HIV, highly active antiretroviral therapy and the heart: a cellular to epidemiological review

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Abstract

The advent of potent highly active antiretroviral therapy (HAART) for persons infected with
HIV-1 has led to a “new” chronic disease with complications including cardiovascular disease
(CVD). CVD is a significant cause of morbidity and mortality in persons with HIV infection. In
addition to traditional risk factors such as smoking, hypertension, insulin resistance and
dyslipidaemia, infection with HIV is an independent risk factor for CVD. This review summarizes:
(1) the vascular and nonvascular cardiac manifestations of HIV infection; (2) cardiometabolic
effects of HAART; (3) atherosclerotic cardiovascular disease (ASCVD) risk assessment,
prevention and treatment in persons with HIV-1 infection.

Keywords

atherosclerotic cardiovascular disease; cardiovascular disease; endothelial dysfunction; highly
active antiretroviral therapy; HIV; prevention

Introduction

The era marred by a mysterious, rapidly lethal virus affecting young homosexual men has
passed. The medical community is now faced with a “new” chronic disease with unclear
long-term complications. Rates of infection with HIV-1 among homosexual men are falling
and are now exceeded by rates of infection among young minority women. The southern
part of the USA has the highest incidence of new HIV-1 diagnosis, 13.7 per 100,000 people [1]. Moreover, African Americans account for nearly half of all new infections and of people living with HIV-1 [1,2]. Although men comprise the largest number of new diagnoses, African American women represent a cohort with the next highest rate of growth and prevalence of HIV-1 infection. Globally, the rates of infection are highest in sub-Saharan Africa, although Eastern Europe and Southeast Asia are now faced with an emerging epidemic attributable in part to the lack of prevention initiatives [3]. In developed countries such as the USA and many parts of Western Europe, patients are now able to survive as long as those who are uninfected and present the medical community with a “new” chronic disease with uncertain long-term complications. Along with a changing global epidemiological landscape and greater survival comes the responsibility to examine the long-term effects of HIV on overall health.

As the demographics and life expectancy of those affected evolve, so does our understanding of the disease. The treatment armamentarium for HIV infection has expanded considerably and, with the advent of highly active antiretroviral therapy (HAART), the life expectancy of HIV-positive persons has markedly increased. As a result of successful virological management, >50% of HIV-positive persons will be >50 years of age by the year 2015. Because these persons are living longer, diseases of older age, including cancers and atherosclerotic cardiovascular disease (ASCVD), now emerge as prominent causes of death in this population [4,5].

**Burden of cardiovascular disease in the HIV-infected population**

Premature ASCVD among HIV-positive persons is a well-known manifestation of the disease and has a significant impact on morbidity and mortality in this population [6,7]. A study from Kaiser Permanente characterized the overall risk of ASCVD in HIV-positive compared with HIV-negative populations. HIV-positive persons had a nearly 50% greater occurrence of myocardial infarction (MI) compared with HIV-negative persons [relative risk (RR) 1.483 (95% confidence interval (CI) 0.33–6.558) in the 2002 group and RR 1.682 (95% CI 0.318–8.902) in the 2007 group] [8,9]. A similar RR for developing MI was observed in a Massachusetts study (RR 1.75; 95% CI 1.51–2.02; P < 0.0001) [10].

There is specific evidence that HIV-1 infection confers a heightened risk of acute coronary syndrome (ACS) that may be as much as 1.5 times higher than that of the uninfected population [9–18]. In a recent report, ACS incidence was elevated by 40% in HIV-positive vs. HIV-negative populations [19]. Additionally, 2- to 6-fold higher rates of ischaemic cardiomyopathy and overall coronary artery disease (CAD) hospitalizations occur in persons infected with HIV-1 compared with uninfected persons [20–22]. HIV-1 infection leads to increased ASCVD rates among all age groups [2,12,21].

