-associated MI and stroke has tripled over the past two decades and now accounts for 2.6 disability-adjusted life-years on an annual basis[18].

The burden of traditional CVD risk factors is high in people with HIV infection. A study published in 2015 on the large VACS VC cohort showed that <2% of patients with HIV had optimal levels of traditional CVD risk factors[20]. However, the increased risk of MI in people with HIV infection persists after adjustment for these risk factors; in the same cohort, the increased risk of MI was approximately 50% after adjusting for Framingham risk factors, comorbidities and substance abuse[4]. The risk of MI was higher in those with higher HIV-1 RNA levels in blood (≥500 copies per ml) and lower $CD4^+$ T cell counts (<200 cells per μl), but the risk was still elevated in those with low HIV-1 RNA levels and high $CD4^+$ T cell counts[4]. Although most of the study participants were men, the risk of MI was also significantly increased in women with HIV infection[21].

As with MI, the risk of stroke is also increased in people with HIV infection[18]. Globally, the risk of stroke in patients with HIV infection is approximately double that in individuals without HIV infection[18], but, in one study from the USA, the HR was 1.40 (95% CI 1.17–1.69), decreasing to 1.21 (95% CI 1.01–1.46) after adjustment for demographic and stroke risk factors[5]. A much higher risk of stroke has been reported in African patients with HIV, in whom initiation of ART is usually delayed after infection, with the highest risk of stroke being during the first 6 months after starting ART[22]. Risk factors for stroke in African patients with HIV infection compared with uninfected patients with stroke included younger age, large-artery disease and a low $CD4^+$ T cell count after initiation of ART[23].

The relationship between use of ART and the risk of MI is not straightforward. Case reports of MI in individuals with HIV infection began to appear soon after the introduction of ART[24] (Table 2). Early protease inhibitors were associated with the incidence of MI in a 2007 report, in which each cumulative year of protease inhibitor use was associated with a 10% increase in the risk of MI, even after adjusting for the changes in blood lipid levels caused by the protease inhibitor therapy[25]. Some of the newer protease inhibitors are likely to be safer. More recent reports indicate that among two widely used, recent-generation protease inhibitors, atazanavir was not associated with an increased risk of CVD compared with darunavir[26,27].

Abacavir, a widely prescribed NRTI, was reported in several observational cohorts to be associated with an increased risk of MI[28–31], possibly because this drug increases vascular inflammation and platelet reactivity[32]. However, other studies, including an FDA meta-analysis[33], do not show an increased risk of MI with abacavir. Nevertheless, US guidelines

recommend that abacavir be avoided or used with caution in individuals at high risk of CVD[34].

The START trial[35] demonstrated unequivocally that starting ART in adults with HIV infection and a $CD4^+$ T cell count of >500 cells per μl reduced mortality and serious AIDS-related and non-AIDS-related events compared with starting ART therapy after the $CD4^+$ T cell count had declined to 350 cells per μl. However, the incidence of cardiovascular events was low in this study, and, although a nonsignificant trend towards a reduction in the risk of cardiovascular events with early initiation of the treatment was observed, no definitive benefit was demonstrated. In substudies of the START trial, early initiation of ART did not improve arterial elasticity[36] and led to increased total and LDL cholesterol (LDL-C) levels in plasma but also to increased HDL-C levels and lower use of antihypertensive medications compared with delayed ART initiation[37]. Therefore, the effect of early initiation of ART on the risk of CVD remains unknown.

Earlier initiation of ART and the use of safer forms of ART from a CVD risk perspective might have resulted in a decrease in the risk of MI over the past decade, but additional studies with longer-term follow-up will be needed to evaluate definitively the effect of early initiation of ART on cardiovascular events. Some studies have reported a declining relative risk of MI in the setting of HIV infection[38], which might be related to the use of newer protease inhibitors[27], better control of HIV infection[39] or modification of traditional CVD risk factors over time[40], including smoking[41]. Thus far, no studies have reported on the effect of integrase inhibitors on cardiovascular events in HIV infection.

Clinical features of HIV-associated CVD

Early reports of coronary heart disease among individuals with HIV infection were remarkably consistent in the described clinical characteristics[11,33,42–47]. Patients with HIV infection and coronary heart disease in these studies were >90% men and had a mean age of 42–50 years, about a decade younger than patients with ACS without HIV infection in the reports with control groups[11]. More than half were current smokers[11,33,42–44,46,47], and, in studies including blood lipid measurements, plasma HDL-C levels were lower in patients with coronary heart disease and HIV infection than in uninfected patients with coronary heart disease[11,43]. As would be expected in the population with HIV infection, single-vessel disease was common[11,43,46,47], and, in those with ACS, risk scores were lower than in individuals with ACS without HIV infection[11]. Therefore, as expected, in-hospital mortality in patients with ACS and HIV infection was not high for that era: 4.8% (9 of 189 patients) in the studies in which this outcome was reported[11,42,43,46,47].

Coronary angioplasty in these early studies was as effective in patients with HIV infection as in patients without HIV infection; however, restenosis was more common in the setting of HIV infection[11,43]. The wide-spread use of coronary stents has reduced the incidence of restenosis, and drug-eluting stents have been shown to reduce cardiovascular events in patients with or without HIV infection[48]. Nevertheless, in a small study in which follow-up coronary angiography was performed routinely in individuals with HIV infection undergoing coronary stenting, the incidence of restenosis with drug-eluting stents was

19%[49]. Total $CD8^+$ T cell count, but not $CD4^+$ T cell count, was associated with restenosis, as was plasma C-reactive protein (CRP) level at follow-up (but not baseline)[49]. These results suggest that persistent inflammation in patients with HIV infection might be causally related to restenosis.

In a contemporary cohort of 226 patients with HIV infection who were followed up for 3 years after hospitalization for ACS, the risk of recurrent ACS was not increased compared with individuals without HIV infection (HR 1.08, 95% CI 0.76–1.54)[50]. HIV infection was significantly associated with all-cause mortality, but this association was not present among individuals with $CD4^+$ T cell counts ≥500 cells per μl. These intermediate-term results are encouraging; however, longer-term follow-up studies of patients with HIV infection and coronary heart disease are lacking.

Imaging studies have provided insight into the features and pathophysiology of HIV-associated coronary heart disease. Overall stenosis was less severe among men with ACS and HIV infection than in matched, uninfected individuals with ACS, although the numbers of diseased coronary vessels and lesions were similar in both groups[51]. In another study, plaque burden assessed as lesion severity in intracoronary ultrasonography findings was also lower in patients with ACS and HIV infection than in patients with ACS without HIV infection[52]. Furthermore, hyperechoic, non-calcified coronary plaques were much more common in patients with HIV (100% versus 35%; $P < 0.05$).

