Atherosclerotic cardiovascular disease (CVD) has become an important cause of morbidity and mortality among individuals with human immunodeficiency virus (HIV) infection with access to antiretroviral medications, as the risk for AIDS has fallen and life expectancy improved. Traditional CVD risk factors are often more common among individuals with HIV infection, and traditional prevention strategies remain important. Recent data have revealed that untreated HIV infection itself amplifies additional pro-atherogenic mechanisms related to immune activation, inflammation, coagulation, and lipoprotein particle changes (e.g. high-density lipoprotein particles). Some of these mechanisms are attenuated, though incompletely, with antiretroviral therapy (ART)-related suppression of HIV replication. Exposure to ART is also associated with variable toxicity that may simultaneously decrease (via viral suppression) and increase CVD risk. Ultimately, additional adjunctive treatment will be needed to mitigate premature CVD risk among contemporary HIV-infected patients with access to ART.

Keywords
Untreated HIV infection • Cardiovascular disease • Antiretroviral therapy

Introduction
For human immunodeficiency virus (HIV)-infected persons with access to effective combination antiretroviral therapy (ART), premature atherosclerotic cardiovascular disease (CVD) is now a leading cause of morbidity and mortality.1 Advancing age, resulting from prolonged life expectancy, and a higher prevalence of traditional risk factors (e.g. smoking) remain important contributors to CVD risk in this context.2,3 However, HIV-specific factors are also pro-atherogenic, both as a consequence of antiretroviral toxicity and HIV infection itself.

Findings from the Strategic Management of AntiRetroviral Therapy (SMART) study, and follow-up biomarker analyses, have fundamentally changed our understanding of HIV-associated CVD pathogenesis and focused attention on the consequences of untreated HIV infection. In SMART, the relative risk for CVD events was 60% greater for a strategy of episodic ART use, when compared with continuous ART use.4 Recent data have further demonstrated that untreated HIV infection amplifies a number of factors that are known to be pro-atherogenic (Figure 1). The purpose of this review is to explore potential mechanisms by which HIV infection, independent of antiretroviral treatment, may increase CVD risk, and in the process identify factors that may be targeted by HIV-specific CVD prevention strategies.

Immune activation and inflammation
Immune dysfunction, activation of lymphocytes, and inflammation are hallmarks of untreated HIV infection that may have broad consequences beyond AIDS-related disease progression.5,6 Important associations between inflammation and CVD pathogenesis are also well established. Elevated C-reactive protein levels, an acute phase reactant, and interleukin (IL)-6 levels, a cytokine released by monocytes and lymphocytes that stimulates C-reactive protein release from hepatocytes, are both independent predictors of CVD events in the general population.7,8 C-reactive protein and IL-6 levels are elevated in HIV-infected patients and predict risk for CVD and all-cause mortality.5,9,10 Specifically in SMART, baseline levels of these biomarkers were associated with excess CVD risk.
During the study, among participants in SMART with HIV suppression at baseline, the increase in IL-6 levels 1 month after stopping ART strongly correlated with the extent of the rise in HIV RNA level during this time ($P = 0.0003$). The mechanisms underlying chronic inflammation and release of cytokines with HIV infection are complex, but may, in part, be a result of HIV replication (even at low levels in the context of ART), activation, and dysregulation of leukocytes (and antigen-presenting cells) and/or damage to the gastrointestinal lymphatic system and mucosal barrier with increased bacterial translocation.