To understand this complex relationship, both vascular and nonvascular cardiac manifestations of HIV-1 infection must be understood.
Nonvascular cardiac manifestations of HIV-1 infection

The cardiovascular manifestations of HIV-1 infection are not limited to ASCVD, but rather are observed in multiple areas of the cardiovascular system. Direct infection of the myocardium is rare in HIV-1 infection but is a consideration in certain persons, primarily those naïve to HAART [23,24]. This infrequency may be a result of the lack of CD4 receptors on the cardiac myocyte cell membrane or an “unproductive” HIV-1 lifecycle in the cardiac myocyte, as described by Lopes de Campos et al. [23,25,26]. Myocarditis in an HIV-positive person can present acutely with direct toxicity from HIV-1 or secondarily from opportunistic infection (toxoplasmosis, cryptococcosis, cytomegalovirus (CMV) infection, tuberculosis (TB) and herpes simplex virus (HSV) infection) affecting the myocardium [27–31]. The endocardium and valve tissue may be involved in HIV infection, especially in persons with a history of injecting drug use [3,32]. Furthermore, rare opportunistic pathogens associated with HIV-1 infection, including TB and Kaposi sarcoma (KS), can manifest as pericarditis or even arterial diseases [33,34].

Intracardiac tumours are rare in HIV-positive persons and typically are pathologically different from those found in HIV-negative persons. In HIV-positive persons, a cardiac tumour is most likely to be a KS or lymphoma, in contrast to the myxomas, fibroelastomas, and sarcomas seen in the HIV-negative population [3,35–37]. In a person with proven cardiac KS, many organ systems are typically involved and mucocutaneous disease is often seen prior to the finding of cardiac involvement. The cardiac lymphomas are typically B-cell lymphomas within the right atrium that can infiltrate the conduction system, leading patients to present with symptomatic conduction disturbances [3,37].

HIV-associated cardiomyopathy

Initially defined as symptomatic systolic dysfunction with a dilated cardiomyopathy in the pre-HAART era, HIV-associated cardiomyopathy now includes both systolic and diastolic dysfunction [38–40]. Prior to HAART, several independent studies estimated the prevalence of systolic dysfunction to be anywhere from 7 to 30% [40]. In the post-HAART era, HIV-associated cardiomyopathy has changed to include a decreased prevalence of systolic dysfunction and an increase in diastolic dysfunction. A meta-analysis of 2242 HIV-positive persons, 98% of whom were on HAART, revealed a prevalence of 8.3 and 43.4% for systolic and diastolic dysfunction respectively. Of the total population studied, 25, 40 and 75% were exposed to protease inhibitor (PI), nonnucleoside reverse transcriptase inhibitor (NNRTI) or nucleoside reverse transcriptase inhibitor (NRTI) therapies, respectively [39]. The postulated pathophysiology for HIV-associated cardiomyopathy includes direct infection of the myocardium by HIV, HAART toxicity, opportunistic infections and ischaemia [40–42]. More studies are needed to further clarify the incidence, pathophysiology, risk factors, prognosis and treatment of persons with HIV-associated cardiomyopathy in the post-HAART era.

Pulmonary arterial hypertension

While HIV can directly cause cardiac disease, the virus has also been linked to pulmonary hypertension. The rate of pulmonary hypertension in HIV-positive persons is 1/200.
compared with 1–2/1 million in HIV-negative persons [43]. The pathophysiologial basis for the vascular damage appears to be related to HIV-1 glycoprotein 120 (gp120)-induced release of inflammatory cytokines [interleukin (IL)-1, IL-6, endothelin-1 and platelet-derived growth factor] along with the activation of alpha-1-adrenoceptor [3,44,45,46]. Given that HIV infection leads to indirect injury to the pulmonary vasculature through this inflammatory cascade, it is accepted that persons with poorly controlled HIV infection are more likely to experience pulmonary hypertension compared with those persons with well-controlled disease. Although persons with undetectable viral load have less risk than those with uncontrolled disease, they still have an increased risk for developing vascular diseases including pulmonary arterial hypertension (PAH) compared with HIV-negative persons.

Additional investigations into the mechanism of pulmonary hypertension within HIV-positive persons found no detectable HIV-1 DNA, RNA or p24 antigens within the lung parenchyma or vasculature. This absence supports the theory of HIV-mediated inflammatory damage to the pulmonary vasculature as the leading aetiology of pulmonary hypertension in this population. HIV can also lead to pulmonary hypertension through other pathways, including congestion from left ventricular dysfunction [World Health Organization (WHO) Class II], or through a predisposition to chronic thromboembolic disease of the pulmonary arteries (WHO Class IV) [46–50]. Regardless of the mechanism of pulmonary hypertension in the HIV-positive population, the treatment is similar to that in HIV-negative persons and relies on vasoactive medications such as calcium channel blockers, diuretics, anticoagulation, prostacyclin analogues and endothelin receptor antagonists [3,51].