A higher prevalence of non-calcified coronary lesions among patients with HIV than in individuals without HIV infection was also reported in a meta-analysis of individuals without coronary symptoms who were evaluated with coronary CT[9]. In nine studies with 1,229 patients infected with HIV and 1,029 controls without HIV infection, the rates of non-calcified coronary plaques were higher in the HIV group (58% versus 17%; OR 3.26, 95% CI 1.30–8.18). Some evidence suggests that these non-calcified plaques are particularly amenable to LDL-C lowering with statin therapy. In a small clinical trial in which patients with HIV infection were randomly assigned to receive atorvastatin or placebo and followed up for 1 year, atorvastatin significantly reduced non-calcified coronary plaque volume compared with placebo[53]. Why individuals infected with HIV have a higher prevalence of non-calcified coronary plaques has yet to be established but does not seem to be related to ART[54] and might be due to chronic inflammation and immune activation in treated HIV infection[55,56].

Mechanisms of HIV-related atherogenesis

The pathogenesis of atherosclerosis in the setting of HIV infection is complex and poorly understood. Underlying mechanisms for HIV-associated ASCVD include the effects of the HIV proteins on immune and vascular cells, the immunodeficiency caused by the HIV infection, co-infection with CMV, microbial translocation from the gut, chronic inflammation and immune cell activation. These factors and their interrelationships are depicted in Fig. 2 and are summarized below.

HIV proteins.

In individuals receiving ART, the HIV infection, although controlled, is not cured and therefore persists even when the virus is undetectable[57], with low-level transcription of HIV genes[58]. HIV-encoded proteins, specifically transactivator of transcription (Tat) and negative factor (Nef), induce inflammation and endothelial dysfunction[59]. In addition, the HIV envelope protein gp120 has been shown to stimulate endothelin 1 production[60]. Therefore, by releasing low levels of certain damaging proteins, the HIV virus itself stimulates atherogenesis.

Immunodeficiency.

$CD4^+$ T cell depletion is the hallmark of HIV infection, and nadir $CD4^+$ T cell count is a rough marker of the severity of immunodeficiency. Nadir $CD4^+$ T cell count was first linked to features of atherosclerosis, such as increased carotid intima-media thickness[61] and increased arterial stiffness[62]. Soon thereafter, lower nadir $CD4^+$ T cell counts were shown to be associated with incident MI in two cohort studies[63,64]. In another report in which cardiovascular events were adjudicated more stringently, type 1 MI (the atherothrombotic type) occurred more commonly in people either with lower $CD4^+$ T cell counts or with detectable HIV RNA[65]. The CD4:CD8 ratio, a marker of immunosenescence, has been predictive of cardiovascular events in some[66,67] but not other[68] studies. Among individuals with HIV infection in New York City, USA, CVD mortality was highest among individuals with detectable viraemia (adjusted rate ratio (RR) 3.53, 95% CI 3.21–3.87), although even individuals with viral suppression had elevated CVD mortality (adjusted RR 1.53, 95% CI 1.41–1.66) compared with the general population[69]. These findings indicate that markers of immune system damage and viral detectability are related to cardiovascular events in patients with HIV. Immune abnormalities persist in individuals with HIV infection even after successful treatment with ART. The mechanisms linking immune system damage in HIV infection to atherosclerosis have not been elucidated. Although non-AIDS-related events, such as MI and stroke, are less common with complete viral suppression, these events still occur at rates considerably higher than in an uninfected population.

CMV co-infection.

Co-infection with CMV might contribute to HIV-associated atherosclerosis. Compared with individuals without HIV infection, patients infected with HIV consistently have a higher proportion of CMV-specific $CD8^+$ T cells, with the highest levels seen in patients with HIV suppression who are receiving long-term ART[70]. CMV-specific responses seem to underlie immunosenescence or immunological ageing in HIV infection[71]. Co-infection with CMV is strongly linked to HIV viral persistence and might also have a role in chronic immune activation and inflammation by expansion of the HIV reservoir[72]. These CMV-specific T cell responses also have been shown to correlate with markers of atherosclerosis, such as carotid intima–media thickness[73–75] and coronary artery calcification[75]. High CMV antibody titres in patients with HIV infection, and titres to other viruses such as herpes simplex virus and varicella-zoster virus, are associated with higher levels of biomarkers that accelerate inflammation and atherosclerosis[74]. Analogously, CMV also has an important role in the coronary atherosclerosis that develops in heart transplantation recipients[76].

Gut microbial translocation.

Impairment of the gut barrier is an early feature of HIV infection, leading to microbial translocation, a process whereby microbial products leak through the intestinal barrier and cause immune activation[77]. Plasma levels of soluble CD14 (sCD14) and lipopolysaccharide are markers of microbial translocation that independently predict HIV disease progression[78] and mortality[79] in individuals who are not receiving ART. Conflicting data exist as to whether these markers are predictive of adverse outcomes in ART-treated individuals; however, gut damage and microbial translocation persist even when HIV infection is suppressed by ART[77]. Plasma levels of inflammatory markers, specifically IL-6 and tumour necrosis factor, have been reported to be higher in individuals with higher levels of markers of microbial translocation[80]. Therefore, microbial translocation is another mechanism that might contribute to the atherogenesis associated with HIV infection. However, interventions targeting this mechanism, including sevelamer[81], rifaximin[80], probiotic administration[82] and mesalamine[83], have not consistently lowered inflammatory markers or T cell activation. As these studies targeted a variety of patient populations (treated versus untreated HIV infection), evaluated different inflammatory markers and were generally short in duration, the definitive role of microbial translocation from the gut in HIV-associated ASCVD remains unclear and requires additional investigation.

Chronic inflammation and immune cell activation.

Latent HIV infection, co-infection with other viruses and microbial translocation all influence atherogenesis by increasing inflammation. HIV infection is associated with high levels in plasma of inflammation and coagulation markers, such as CRP, IL-6 and D-dimer, and these biomarkers strongly predict cardiovascular events and all-cause mortality in individuals with HIV infection[84–86]. Arterial and lymph node inflammation as assessed by FDG-PET and CT imaging are higher in patients with HIV infection than in individuals without HIV infection, and this increased inflammation correlates with higher circulating levels of CRP, IL-6 and activated monocytes[87,88].

Inflammation offers a potential therapeutic target for the reduction of cardiovascular events in individuals with or without HIV infection; some postulated therapies to lower inflammation in HIV infection are depicted in Fig. 2. In patients with atherosclerosis without HIV infection, the beneficial effect of statin therapy is thought to be due not only to a reduction in plasma LDL-C levels but also to a reduction in inflammation[89]. In the presence of HIV infection, the anti-inflammatory effects of statins on markers of inflammation seem to be attenuated[90,91].Changing protease-inhibitor-based regimens to integrase inhibitors does not consistently reduce inflammatory parameters[92], and intensification of ART does not have a major salutary effect on inflammatory markers[93,94]. Short studies of aspirin therapy also had no effect on inflammatory markers in HIV infection[95]. Taken together, these findings suggest that strategies in addition to ART and targeting of traditional CVD risk factors are needed to reduce inflammation with the aim of lowering the risk of ASCVD in the setting of HIV infection.