Despite effective treatment with ART, chronic immune activation persists during HIV infection. Among SMART participants with undetectable HIV RNA levels, high-sensitivity C-reactive protein and IL-6 levels were elevated by 38 and 60%, respectively, when compared with controls from the general population cohort Multi-Ethnic Study of Atherosclerosis (MESA). Furthermore, HIV ‘elite controllers’ (individuals capable of maintaining undetectable HIV RNA levels in the absence of ART), as well as those with ART-associated HIV suppression, both exhibit greater activation of CD8$^+$ and CD4$^+$ T-cells when compared with uninfected persons. Among patients in the Women’s Interagency HIV Study, greater T-cell activation (of either CD8$^+$ or CD4$^+$ cells) was associated with subclinical arterial disease defined either by the ultrasound presence of carotid lesions or impaired carotid artery distensibility. The contribution of co-pathogens may also contribute to accelerated atherosclerosis in HIV patients. Hsue et al. described greater T-cell activation, high-sensitivity C-reactive protein levels, and carotid artery intima–media thickness (CIMT) among HIV-infected vs. uninfected persons, and cytomegalovirus-specific T-cell responses were independently associated with CIMT. Cumulatively, these data suggest that suppression of HIV replication below the level of detection by clinical assays will not fully attenuate chronic activation of the host’s immune system, and anti-inflammatory treatments should be studied as part of comprehensive CVD prevention in this population.

Alterations in lipids and lipoproteins

Human immunodeficiency virus infection has a profound impact on blood lipids. Early in the epidemic, Grunfeld et al. described elevated triglyceride (TG) levels in patients with AIDS resulting from decreased clearance of TG, in part, through cytokine-mediated decrease in lipase activity. Among HIV-infected patients
in the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study, the relative risk of myocardial infarction for each doubling of TG level was 1.67, and fell to 1.11 after adjustment for traditional risk factors and other lipid levels. Pro-atherogenic changes in low-density lipoprotein cholesterol (LDL-C), including increases in small dense LDL, are also described among HIV-infected individuals, but in large part have been attributed to ART exposure vs. HIV infection per se.

The primary lipoprotein alteration related to untreated HIV infection is a decline in high-density lipoprotein cholesterol (HDL-C). Among patients in the Men AIDS Cohort Study (MACS), HDL-C declined following HIV seroconversion. After initiation of ART in MACS, HDL-C remained ~10 mg/dL below pre-infection levels while total cholesterol (TC) exceeded pre-infection levels. In SMART, both TC and LDL-C declined after stopping ART, but the HDL-C decline was such that the TC/HDL-C ratio actually increased. Thus, whether in the treated or untreated state, HIV infection adversely affects the total to HDL cholesterol ratio—one of the best lipoprotein indices in terms of predicting CVD event risk. This is also consistent with HDL-C declines described in other states of chronic inflammation, including systemic lupus erythematosus.

The atheroprotective mechanisms of HDL include reverse cholesterol transport (RCT) as well as pleiotropic effects related to antioxidant and anti-thrombotic properties. The acute phase response in general has been associated with changes in HDL structure and function including lower levels of HDL-C and the HDL-associated apolipoprotein A1, impaired cholesterol efflux from macrophages, and a reduced ability to inhibit oxidation of LDL. Furthermore, the HIV-nef protein has been shown to block ATP-binding cassette transporter A1-dependent cholesterol efflux, resulting in the accumulation of lipids in macrophages. In the later stages of RCT, HIV infection up-regulates cholesteryl ester transfer protein, which facilitates the delivery of cholesterol esters by HDL-C to atherogenic lipoprotein particles. Thus, both chronic inflammation and HIV infection are associated with pro-atherogenic changes to the function and structure of HDL particles.

Methods that characterize HDL particle size and number, such as nuclear magnetic resonance spectroscopy, allow further assessment of HDL structure that informs clinical risk beyond traditional chemical measures of cholesterol (e.g. HDL-C). In SMART, the total HDL particle number at baseline, and the concentration of large and small HDL particles in particular, were inversely associated with CVD risk. Among SMART participants with previously suppressed HIV RNA levels, the drop in total HDL particle concentration after stopping ART was inversely associated with rise in HIV RNA levels. In a smaller study of patients with untreated HIV infection, small HDL particle concentration was inversely associated with IL-6 levels. The risk for CVD in SMART when considering both baseline IL-6 levels and HDL particle concentration is presented in Figure 2. After adjusting for levels of either high-sensitivity C-reactive protein or IL-6 in SMART, the HDL particle associations with CVD were attenuated but still present. Finally, among HIV-infected persons in MACS receiving ART, the concentration of total HDL particles remained less than for uninfected persons. Hence, HIV-associated low HDL is in part the result of HIV-related inflammation and appears to contribute to excess CVD risk in this context.