**Vascular manifestations of HIV infection**

HIV-1-related vascular disease affects the cardiopulmonary system and the peripheral vascular system. HIV-1 infection and associated opportunistic infections such as CMV infection and TB have been linked with direct invasion of the vasculature in children leading to aneurysmal vascular disease in the aorta, great vessels, and the cerebrovascular system [52]. The extension of vascular disease has been confirmed in studies showing a higher incidence of stroke in HIV-positive vs. HIV-negative populations (3.3 vs. 1.7 per 1000 person-years, respectively) [4].

In addition to increased incidence of stroke demonstrating HIV-associated effects on vascular health, researchers have been able to demonstrate pathological changes in the vasculature in HIV-positive persons. Some studies have demonstrated increased carotid intima-media thickness (CIMT) in HIV-positive persons compared with matched HIV-negative controls. Van Vonderen et al. [53] showed that HIV-positive persons had 10.8% greater CIMT (P < 0.001) and greater stiffness of their arteries (femoral and carotid) compared with controls. This contrasts with a study by Kaplan et al. investigating the Women’s Interagency Health Study (WIHS) and Multicenter AIDS Cohort Study (MACS) population which showed no significant association between CD4 T-cell count, HIV-1 viral load and CIMT. They did, however, note a 70–100% increase in carotid lesions in HIV-positive persons with CD4 count < 200 cells/μL. Interestingly, the WIHS/MACS study did not show an association between this vascular disease and time on HAART [54].
The association between vascular disease and HIV-1 positivity, regardless of the severity of HIV-1 viral load, points to the contribution of increased atherogenic lipoproteins and chronic inflammation as mediators of the observed increased prevalence of vascular disease [46,55].

Pathophysiology of HIV-related vascular disease

Three mechanisms contribute to an increased prevalence of vascular disease among HIV-positive persons: (1) direct HIV-1-mediated damage to the vascular endothelium and associated chronic inflammation related to HIV-1 viral replication, (2) side effects/off-target effects from antiretroviral pharmacotherapy and (3) changes in traditional risk factors including dyslipidaemia and tobacco abuse [46,56].

Direct HIV-mediated damage and associated chronic inflammation—HIV-1 has long been known to directly injure the vascular endothelium in a mechanism similar to that of CMV, HSV and Epstein–Barr virus (EBV) [57–59]. After infection by HIV-1, the vascular endothelium induces an inflammatory response consisting of leucocyte recruitment, platelet adhesion and coagulation system derangements in mechanisms similar to that seen with tobacco use, diabetes, hypertension and dyslipidaemia. This effect is present in both HAART-naïve individuals and HIV-positive persons on HAART [6,58,60–65].

In large population studies, rates of thrombotic disease appear to be 2–10 times higher in the HIV-positive population than in the HIV-negative population. The likelihood of thrombosis and the severity of viral infection are related, as persons with AIDS (CD4 count < 200 cells/μL) have twice the risk for thrombosis compared with those HIV-positive persons with a CD4 count > 200 cells/μL [47]. The coagulation abnormalities appear to be related to HIV-mediated changes in coagulation factors. HIV-1 infection can lead to the release of lipopolysaccharide (LPS). LPS release can increase tissue factor, leading to a coagulation system imbalance, increases in D-dimer and an overall increased risk of thrombosis [46,66–69]. Further derangements in the coagulation system include changes in antithrombin (decreased), lupus anticoagulant (present in up to 70% of HIV-infected patients), anticardiolipin (present in 46–90% of HIV-infected persons), protein S (acquired deficiencies in up to 75% of HIV-positive subjects), and protein C (decreased) [47,70–74]. Thromboembolic events in infected persons may manifest in various anatomic locations including the pulmonary, retinal, subclavian and popliteal arteries as well as the deep venous system.

HIV-1 can also directly infect the dendritic cells within the arterial wall leading to atherosclerotic changes [47]. Once the cells are infected, HIV-1 proteins may have the ability to activate smooth muscle and foam cell proliferation and engulfment by macrophages and, ultimately, contribute to the formation of an eccentric plaque causing flow-limiting atherosclerotic disease [47].