Although T cell activation is a strong predictor of HIV disease progression[96], inflammatory and coagulation biomarkers, including IL-6, soluble tumour necrosis factor receptor type I

(sTNFRI), tumour necrosis factor receptor type II (TNFRII), kynurenine:tryptophan ratio and D-dimer, but not T cell activation, were predictive of non-AIDS events including CVD[97]. Some studies have implicated T cell activation in HIV infection with other indices of atherosclerosis, including carotid artery intima-media thickness[98] and arterial stiffness[99]. The effect of T cell activation in HIV-associated vascular disease seems to be at the microvascular level, which serves as the stimulus for flow-mediated vasodilatation (a marker of macrovascular disease)[100]. Therefore, T cell activation in HIV infection might worsen microvascular disease, leading to endothelial dysfunction and subsequent cardiovascular events.

Canakinumab, a monoclonal antibody targeting IL-1β, was evaluated in a randomized, placebo-controlled trial involving 10,061 patients with previous MI and a high-sensitivity CRP (hsCRP) level of ≥2 mg/l (reF.[101]).The three doses of canakinumab that were tested all reduced hsCRP levels, ranging from 26% reduction with the 50 mg dose to 41% with the 300 mg dose, but did not affect LDL-C levels. At the intermediate and higher doses, canakinumab reduced the primary composite end point of CVD-related death, MI and stroke. Patients who had a hsCRP reduction to <2 mg/l had significant reductions in cardiovascular events, CVD-related mortality and all-cause mortality, whereas no significant reduction in these outcomes was observed in patients who did not achieve the hsCRP reduction to this level[102]. Similar findings were reported for individuals who achieved on-treatment IL-6 levels below the study median value of 1.65ng/l — namely, a 32% reduction in major adverse cardiovascular events, a 52% reduction in CVD-related mortality and a 48% reduction in all cause mortality[103]. Canakinumab therapy was associated with a higher incidence of fatal infection than placebo[101].

Would canakinumab reduce cardiovascular events in individuals infected with HIV? In a small study in patients with HIV infection, our group has shown that canakinumab therapy significantly reduced plasma IL-6 and hsCRP levels, with no effect on CD4, CD8 or RNA viral levels[104]. Inflammation in the bone marrow and arterial inflammation were reduced after a single dose of canakinumab. By contrast, in another study published in 2018, low-dose methotrexate significantly lowered the $CD8^+$ T cell count but had no effect on inflammatory markers or endothelial function[105]. However, low-dose methotrexate did favourably affect specialized ultrasonography indices in the brachial artery[106]. These preliminary studies with inflammatory biomarkers as surrogate end points will hopefully lead to clinical trials on anti-inflammatory treatments with cardiovascular events as end points in the population living with HIV.

As previously noted, markers of inflammation and coagulation predict cardiovascular events in individuals with HIV infection[84–86]. A summary of markers studied in different cohorts of patients with HIV infection and the association with clinical outcomes is shown in Table 3. The strong relationship between inflammatory and coagulation markers is striking and apparent even in the setting of diverse HIV-infected populations including men, women and older and younger individuals. In combined data from three large cohorts of patients with HIV infection, IL-6 and D-dimer levels in plasma were independently associated with the risk of serious non-AIDS events or death, with an estimated 37% reduction in non-AIDS events or death resulting from a 25% decrease in IL-6 or D-dimer levels[107]. Aside from

prediction of clinical events, plasma levels of soluble CD163 (sCD163), a marker of macrophage activity, was associated with higher levels of arterial inflammation in HIV infection[87].

In the general population, the immune system has been implicated in atherosclerosis as well as in conduction system disorders, myocarditis and heart failure with preserved ejection fraction[108]. In particular, the role of haematopoietic stem cells, inflammation and macrophages has been associated with these conditions; therefore, it is plausible that immune system abnormalities that are present in HIV infection underlie HIV-associated CVDs. HIV infects $CD4^+$ T cells, most of which reside in secondary lymphoid tissues, such as the lymph nodes[109]. Myeloid cells, which include monocytes, dendritic cells and macrophages, have a crucial role in HIV disease pathogenesis[110,111]. Macrophage infiltration has been observed in the hearts of monkeys infected with simian immunodeficiency virus (SIV), and macrophage infiltration correlated with fibrosis and cardiac pathology[112]. Anti-inflammatory therapy with natalizumab (a monoclonal antibody against the cell adhesion molecule α4 integrin) reduced the number of macrophages in cardiac tissue as well as cardiac pathology in this animal model[113]. Monocyte and macrophage markers, including sCD163 and sCD14 levels in plasma and $CD14^+CD16^+$ cell counts, have been linked to subclinical atherosclerosis in HIV infection in a variety of studies[113].

A 2018 study showed that biomarkers in HIV infection can be grouped into clusters, with each cluster related to a cardiac phenotype[114]. For example, the inflammatory phenotype is characterized by higher levels of CRP, IL-6 and D-dimer, whereas the cardiac phenotype comprised a clustering of higher levels of protein ST2 (also known as IL-1 receptor-like 1), N-terminal pro-B-type natriuretic peptide and growth/differentiation factor 15. Diastolic dysfunction was common in the inflammatory group of biomarkers, and pulmonary hypertension was more common in the cardiac group of markers. Both phenotypes were associated with a threefold increase in mortality over a 6.9-year follow-up after adjustment for other prognostic variables. Biomarker clusters in patients with HIV might be helpful for selecting patients for appropriate therapy to reduce cardiovascular events.

ART-related mechanisms.

The most obvious mechanism by which ART increases the risk of CVD is through worsening of blood lipid levels. The increase in LDL-C levels with protease inhibitors seems to result from increased cholesterol absorption rather than increased synthesis[115]. Whereas some ARTs increase LDL-C levels, other ARTs, particularly older protease inhibitors, induce hypertriglyceridaemia, with ritonavir being the worst culprit[116]. Interestingly, in the large D:A:D study[117], even after adjustment for blood lipid levels, cumulative exposure to the NRTIs abacavir or didanosine or to the protease inhibitors lopinavir–ritonavir or indinavir was associated with an increased risk of MI. Newer protease inhibitors, as well as the integrase inhibitor raltegravir and the virus-entry inhibitor maraviroc, have favourable effects on lipid levels, particularly compared with older types of ARTs[118].

ART might also increase the risk of ASCVD through other mechanisms. Insulin resistance, lipodystrophy and other patterns of fat distribution can contribute to atherogenesis. The

NRTI abacavir has been linked to an increased risk of MI in some[28–31] but not all studies[33]. This increase in risk has been attributed to increased platelet reactivity[32] and to endothelial dysfunction[119]. In the D:A:D study[26], a difference in the risk of MI was noted between the widely used protease inhibitors, atazanavir and darunavir, with atazanavir being associated with a lower risk of MI than darunavir. This reduced risk of MI has been suggested to reflect a protective effect of atazanavir given the bilirubin-raising activity of the drug[120]. Overall, we emphasize that current ART regimens are associated with a much lower risk of CVD than older ART regimens.