Coagulation

Recent data suggest that HIV infection may result in a pro-coagulant state that has broad consequences for premature end-organ disease, both CVD and non-CVD related. D-dimer, fibrinogen, and other markers of coagulation (e.g. factor VIII and von Willebrand factor) are predictors of CVD and mortality risk in the general population. The risk for incident CVD or all-cause mortality for highest vs. lowest D-dimer levels at baseline are reported for HIV-infected participants in SMART and for the general population.
Table 1  Risk of cardiovascular disease or death by d-dimer levels in general population and human immunodeficiency virus-infected cohorts

<table>
<thead>
<tr>
<th>Study sample</th>
<th>MESA (general population)</th>
<th>SMART (HIV infected)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrolment characteristics</td>
<td>Free of clinical CVD at enrolment</td>
<td>Median CD4 601 cells/mm³; 82% on ART</td>
</tr>
<tr>
<td>Number of participants</td>
<td>6391</td>
<td>898 (nested case–control)</td>
</tr>
<tr>
<td>Age in years, [mean (range)]</td>
<td>62 (45–84)</td>
<td>50 (23–76)</td>
</tr>
<tr>
<td>d-dimer level, [median (µg/mL)]</td>
<td>0.20</td>
<td>0.27</td>
</tr>
<tr>
<td>CVD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Events</td>
<td>307</td>
<td>248</td>
</tr>
<tr>
<td>Risk by 4th/1st quartile of baseline d-dimer level (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Univariate</td>
<td>2.3 (1.66–3.18)</td>
<td>2.2 (1.4–3.6)</td>
</tr>
<tr>
<td>Adjusteda</td>
<td>1.3 (0.90–1.85)</td>
<td>2.4 (1.4–3.9)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Events</td>
<td>210</td>
<td>85</td>
</tr>
<tr>
<td>Risk by 4th/1st quartile of baseline d-dimer level (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Univariate</td>
<td>5.8 (3.6–9.3)</td>
<td>12.4 (4.2–37.0)</td>
</tr>
<tr>
<td>Adjusteda</td>
<td>2.8 (1.7–4.6)</td>
<td>11.6 (3.8–35.7)</td>
</tr>
</tbody>
</table>

SMART and MESA d-dimer findings have been previously reported. In SMART, after adjustment for age, race, ART use, HIV RNA level, CD4 count, treatment group, co-infection with hepatitis B or C, smoking status, body mass index, prior CVD, diabetes, total-to-high-density lipoprotein cholesterol ratio, and use of blood pressure or lipid-lowering therapy, odds ratios (95% CI) were similar for CVD (2.5; 1.4–4.3) but were more extreme for all-cause mortality (41.2; 7.5–225.6). In SMART, risk for death was reported up to the study protocol change in January 2006, but risk for CVD included additional follow-up until July 2007. SMART and MESA used the same core laboratory for d-dimer measures, and in SMART, 90% of deaths were non-AIDS related with 28% attributable to CVD. Higher d-dimer levels were independently associated with risk for CVD in SMART but not MESA (and the association in SMART became stronger when adjusted for additional traditional and HIV-specific risk factors; Table 1). Pro-coagulant activity may, in part, be driven by HIV replication and immune activation, though specific changes in pro-thrombotic and anti-thrombotic pathways in untreated and treated HIV infection, compared with uninfected persons, has not been well described.