Opportunistic infections such as CMV or HSV-1 infection can independently lead to endothelial dysfunction. This was first seen in studies investigating transplant recipients who had accelerated rates of cardiac allograft vasculopathy [46,75–79]. Through their investigation into carotid artery distensibility, investigators have demonstrated that women with higher CMV immunoglobulin G antibody levels have more severe vascular disease.
regardless of their HIV-1 viral load. This finding supports CMV as an independent cause for endothelial dysfunction [46,80]. This will lead to investigation into CMV eradication in HIV-positive persons as an adjunctive approach aimed at reducing rates of cardiovascular complications [46].

An alternative explanation for HIV-mediated endothelial dysfunction involves intestinal microbe translocation as a result of mucosal barrier breakdown during acute infection. This may lead to chronic, low-level inflammation in HIV-positive patients. This “leaky gut” may lead to persistent immune activation, including release of LPS – a potent proinflammatory molecule.

Cardiometabolic effects of HAART—Investigations concerning drug-related risk in HIV-positive persons have focused predominantly on PIs, although there are data to suggest that NRTIs also contribute to increased cardiovascular risk [81]. Older PIs have been associated with dyslipidaemias (70% of patients) and lipodystrophy (25–62% of patients). These effects are not seen as frequently with newer generation PIs. PIs are also known to contribute to endothelial dysfunction, deregulation of the coagulation cascade, and insulin resistance (25–60% of patients).

The fat wasting in early generation PI-related lipodystrophy extends from the face, buttocks and extremities and coexists with abnormal fat accumulation in the torso and neck [3,6,58,82–85]. The mechanism for these lipodistributive changes may be related to inhibition of cis-9-retinoic acid and peroxisome proliferator-activated receptor gamma (PPAR-γ). This inhibition leads to adipocyte cell death and reduction in the adipocyte regeneration rate. These phenotypic changes lead to increases in circulating triglycerides and lipid derangements, including increased total cholesterol, low-density lipoprotein (LDL) cholesterol and triglyceride levels alongside decreased high-density lipoprotein (HDL) cholesterol levels [3,83,86].

Protease inhibitors can also lead to atherosclerotic disease secondary to an up-regulation of CD-36-dependent cholesteryl ester by specific PIs (ritonavir, indinavir and amprenavir) within vascular macrophages that promote atherosclerotic plaque formation. This mechanism was detailed in a CD-36 knockout mouse population that demonstrated protection from PI-induced plaque formation in the CD-36-dependent cholesterol ester knockout mice [3,6,46,87].

Work by Lewis et al. has demonstrated that NRTIs induce mitochondrial toxicity that may manifest as dysfunction of various organs, including the heart [88–90]. Similar to PI-related toxicity, NRTI-induced mitochondrial toxicity has multiple proposed mechanisms. One involves NRTIs inhibiting DNA polymerase-γ, which ultimately results in depleted mitochondrial DNA and dysfunction [88,89]. Other mechanisms include mitochondrial DNA mutations, induced oxidative stress, and alterations to protein synthesis [88,89,91,92].

Although it is clear that components of HAART are related to cardiac toxicity, the benefits of treating the viral infection are clearly superior to the risks of the medications. Several studies, including the Strategic Management of Antiretroviral Therapy (SMART) study, have
demonstrated superiority of an early HAART strategy over a CD4-based regimen [93]. The Food and Drug Administration mitigates any risk of HAART-related cardiotoxicity by performing trials before any new agents are approved [94].

**Changes to traditional risk factors**—There appears to be a higher prevalence of traditional risk factors such as hypertension, diabetes, lipid abnormalities and tobacco use among HIV-positive persons when compared with HIV-negative persons [9]. The infection itself often leads to early decreases in HDL cholesterol and elevations in triglycerides, with a delayed decrease in LDL cholesterol later in the disease’s course, possibly increasing the risk for cardiovascular disease [3,6,8,95]. Additionally, the rate of tobacco use is significantly higher in HIV-positive persons compared with uninfected persons. A 2009 NIH report described 50–70% of HIV-positive persons smoking vs. only 19% of HIV-negative persons [96]. Importantly, these changes in traditional risk factors, such as increased rates of tobacco abuse in HIV-positive persons, must be accounted for while interpreting data from trials estimating risk differences between HIV-positive and HIV-negative persons.