Understanding the role of inflammation and inflammatory biomarkers in the general population with coronary heart disease has taken several decades to establish[121,122], including ascertaining which markers have prognostic importance as opposed to being on the causal pathway. Although research on inflammatory biomarkers of the risk of CVD in HIV infection has been performed, much additional work is needed to identify the best biomarker in the setting of HIV infection along with the effect of HIV-related factors (including immune dysfunction) and traditional CVD risk factors. Identifying how ART, treatments for CVD and potential anti-inflammatory strategies change these inflammatory pathways and biomarkers will also be critical to advance the field. Of note, risk calculators used in the general population are inaccurate in patients infected with HIV and systematically underestimate risk[123]. Using non-biased methods, such as proteomics, which have been used in the general population, might be helpful to develop HIV-specific risk scores[124].

Management of CVD risk in HIV infection

Dyslipidaemia.

The onset of HIV infection is associated with a decline in total cholesterol, LDL-C and HDL-C levels[125]. In a study comparing patients with HIV infection with matched uninfected controls, the group with HIV infection had lower HDL-C and LDL-C levels and higher triglyceride, CRP and IL-6 levels[126]. Because starting ART is now recommended at the time of initial HIV diagnosis, the lipid pattern of untreated HIV infection is seen only among individuals who live in resource-limited settings and, therefore, do not have access to ART. Of note, in a meta-analysis of 80 studies, the greatest risk of CVD in HIV infection was found to be in sub-Saharan Africa and the Asia Pacific regions[18].

The effect of ART on blood lipid levels varies across the classes of ART drugs and between drugs within the same class, as broadly summarized in Table 4 (of note, this summary is not meant to be comprehensive). The effects of individual drugs are difficult to ascertain because HIV treatment typically requires three or four drugs. Generally, protease inhibitors, NRTIs and non-NRTIs (NNRTIs) all increase triglyceride levels and can increase LDL-C levels. LDL-C and triglyceride levels increase more with dual than with single protease inhibitor therapy.

Important differences have been described between protease inhibitors; in a report from the D:A:D study[116], ritonavir and ritonavir-containing regimens increased triglyceride and LDL-C levels more, saquinavir caused less abnormally low HDL-C levels and nelfinavir was

associated with fewer patients presenting with a high total cholesterol:HDL-C ratio compared with other protease inhibitors. In another study, LDL-C level increased by a mean of 2.0 mmol/l with initiation of ritonavir, 0.8 mmol/l with indinavir and 1.2 mmol/l with nelfinavir[127]. Ritonavir, but not the other two protease inhibitors, was associated with very elevated plasma triglyceride levels. Ritonavir can sometimes cause extreme hypertriglyceridaemia, with levels >10 mmol/l, and result in pancreatitis. Lower doses of ritonavir than those used in the study are now usually used, but hypertriglyceridaemia is also seen with combinations of ritonavir-saquinavir and ritonavir-lopinavir. Compared with these older protease inhibitors, use of atazanavir and darunavir is associated with more favourable lipid profiles[128].

NNRTIs also increase LDL-C levels but do not decrease HDL-C levels[13]. Among NNRTIs, efavirenz was associated with slightly more patients developing hypercholesterolaemia and hypertriglyceridaemia than nevirapine[116]. Efavirenz has been associated with greater increases in total cholesterol and LDL-C but not total cholesterol:HDL-C ratio compared with the atazanavir-ritonavir combination[129]. Compared with the NNRTI rilpivirine, efavirenz is associated with higher total cholesterol, HDL-C, LDL-C and triglyceride levels[130]. The newer formulation of the NRTI tenofovir (tenofovir alafenamide) is associated with higher levels of both LDL-C and HDL-C, but similar total cholesterol:HDL-C ratio, compared with the older formulation (tenofovir disoproxil fumarate), which has a lipid-lowering effect[131].

Newer ARTs, such as the integrase inhibitors, the CC-chemokine receptor 5 (CCR5)-co-receptor antagonist maraviroc and second-generation protease inhibitors, such as atazanavir, favourably affect lipid levels, especially compared with older ARTs, and are associated with improvements in surrogate markers of atherosclerosis, such as flow-mediated vasodilatation and carotid intima-media thickness[132]. The integrase inhibitors dolutegravir and raltegravir seem to affect blood lipids in a similar way[133].

Across various studies, the prevalence of hyperlipidaemia among people living with HIV ranges from 28% to 80%, with hypertriglyceridaemia being the most common abnormality[134]. Intrinsic differences in study populations and the evolution of ART over time are probable explanations for this broad range. Most of the studies described here were of fairly short duration and were usually done in North American or European populations. However, ART is now initiated most often in people living in sub-Saharan Africa, where data defining the metabolic effects of treatment are scarce. In a 2018 meta-analysis of 14 trials and including a total of 21,023 individuals from this region, ART was associated with an increased risk of hypertriglyceridaemia (RR 2.05, 95% CI 1.51–2.77); however, no consistent associations were observed between ART and raised blood pressure, blood glucose levels, glycated haemoglobin (HbA_{1c}) levels or other blood lipids[135]

In one study, hypertriglyceridaemia in patients with HIV infection was related to their higher intake of total fat, saturated fat and cholesterol compared with individuals without HIV infection[136]. Saturated fat intake was strongly correlated with triglyceride levels, suggesting that dietary modification to decrease saturated fat intake might be a logical approach to control high triglyceride levels in patients with HIV infection.

Until recently, guidelines for cholesterol management have not specifically addressed individuals living with HIV. The 2016 ESC/European Atherosclerosis Society (EAS) guidelines devote a short section to individuals with HIV infection and recommend dietary changes and exercise, as well as switching, when feasible, to a more 'lipid-friendly' ART[137]. The guidelines also state that statin therapy should be considered to achieve the target LDL-C level of 2.8 mmol/l, the same target that is recommended for other patients at high risk of CVD. The US National Lipid Association recommended considering HIV infection as an independent risk factor for selecting drug therapy to lower LDL-C levels[138]. The 2018 ACC/AHA guidelines state that HIV infection can be considered a CVD risk enhancer, which would favour starting moderate-intensity or high-intensity statin therapy[139].

Many clinical trials have documented that LDL-C lowering, usually with statin therapy, reduces the risk of cardiovascular events across a broad spectrum of patients without HIV infection. Similar data are not yet available for people with HIV infection; however, the REPRIEVE trial[140], launched in 2015, will address this issue. As previously noted, in a small, randomized trial in patients with HIV infection, atorvastatin significantly reduced non-calcified coronary plaque volume compared with placebo during a follow-up of 1 year[53].

Drug–drug interactions are important considerations when initiating lipid-lowering drugs in patients infected with HIV. A systematic review of 18 statin trials in patients with HIV infection receiving ART demonstrated that statin therapy can be administered safely in this patient population[141]. Use of lovastatin and simvastatin with protease inhibitors is contraindicated owing to the risk of rhabdomyolysis from high statin levels in blood[134]. Use of ritonavir with protease inhibitors seems to increase the area under the curve for atorvastatin as well; therefore, guidelines from the Infectious Diseases Society of America suggest starting at lower doses of atorvastatin in individuals receiving protease inhibitor-based regimens[142]. Rosuvastatin levels in blood increase when used with atazanavir-ritonavir and lopinavir-ritonavir; therefore, the dose of rosuvastatin should be limited to 10 mg when used in combination with these drugs[143]. Pravastatin and fluvastatin are safer to use in combination with ART but do not lower LDL-C levels as much as atorvastatin or rosuvastatin. Pravastatin and fluvastatin were widely used after the introduction of ART but are less popular now owing to the growing realization, reflected in contemporary guidelines, that greater degrees of LDL-C lowering yield greater reductions in the risk of cardiovascular events[144]. Pitavastatin might be a good compromise for some people with HIV infection; this drug is metabolized via glucuronidation, thereby avoiding drug–drug interactions[145], and, at higher doses, pitavastatin shows moderate LDL-C lowering. In one randomized study in patients with HIV infection, pitavastatin (4 mg per day) reduced LDL-C level by 31% and pravastatin (40 mg per day) reduced LDL-C level by 21% from baseline levels, with similarly low rates of adverse effects for both statin treatments[146]. According to a 2018 study, as many as 50% of individuals with HIV infection were eligible for statin therapy on the basis of at least one US guideline, but not all the eligible patients were prescribed statins[147]. Even when individuals are receiving statin therapy, those with HIV infection might not achieve as much lipid lowering as individuals without HIV infection; namely, a meta-analysis of studies in people living with HIV infection demonstrated that only a low percentage achieved the expected reduction in LDL-C level after initiation of statin

therapy[148]. From 2007 to 2014, the percentage of individuals with HIV infection taking a contraindicated (owing to their ART) statin decreased; however, this decreasing trend was attenuated in 2015 owing to an increase in the use of the ART cobicistat[149].

In individuals with HIV infection who do not tolerate statins, ezetimibe is a safe option, albeit with limited LDL-C lowering efficacy[150]. Ezetimibe can be used in addition to a maximally tolerated statin dose for individuals with HIV infection who are at a very high risk of CVD and do not achieve satisfactory LDL-C lowering with statin therapy alone. Use of bile acid sequestrants is not appropriate in the setting of HIV infection because these agents increase plasma triglyceride levels and their effect on the absorption of ARTs is unknown[151]. Individuals with HIV infection often have a high pill burden, and an add-on therapy might present additional challenges.

Switching ART to drugs that do not adversely affect blood lipids is worthwhile as long as viral suppression is maintained. Switching from older protease inhibitors to integrase inhibitors improves blood lipid levels, but at the cost of an increased rate of virological failure[152] and, therefore, is not recommended for individuals with a history of virological failure. In another study of patients with HIV infection and high risk of CVD, continuing on a ritonavir-boosted protease inhibitor regimen or switching to dolutegravir (an integrase inhibitor) was associated with similar rates of virological failure after 48 weeks; however, total cholesterol, LDL-C and triglyceride levels all improved ($P < 0.0001$) in the dolutegravir group[153]. For those not already taking a statin, adding statin therapy is probably preferable to switching the type of ART; in one study, adding rosuvastatin (10 mg per day) was better tolerated and yielded better blood lipid results than switching[154].

The common problem of hypertriglyceridaemia in patients with HIV infection should first be addressed by reducing intake of carbohydrates, including alcohol. When plasma triglyceride levels exceed 10 mmol/l, pancreatitis is a serious risk and immediate treatment is required, but lower levels of hypertriglyceridaemia are not benign because they probably increase the risk of CVD. Fibrates are widely used to lower triglyceride levels in people without HIV infection but have a drug–drug interaction with statins and some types of ART. A change in ART to drugs that induce less hypertriglyceridaemia is often the best approach.

Diabetes and the metabolic syndrome.

Whether HIV infection itself is associated with an increased risk of diabetes or whether the increased risk is related only to specific ART drugs has been controversial. Protease inhibitors and the thymidine analogue stavudine can cause insulin resistance[118]; however, these drugs are now not often used owing to their toxicity. In a large cohort study from Denmark, the risk of diabetes among patients with HIV infection was nearly triple that of the general population in 1996–1999, but this excess was absent in 1999–2010 (reF.[155]). Conversely, a cross-sectional study from sub-Saharan Africa published in 2018 reported a higher prevalence of diabetes and a HbA_{1c} level of ≥6% in people living with HIV infection compared with uninfected controls[156].

Lipodystrophy is a syndrome that results in central adiposity from fat accumulation in the dorsocervical region, increased or preserved visceral fat and peripheral fat loss[157] and can be

divided into lipoatrophy and lipohypertrophy[158]. Excess visceral adiposity is associated with insulin resistance among individuals with or without HIV infection[159]. Lipodystrophy develops in 20–35% of patients taking older protease inhibitors or the NRTIs didanosine or stavudine[160,161]; however, newer protease inhibitors, such as atazanavir, do not seem to cause lipodystrophy[37,160,161]. Lipodystrophy is often associated with insulin resistance, impaired glucose tolerance, hypertriglyceridaemia, low HDL-C levels and hypertension.

Reported rates of metabolic syndrome in people with HIV infection range from 8.5% to 52%, with rates at the lower end of this range seen in multicentre studies in which patients had less exposure to ART and rates at the higher end found in Latin American countries[118]. Metabolic syndrome usually develops in the first 3 years after starting an ART regimen that includes lopinavir-ritonavir or stavudine. According to most studies, metabolic syndrome is a predictor of cardiovascular events and death in people living with HIV infection, as in individuals without the infection[118]. Among the general population, development of chronic kidney disease is increased in the setting of metabolic syndrome[162], and blood pressure is a component of metabolic syndrome using Adult Treatment Panel III (ATP III) criteria[163].

The prevalence of hypertension and chronic kidney disease does not seem to be higher than normal in people with HIV infection, with the exception of a higher incidence of chronic kidney disease among patients exposed to some ART regimens[164]. Nevertheless, hypertension and prehypertension have been shown to be risk factors for cardiovascular events in people with HIV infection, just as in individuals without the infection[165]. Similarly, chronic kidney disease, defined as either albuminuria or a decreased glomerular filtration rate, is associated with an increased risk of cardiovascular events in patients with HIV infection[166]. Among 35,357 patients with HIV in the D:A:D cohort, lower glomerular filtration rate was strongly associated with a higher risk of CVD[167].

Smoking.

The prevalence of cigarette smoking among individuals with HIV infection is extremely high. In a large cohort study from Denmark, nearly half of people with HIV infection smoked compared with one-fifth of people without HIV infection[168]. All-cause mortality was much higher among smokers than nonsmokers with HIV infection. For example, an individual aged 35 years and living with HIV infection had a median life expectancy of 62.6 years (95% CI 59.9–64.6 years) if a smoker and 78.4 years (95% CI 70.8–84.0 years) if a nonsmoker. More life-years were lost owing to smoking than to HIV (12.3 versus 5.1). The population-attributable risk of death due to smoking was 61.5% in individuals with HIV and 34.2% among people without the infection. These statistics emphasize the importance of stopping smoking for patients with HIV infection.