**ASCVD risk assessment in patients with HIV infection**

**Past models and limitations**

As the life expectancy of HIV-positive persons continues to increase as a result of the availability of safer and more potent HAART, effective ASCVD risk assessment tools are needed in this population. The Framingham risk calculator is still widely taught and commonly accepted as a predictor of cardiovascular risk in the general population. The Framingham risk score has consistently been shown to underestimate risk in the HIV-infected population, probably because of the absence of HIV-specific risk factors in the equation [97]. Modified Framingham scores, such as the Framingham risk score for stroke (FRS-S), have also proved to be inaccurate. The FRS-S predicted a lower risk for stroke (observed 4.9% vs. actual 6.6% 10-year risk) in the HIV-positive population, although data show a higher incidence (3.3 vs. 1.7 per 1000 person-years in the HIV-positive vs. HIV-negative populations, respectively) [4]. The model is based on data from the 1990s and does not include HIV status. This discrepancy between predicted and actual incidences is probably attributable to the lower average age of stroke in the HIV-positive population [4]. More recently, the American College of Cardiology/American Heart Association (ACC/AHA) released a pooled cohort ASCVD risk calculator for cardiovascular risk assessment [98]. A limitation of this calculator, however, is that it has not been validated specifically in the HIV-positive population and does not include factors such as HAART exposure, viral load, and opportunistic infections.

The HIV Outpatient Study (HOPS) helped to define how HIV-specific factors contribute to the risk of ASCVD. Their investigation yielded the “attributable risk” for different factors in overall ASCVD risk. A CD4 count of < 500 cells/μL had an attributable risk of 25.6%, which was comparable to that for tobacco use (26.7%) and less than the attributable risks of age (49.2%) and hypertension (34.4%). The attributable risk of a CD4 count of < 500 cells/μL was higher than the attributable risk associated with elevated LDL cholesterol (21.5%), low HDL cholesterol (21.5%), male gender (20.9%) and diabetes (2.4%) [99].
New models

The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) CHD risk equation is an effort to tailor a risk calculator more specific to the HIV-positive population, incorporating traditional risk factors (age, sex, family history of ASCVD, systolic blood pressure, smoking status, and total cholesterol:HDL cholesterol ratio) with duration of PI therapy, given their association with ASCVD. This model tended to better estimate the risk of developing CVD compared with the Framingham risk score [100–102]. The D:A:D model tends to provide a higher risk as time on HAART increases [103].

Endothelial dysfunction is a major underlying component of CVD and holds diagnostic, prognostic and therapeutic significance. Endothelial dysfunction is associated with increased cardiovascular events, including MI [58,104–108]. Given the biochemical pathways leading to endothelial dysfunction, investigations are underway as to whether contributors [soluble intercellular adhesion molecules (sICAMs), tissue plasminogen activator molecules (t-PAs) and plasminogen activator inhibitor (PAI-1)] to this “dysfunction cascade” could be used as biomarkers to more reliably predict risk [61,62,109–113].

As our understanding of the interplay between HIV and the cardiovascular system evolves, especially regarding endothelial dysfunction and its role in cardiovascular risk, newer tools for the prediction of cardiovascular risk may emerge. These options may use existing models such as the Framingham or ACC/AHA Pooled ASCVD Risk calculator as a backbone with modifiers to account for HIV-positive patient-specific variables such as PI therapy, duration of HIV-1 infection, biomarkers of chronic inflammation and cardiovascular imaging [4].

ASCVD biomarkers in HIV-1 infection

Inflammatory markers such as high-sensitivity C-reactive protein (hsCRP), IL-6, n-dimer and soluble vascular cell adhesion molecule-1 (sVCAM-1) have been studied in the context of risk stratification in ASCVD [4,46,114]. The most studied of these, hsCRP, is elevated in HIV-positive persons compared with matched controls (39.3% vs. 23.6%, respectively; P = 0.03) [115]. As shown in the JUPITER trial, treating HIV-negative persons with normal LDL cholesterol and elevated hsCRP (> 2.0 mg/L) with rosvastatin led to a 44% reduction in the primary vascular event endpoint. This reduction in mortality was associated with the reduction in hsCRP [46,109,112,116]. More data are needed to determine if hsCRP levels could be used to guide therapy and whether it will be applicable to the HIV-positive population [114,117]. A nationwide study, the Randomized Study to Prevent Vascular Events in HIV (REPRIEVE) trial, is now enrolling patients to help answer this and other related questions. It will randomize HIV-positive persons without an ASCVD history and with a low risk to develop ASCVD to receive a low-dose statin, pitavastatin, or placebo. This HIV-positive group on statin therapy will be compared with HIV-positive controls on placebo to determine if the statin helps reduce markers of inflammation and, more importantly, reduce the incidence of ASCVD [118].