Smoking cessation programmes are reported to have the same modest success rates in people with HIV infection as has been reported in individuals without HIV infection. In a meta-analysis of eight trials including 1,822 patients with HIV who were smokers, behavioural interventions increased abstinence rates by half (relative risk 1.51, 95% CI 1.17–1.95)[169], and a meta-analysis of smoking cessation interventions demonstrated that long-term outcomes were similar among individuals with or without HIV infection[170]. In one study, physicians trained to provide smoking cessation counselling and treatment for

individuals living with HIV infection succeeded in significantly increasing smoking cessation rates and decreasing relapse rates[171]. Potential drug-drug interactions between ART and drugs for smoking cessation have not been well studied. Studies of varenicline, bupropion and nicotine-replacement therapy in people with HIV infection have generally been small, short and uncontrolled but have shown similar safety and success rates to reports in individuals without HIV infection[172,173].

The effect of smoking cessation on the rates of subsequent cardiovascular events was reported for a large cohort in the D:A:D study[174]. At baseline, 11,951 participants (44%) were currently smoking and during the follow-up period, 69% of them stopped smoking at least once. The incidence RR for MI compared with never smokers decreased from 3.73 (95% CI 2.46–5.64) within the first year of smoking cessation to 3.00 (95% CI 1.84–4.88) within 1–2 years, to 2.62 (95% CI 1.42–4.83) at 2–3 years and to 2.07 (95% CI 1.19–3.63) after >3 years. Similar trends were seen for total coronary events and total cardiovascular events. Although cardiovascular event rates were still approximately double the rate in never smokers after 3 years, the rates were much lower than the rates in individuals who continued smoking, making smoking cessation a very desirable therapeutic goal.

Conclusions

In summary, atherosclerosis in the setting of HIV infection continues to be an important health concern that has implications on mortality, particularly in the future as this patient population continues to age. In the 20 years since the initial descriptions of MI were reported in patients with HIV infection[175], ART has transformed HIV infection into a chronic disease condition, and progress has been made in determining the contribution of ART, chronic inflammation and immune activation as well as traditional CVD risk factors to this disease process. However, much work remains to elucidate further the underlying mechanisms for HIV-associated ASCVD as well as therapeutic strategies to lower the risk of CVD and treat CVD in patients with HIV infection, which will include implementation studies to improve outcomes and CVD management for people living with HIV infection.

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$CD4^+$ T cell counts

T cell subset that has a role in the immune system response against pathogens, infections and illnesses. a normal $CD4^+$ T cell count is 500–1,500 cells per μl of plasma. $CD4^+$ T cells are the main target cell of HIV, and the $CD4^+$ T cell count is used to monitor the status of the HIV infection and the efficacy of the antiretroviral therapy.

Nadir $CD4^+$ T cell count

The lowest $CD4^+$ T cell count an individual has had, which serves as a marker for immunodeficiency.

Immunosenescence

Changes to the immune system that can be associated with age.

Viraemia

Presence of viral particles in the blood.

Latent HIV infection

A dormant or non-replicative HIV infection within a cell; in this state, the virus is not actively infecting other cells and individuals do not usually have noticeable symptoms.

Virological failure

Refers to the failure of the HIV treatment to supress the virus completely; the virus is detectable in the blood (>200 copies per ml). This failure can occur as a result of drug resistance, drug toxicity or noncompliance with antiretroviral therapy.

Key points

- As improvements to antiretroviral therapies have led to better control of HIV infection (although not cured it), individuals with HIV infection are now ageing, and cardiovascular disease is an important health concern in this patient population.
- Traditional risk factors including dyslipidaemia, hypertension, cigarette smoking, diabetes mellitus and metabolic syndrome are common among people with HIV infection and increase the risk of cardiovascular disease.
- In addition to traditional risk factors, characteristics related to HIV infection, including low $CD4^+$ T cell count, nadir $CD4^+$ T cell count and viral detectability, and some antiretroviral therapies are independently associated with increased risk of cardiovascular disease.
- In the setting of treated suppressed HIV replication, chronic inflammation and immune activation persist and are strongly predictive of mortality and cardiovascular events.
- Potential strategies to reduce the risk of cardiovascular disease in patients with HIV infection include targeting traditional risk factors, initiation of antiretroviral therapy to reduce inflammation and other approaches to lower inflammation, including gut-related interventions, statin therapy and immune modulators.

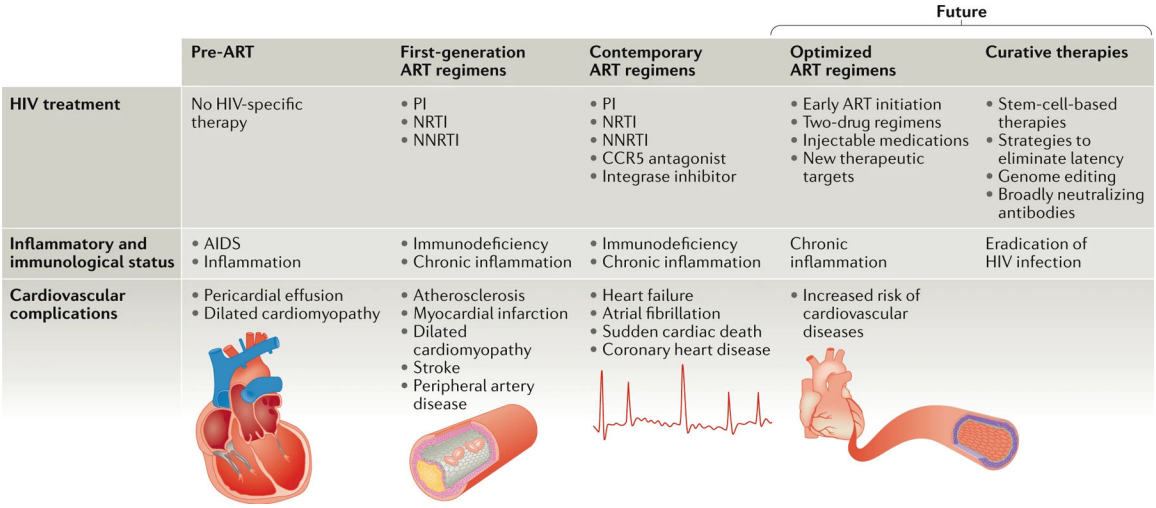

Fig. 1 |. Overview of changes in HIV treatment and HIV-associated cardiovascular diseases. The types of cardiovascular complications associated with HIV infection have changed in the pre-antiretroviral therapy (ART) and ART eras and are likely to continue evolving in the future as new medications and treatment approaches emerge. In the pre-ART era, dilated cardiomyopathy and pericardial effusions were the most commonly reported cardiovascular issues in patients infected with HIV[14,176]. After the introduction of protease inhibitors (PIs) in the late 1990s, atherosclerotic complications including myocardial infarction were described[177,178]. More recently, reports of heart failure and rhythm abnormalities are now emerging in the setting of HIV infection[3,6]. In the future, among individuals with access to ART, HIV infection will be a chronic disease state with increased risk of coronary artery disease[19]. CCR5, CC-chemokine receptor 5; NNRTI, non-nucleoside reverse-transcriptase inhibitor ; NRTI, nucleoside reverse-transcriptase inhibitor.

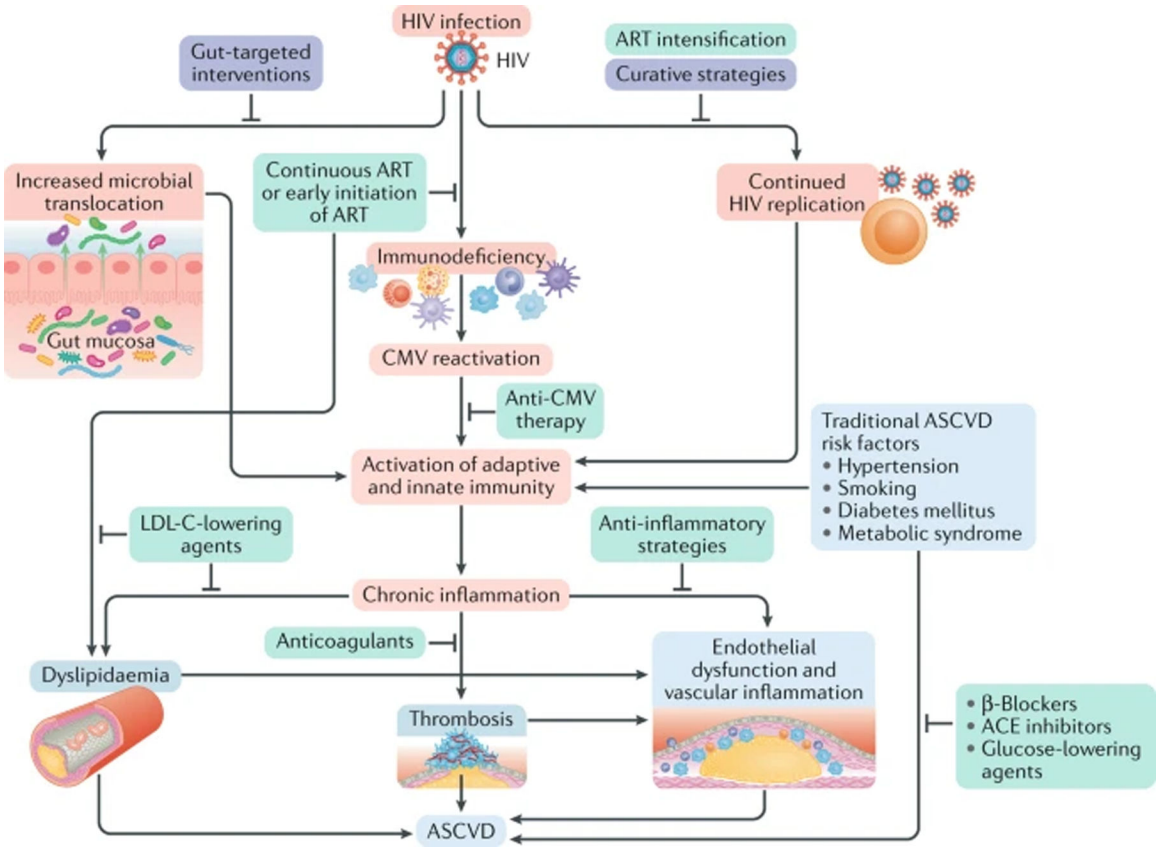

Fig. 2 |. Pathophysiology and management of HIV-associated atherosclerotic cardiovascular disease.

Schematic representation of the effects of HIV infection (in red) and the available strategies (in green), as well as approaches under investigation (in purple), for reducing the risk of atherosclerotic cardiovascular disease (ASCVD) and chronic inflammation in this patient population. In the setting of HIV infection, the increased microbial translocation from the gut, the continued HIV viral replication and the HIV-induced immunodeficiency, along with traditional ASCVD risk factors, contribute to immune cell activation and chronic inflammation. HIV-specific interventions to reduce the risk of ASCVD include strategies targeted at co-infections (such as *Cytomegalovirus* (CMV) infection), use of newer antiretroviral therapies (ARTs) and intensification of ART. Strategies aimed at eradicating the HIV infection are under investigation. Treatments targeting traditional ASCVD risk factors, such as hypertension, diabetes mellitus, smoking and metabolic syndrome, are also critical for reducing the risk of ASCVD in patients with HIV infection. Use of anticoagulants, β-blockers, angiotensin-converting enzyme (ACE) inhibitors and LDL cholesterol (LDL-C)-lowering agents (such as statins and PCSK9 inhibitors) reduce the risk of ASCVD in patients with cardiovascular disease without HIV infection and might, therefore, be useful in reducing the risk of HIV-associated ASCVD. Finally , strategies to lower inflammation, such as canakinumab, which has been reported to reduce cardiovascular events significantly in a non-HIV patient population, might also reduce the risk of HIV-associated ASCVD.

Table 1 |

Commonly used antiretroviral drugs

Class	Mechanism of action[179]	Generic name	Abbreviation	Brand name	Year of FDA approval
Protease inhibitors	Selectively bind to HIV proteases and inhibit cleavage of Gag-Pro-Pol polyproteins in HIV-infected cells, resulting in the production of immature, non-infectious virions	Atazanavir	ATV	Reyataz	2003
		Darunavir	DRV	Prezista	2006
		Fosamprenavir	FOS-APV, FPV	Lexiva	2003
		Ritonavir	RTV	Norvir	1996
		Saquinavir	SQV	Invirase	1995
		Tipranavir	TPV	Aptivus	2005
Nucleoside reverse-transcriptase inhibitors	Inhibit viral replication through competitive binding to the HIV enzyme reverse transcriptase, leading to termination of DNA chain elongation	Abacavir	ABC	Ziagen	1998
		Emtricitabine	FTC	Emtriva	2003
		Lamivudine	3TC	Epivir	1995
		Tenofovir fumarate disoproxil	TDF	Viread	2001
		Zidovudine	AZT	Retrovir	1987
Non-nucleoside reverse-transcriptase inhibitors	Prevent HIV reverse transcriptase from adding new nucleotides to the DNA chain, leading to a decline in viral replication	Doravirine	DOR	Pifeltro	2018
		Efavirenz	EFV	Sustiva	1998
		Etravirine	ETR	Intelence	2008
		Nevirapine	NVP	Viramune	1996
		Rilpivirine	RPV	Edurant	2011
CCR5 antagonist	Entry inhibitor; binds to the cell membrane receptor CCR5, thereby blocking the entry of CCR5-tropic viruses into $CD4^+$ T cells	Maraviroc	MVC	Selzentry	2007
Integrase inhibitors	Prevent binding of the pre-integration complex to the host cell DNA, terminating the integration step of HIV replication	Dolutegravir	DTG	Tivicay	2013
		Raltegravir	RAL	Isentress	2007
Fusion inhibitor	Prevents viral fusion to $CD4^+$ T cells by binding to the HIV envelope glycoprotein 41	Enfuvirtide	T-20	Fuzeon	2003
Pharmacokinetic enhancer	Protease inhibitors combined with integrase inhibitors to improve potency of the antiviral agent and to decrease pill burden by increasing trough drug concentration, drug half-life and peak concentration (C_{max}) in plasma	Cobicistat	COBI	Tybost	2014
Post-attachment inhibitor	Monoclonal antibody that binds to the CD4 molecule and blocks viral entry into the cell	Ibalizumab	IBA	Trogarzo	2018

CCR5, CC-chemokine receptor 5.