Imaging

In persons infected with HIV, imaging may play an important role in identifying those at increased ASCVD risk, as well as monitoring ASCVD progression and treatment. Coronary
artery calcium (CAC) is a promising tool for predicting ASCVD risk in an intermediate-risk population. In a report from Fitch et al., CAC score was significantly elevated in HIV-positive persons compared with matched HIV-negative controls (mean CAC scores 72 ± 25 and 18 ± 7, respectively; \( P = 0.02 \)). Investigators also assessed the burden of noncalcified lesions in the populations with computed tomography (CT) angiography. The number of diseased, noncalcified coronary artery segments was higher in the HIV-positive cohort with (1.26 ± 0.31; \( P = 0.01 \)) and without (1.02 ± 0.18; \( P = 0.04 \)) metabolic syndrome when compared with HIV-negative controls (0.45 ± 0.16) [119]. This suggests a disproportionate prevalence of noncalcified coronary artery lesions in HIV-positive persons compared with the HIV-negative population.

A more recent study looked at CAC scores in a group of HIV-positive men. The prevalence of a CAC score > 0 was similar in HIV-positive and HIV-negative men (CAC scores 53.1 and 52.0, respectively). Again, noncalcified lesions were studied with CT angiography and were more prevalent and extensive in the HIV-positive men compared with the HIV-negative men in the Multicenter AIDS Cohort Study (63.3% vs. 53.1%, respectively; prevalence ratio 1.25). The two studies detailed above suggest that HIV alone may increase the risk for noncalcified coronary plaque in persons with HIV. These plaques are lipid rich and may be more likely to become unstable, potentially leading to ACSs [120,121].

**History of CVD therapy in HIV-positive subjects**

The association between HIV and ASCVD led to studies investigating whether treatment of HIV infection would reduce the ASCVD risk. These investigations led to two accepted principles: (1) benefits of early HIV-1/AIDS treatment outweigh the risks associated with therapy and (2) pharmacotherapy for HIV-1/AIDS, particularly with PIs, leads to changes in cardiovascular risk profiles.

Several studies have investigated the risk–benefit relationship of the treatment of HIV-1. An investigation within the Veterans Affairs system demonstrated that the overall death rate among HIV-positive persons dropped significantly after initiation of HAART across the USA [122,123]. This probably reflects the marked reduction in HIV-related complications and deaths avoided through the reduction in viral loads and improvement in CD4 counts.

Contrary to the Veterans Affairs study, the D:A:D study of 23,437 persons showed that the risk of MI corresponded to the duration of exposure to HAART (RR 1.26 per year; 95% CI 1.12–1.41; \( P < 0.0001 \)) [8,100]. Later subgroup analysis of the D:A:D data showed that this risk relationship was present only with PIs and was not found with NNRTI-based regimens [8,100]. The D:A:D results may reflect the limited options in HAART agents and nontolerance of treatment regimens during their study period [6]. Interestingly, in the D:A:D study, HIV disease markers such as CD4 count and HIV RNA viral load were not predictive of ASCVD risk while traditional risk factors (age, sex, diabetes mellitus, smoking, hypertension and dyslipidaemia) were predictive of ASCVD [8,100].

These studies highlight a clinical conundrum between treatment of HIV-1 to prevent opportunistic infections and potential medication-related complications. The concept of a
“sweet spot” of HIV-1 activity (CD4 based) where HAART should be initiated and stopped has been explored.

The SMART study examined whether set cut-offs for starting and stopping HAART would help prevent HIV-related deaths and ASCVD [93]. Study participants were randomized to continuous HAART use or to an episodic HAART regimen based on regularly assessed CD4 counts. The episodic group was initiated on HAART when CD4 counts fell below 250 cells/μL and discontinued when CD4 counts were above 350 cells/μL. Interim data analysis led to the study being stopped early because of a clear increase in adverse outcomes, including ASCVD, among those patients in whom HAART was given on an intermittent basis. Hypotheses for the mechanism behind the adverse events include inflammation related to waxing and waning viral loads and increase in the total:HDL cholesterol ratio [6,8,84,124].

The recently published US Military HIV Natural History Study examined the relationship between time of HAART initiation and the risk for AIDS and immune reconstitution. Their results showed that a 12-month delay in HAART initiation after seroconversion reduced the chance of restoring immune function and lowered the risk of developing AIDS [125].

The Strategic Timing of AntiRetroviral Treatment (START) trial is ongoing with results expected in 2016. Similar to the SMART trial, it randomizes patients to an immediate HAART regimen, started upon HIV diagnosis, or a deferred regimen, started when the CD4 count is < 350 cells/μL or if AIDS is diagnosed [126].

These trials support an expert consensus that the benefits of consistent, early HAART are “highly favourable” over the risks of HAART-associated cardiovascular complications [6,122].

**CVD treatment and prevention moving forward**

Preventing CVD among HIV-positive persons should incorporate previously known evidence expanded to include new understanding of HIV-1-specific pathophysiology and pharmacology (fig 1). Known risk factors still contribute to CVD in HIV-positive subjects, as confirmed by the HOPS [127]. All infected persons should have traditional cardiovascular risk factors (dyslipidaemia, insulin resistance, hypertension, smoking, sedentary lifestyle, weight and family history) regularly assessed [85,128]. The 2013 guidelines for primary care physicians from the Infectious Diseases Association of America recommends a fasting lipid panel when enrolling in HIV care and then within 1–3 months after starting HAART [128]. Haemoglobin A1c values should also be assessed prior to and 1–3 months after starting HAART to monitor for metabolic derangements [128]. While the abovementioned guidelines outline the primary care goals for HIV-positive persons, recent data presented at the International AIDS Conference suggested HIV-positive patients’ HTN and hyperlipidaemia were not as aggressively managed for HIV-positive persons compared with matched HIV-negative controls, suggesting that improvements are needed in the primary care setting for the HIV-positive population [129].

Once a complete ASCVD risk profile has been assessed, aggressive treatment and prevention strategies should be employed. Hyperlipidaemia can be effectively managed with
appropriate statin choices (Table 1). Results from the REPRIEVE trial may change when clinicians prescribe statins for HIV-positive persons [118]. Simvastatin, atorvastatin and lovastatin should be avoided as these are metabolized by CYP3A4 with the potential to interact with several antiretroviral medications such as ritonavir, atazanavir and saquinavir [3, 84, 128]. These PIs inhibit the CYP3A4 enzyme that normally metabolizes these statins [130]. If these PI-induced risk factors lead to an unfavourable risk profile, changing the PI to another reverse transcriptase inhibitor is an acceptable alternative. This substitution was studied and found to not affect virological control while it improved lipid profiles and the prevalence of metabolic syndrome [3, 131, 132].

Some evidence exists supporting treatment of the lipodystrophy associated with HIV infection and its treatments. Untreated lipodystrophy is known to contribute to insulin resistance and impaired glucose metabolism, which can accelerate atherosclerosis [133]. The first approved therapy for HIV-related lipodystrophy, Tesamorelin, is a growth hormone-releasing hormone analogue that leads to the release of growth hormone and a 15–18% reduction in visceral fat [84, 134, 135].

**Cardiac surgery in HIV infection**

As persons with HIV live longer, advanced CVD is now more frequently identified at a younger age – at times leading to consideration of cardiac surgery for treatment. Studies have demonstrated no increased peri-operative risk attributable to the HIV-1 infection alone and surgery does not seem to change the disease course [136]. The neutral effect of HIV-1 on cardiac surgical risk has led some to advocate consideration of HIV-positive persons for cardiac transplantation when indications such as fulminant HIV cardiomyopathy and end-stage ischaemic and nonischaemic cardiomyopathy are present. If cardiac transplant for HIV-positive persons occurs, investigations into immunosuppressant therapies peri- and post-transplant will be important as some of these medications may impact viral replication and interact with HAAR.

**Future directions**

The HIV epidemic has markedly transformed the perception of infectious diseases globally. Our understanding of HIV-associated CVD risk is steadily advancing. Moving forward, preventive care for HIV-positive persons will need to adapt quickly to our current understanding of virology, biochemical pathways, pharmacology, toxicology and pathogenesis. Research efforts will need to include HIV-1-specific markers (such as CD4 count, HIV RNA viral load and medication regimen components) to better characterize their interactions and help predict risk. Risk prediction will probably incorporate known models such as the 2013 ACC/AHA ASCVD Risk Estimator in addition to biomarkers and imaging modalities.