Table 2 |

Effect of antiretroviral therapy on the risk of cardiovascular disease

Study (year)	Study population	ART	Number of patients	Follow-up	Cardiovascular end points	Findings	Refs
Bozzette et al. (2003)	Patients with HIV infection who received care at a VA centre	Combination therapy with PIs, nucleoside analogues and NNRTIs	36,766	8.5 years	CVD and cerebrovascular disease	Use of ART was associated with a reduction in the risk of CVD	180
D:A:D study group (2003)	Patients with HIV infection	Combination regimen including a PI or an NNRTI	23,468	2.2 years	MI	Use of ART was associated with a 26% relative increase in rate of MI per year of exposure	181
SMART (2006)	Patients with well-controlled HIV infection; cohort from 33 countries	Continuous ART versus episodic use of ART	5,472	16 months	Opportunistic disease or death from any cause; major cardiovascular, renal or hepatic disease	Continuous ART reduced the risk of CVD compared with episodic use of ART	182
D:A:D study group (2007)	Patients with HIV infection	PIs or NNRTIs	23,437	5.2 years	MI	Exposure to PIs was associated with a higher rate of MI per year of exposure	25
D:A:D study group (2008)	Patients with HIV infection	NRTIs	33,347	7.2 years	MI	Use of abacavir or didanosine in the previous 6 months was associated with increased risk of MI	28
Stein et al. (2015)	Patients with HIV infection without known CVD or diabetes mellitus who were initiating their first ART	NRTI, PI or integrase inhibitor	328	6.4 years	Changes in carotid artery IMT	Atazanavir had a protective effect, with slower carotid IMT progression in the setting of high plasma bilirubin levels compared with other ART regimens	183
START (2015)	Patients with HIV infection; cohort from 35 countries	Immediate initiation of ART versus deferred initiation of ART	4,299	6.4 years	MI, stroke, coronary revascularization or CVD-related death	Early initiation of ART did not significantly reduce the incidence of the cardiovascular end point	184
Marconi et al. (2018)	Individuals with or without HIV infection and without known CVD	NRTI, PI or NNRTI	96,381	8.8 years	CVD including acute MI, heart failure and stroke	Decreased risk of CVD in the setting of high plasma bilirubin levels irrespective of HIV infection status	120
Elion et al. (2018)	Patients with HIV infection	NRTI	8,265	12 years	Type 1 and type 2 MI	Use of abacavir in the past 6 months was associated with increased risk of MI	31
D:A:D study group (2018)	Patients with HIV	PIs	49,709	>15 years	CVD	Use of ritonavir-boosted darunavir but not ritonavir-boosted atazanavir was associated with increased risk of CVD	27

ART, antiretroviral therapy ; CVD, cardiovascular disease; IMT, intima–media thickness; MI, myocardial infarction; NNRTI, non-nucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor ; VA , Veterans Affairs.

Table 3 |

Associations of inflammatory and coagulation biomarkers with mortality in HIV infection

Study (year)	Study population	Number of patients	Follow-up	Findings	Refs
SMART (2008)	Patients with well-controlled HIV infection; cohort from 33 countries	5,472	3,700 person-years	• IL-6 and D-dimer levels in plasma were strongly associated with all-cause mortality • IL-6, hsCRP and D-dimer levels in plasma were associated with increased risk of CVD	84,185
FRAM (2010)	Patients with HIV infection	922	5 years	Fibrinogen and CRP levels were strong and independent predictors of mortality	186
ALLRT (2014)	Patients with HIV infection who had achieved virological suppression within 1 year after ART initiation	143	48–64 weeks after ART initiation	High IL-6, sTNFRI, sTNFRII and D-dimer levels in plasma and KT ratio at 1 year were associated with increased risk of non-AIDS events	97
VACS (2016)	Patients with HIV infection and individuals without infection	2,350	6.9 years	HIV infection was associated with elevated IL-6, sCD14 and D-dimer levels in plasma, which are associated with mortality	187
MACS (2016)	Patients with well-controlled HIV infection	670	Up to 18 years	IL-6 and sCD14 levels in plasma were predictive of mortality	188
START (2017)	Patients with HIV infection; cohort from 35 countries	4,299	3.2 years	Baseline IL-6 and D-dimer levels in plasma were associated with the risk of AIDS, serious non-AIDS events or death	189

ART, antiretroviral therapy ; CRP, C-reactive protein; CVD, cardiovascular disease; hsCRP, high-sensitivity C-reactive protein; KT, kynurenine:tryptophan; sCD14; soluble CD14; sTNFRI, soluble tumour necrosis factor receptor type I; sTNFRII, soluble tumour necrosis factor receptor type II.

Table 4 |

Effect of antiretroviral therapies on blood lipid levels[190]

Class	Drug	Effect on blood lipids	Refs
Protease inhibitors	Atazanavir	Increases HDL-C and decreases LDL-C levels	191
	Darunavir	Increases HDL-C levels	191
	Fosamprenavir	Hypertriglyceridaemia	192
	Ritonavir[a]	Increases HDL-C levels	191
	Saquinavir	Neutral	192
	Tipranavir	Dyslipidaemia	192
NRTIs	Abacavir	Increases total cholesterol, LDL-C and HDL-C levels	193
	Lamivudine	Increases total cholesterol, LDL-C and HDL-C levels	193
	Tenofovir fumarate disoproxil	Lowers LDL levels	194
	Zidovudine	Hypertriglyceridaemia	194
NNRTIs	Efavirenz	Increases total cholesterol, LDL-C, HDL-C and triglyceride levels	193
	Nevirapine	Neutral or decreases lipid levels	195
	Rilpivirine	Neutral	193
Integrase inhibitors	Dolutegravir	Neutral	133
	Raltegravir	Increases HDL levels	191

HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; NNRTI, non-nucleoside reverse-transcriptase inhibitor ; NRTI, nucleoside reverse-transcriptase inhibitor.

[a]Although ritonavir is a protease inhibitor, this drug is generally used as a pharmacokinetic enhancer.