HIV-positive persons presently live in an era with less uncertainty and the potential for extended longevity with a chronic disease. These subjects must be identified early and aggressively managed from infectious disease, health maintenance and preventive perspectives. Accurately assessing cardiovascular risk and initiating appropriate prevention strategies is an essential component of the care of this now manageable, chronic disease.
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HIV-Specific Risk Factor Management

Traditional Risk Factor Management

HIV Education and Counselling

Universal Screening to Identify HIV-positive persons

Fig. 1.
Overview HIV atherosclerotic cardiovascular disease (ASCVD) care.
Fig. 2.
Mechanisms of HIV-associated atherosclerotic cardiovascular disease (ASCVD). HAART, highly active antiretroviral therapy; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; LPS, lipopolysaccharide; PAI-1, plasminogen activator inhibitor; PI, protease inhibitor; PPAR-γ, peroxisome proliferator-activated receptor gamma; sICAM, soluble intercellular adhesion molecule; TGs, triglycerides.
Fig. 3.
The effects of highly active antiretroviral therapy (HAART) on atherosclerotic cardiovascular disease (ASCVD).
Table 1

Statin considerations in HIV-positive persons on highly active antiretroviral therapy (HAART) [128,137]

<table>
<thead>
<tr>
<th>Statin</th>
<th>Protease inhibitor</th>
<th>Interaction/prescribing recommendation</th>
<th>NNRTI</th>
<th>Interaction/prescribing Recommendation</th>
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<tr>
<td>Atorvastatin</td>
<td>Tipranavir/ritonavir</td>
<td>Significantly increased atorvastatin AUC</td>
<td>Efavirenz</td>
<td>Decrease atorvastatin AUC</td>
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<td></td>
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<td>Avoid atorvastin</td>
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<tr>
<td></td>
<td>Darunavir + ritonavir</td>
<td>Increased atorvastatin AUC</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fosamprenavir</td>
<td>Do not exceed 20 mg daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fosamprenavir + ritonavir</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Saquinavir + ritonavir</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nelfinavir</td>
<td>Increased atorvastatin AUC</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Do not exceed 40 mg daily</td>
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<td></td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>Nelfinavir</td>
<td>Not recommended</td>
<td>Etravirine</td>
<td>May increase fluvastatin AUC. May need to lower fluvastatin starting dose</td>
</tr>
<tr>
<td></td>
<td>All others</td>
<td>No known significant interactions</td>
<td>Delavirdine</td>
<td></td>
</tr>
<tr>
<td>Lovastatin</td>
<td>All</td>
<td>Significant increase in Lovastatin AUC</td>
<td>Delavirdine</td>
<td>Not recommended</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Contraindicated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>Atazanavir</td>
<td>No dose limitations</td>
<td>All others</td>
<td>Acceptable with appropriate dosing and monitoring</td>
</tr>
<tr>
<td></td>
<td>Darunavir + ritonavir</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lopinavir + ritonavir</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pravastatin</td>
<td>Darunavir</td>
<td>Increases pravastatin AUC</td>
<td>Efavirenz</td>
<td>Decreases pravastatin’s AUC so may need higher starting dose</td>
</tr>
<tr>
<td></td>
<td>All others</td>
<td>Decrease pravastatin AUC</td>
<td>Etravirine</td>
<td>No change in dosage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acceptable with appropriate dosing and monitoring</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>Atazanavir + ritonavir</td>
<td>Increase rosvastatin AUC</td>
<td>All</td>
<td>Acceptable with appropriate dosing and monitoring</td>
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<tr>
<td></td>
<td>Tipranavir + ritonavir</td>
<td>Limit dose to 10 mg once daily</td>
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<tr>
<td></td>
<td>Lopinavir + ritonavir</td>
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<tr>
<td>Simvastatin</td>
<td>All</td>
<td>Significant increase in simvastatin AUC</td>
<td>Efavirenz</td>
<td>Decrease simvastatin AUC</td>
</tr>
<tr>
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<td></td>
<td>AUC, Contraindicated</td>
<td>Etravirine</td>
<td>Acceptable with appropriate dosing and monitoring</td>
</tr>
</tbody>
</table>

AUC, area under the plasma drug concentration–time curve; NNRTI, nonnucleoside reverse transcriptase inhibitor.