Higher d-dimer levels were more strongly associated with risk for all-cause mortality (than for CVD), and these associations were more extreme for HIV-infected (SMART) compared with uninfected (MESA) individuals (Table 1). d-dimer has also been associated with non-atherosclerotic outcomes in the general population. Clinically, risk for venous thrombo-embolic disease has been evaluated using d-dimer levels for some time. In MESA, d-dimer levels predicted cancer mortality as well as CVD. Coagulation and fibrinolysis are key features of sepsis, and d-dimer levels are associated both with the severity of sepsis on presentation and the risk for subsequent mortality. Similarly, among patients presenting with community-acquired pneumonia, d-dimer predicted disease severity and subsequent mortality. Finally, higher d-dimer levels are associated with functional decline, as well as mortality, in elderly patients. The pronounced d-dimer odds ratios for all-cause mortality among participants in SMART (Table 1) are consistent with these data, and further suggest that HIV-related activation of coagulation pathways has important consequences for a broad range of end-organ diseases, beyond CVD. Higher baseline fibrinogen levels among HIV-infected participants in Study of Fat Redistribution and Metabolic Change in HIV Infection (FRAM) were associated with increased mortality risk, independent of traditional risk factors, C-reactive protein level, or CD4 count, though whether this differs from fibrinogen risk prediction among uninfected populations is not clear.

Whereas thrombotic activity is intuitively connected to vascular disease, additional epidemiological data suggest that the pro-coagulant state associated with HIV infection increases the disease risk beyond triggering events in the short term, and this risk is not fully attenuated by ART use. Baseline d-dimer levels in SMART predicted mortality risk equally over the near (<2 years) and longer (>2 years) term, and were not attenuated by adjustment for the HIV RNA level, CD4 count, or traditional CVD risk factors. In another HIV case–control study, d-dimer levels, but not high-sensitivity C-reactive protein, predicted incident CVD events occurring either within 4 months or after 2 years. Finally, although changes in d-dimer levels are correlated with changes in HIV RNA levels after stopping or starting ART, d-dimer remained 49% elevated for patients in SMART with undetectable HIV viral loads when compared with general population controls from MESA. Similar to the case with inflammation, adjunct treatments will be needed in combination with ART to attenuate pro-coagulant activity.

Recent pathogenesis studies suggest that HIV infection may modulate coagulation activity via tissue factor (TF) pathways as...
well as platelets. In a retrospective case–control study, soluble TF levels measured ~4 months prior to the CVD event were elevated when compared with HIV-infected patients who did not have a subsequent CVD event.\(^5\) In another cross-sectional comparison, monocyte expression of TF correlated directly with HIV RNA levels and was increased between HIV-infected vs. uninfected persons.\(^4\) In this same study, TF expression on monocytes also correlated with CD14 levels and with soluble CD14, a marker of monocyte responsiveness to lipopolysaccharide exposure.\(^4\) Lipopolysaccharide levels are an indicator of plasma exposure to bacteria, and prior sentinel HIV pathogenesis studies suggest that increased microbial translocation across intestinal mucosal surfaces—a consequence of permanent damage to gastrointestinal associated lymphatic tissue—directly contributes to chronic immune activation among individuals with HIV infection.\(^1\)\(^4\)\(^6\) Cumulatively, these data support the hypothesis that HIV replication and immune activation drives coagulation and fibrinolysis, in part, via up-regulation of TF pathways.

Platelets provide an additional link between HIV-mediated inflammation and coagulation, as they are activated at sites of infection or injury and interact with monocytes, lymphocytes, and endothelial cells.\(^7\)\(^8\)\(^9\) Among patients with untreated HIV infection, thrombocytopenia is a classic haematologic abnormality that worsens with advancing HIV disease.\(^5\) In a small study of 27 patients with thrombocytopenia initiating ART, declines in plasma HIV RNA were associated with a rise in platelet counts, and over half of the participants attained platelet counts in the normal range.\(^5\)\(^6\) Human immunodeficiency virus-1 also binds, and is highly associated, with platelets in the blood, which has been postulated to facilitate clearance and/or dissemination of the virus.\(^5\)\(^1\)\(^2\)\(^3\)

Beyond their role in acute atherothrombotic events (e.g. myocardial infarction), chronic platelet activation may promote atherogenesis through interactions with endothelial surfaces.\(^7\) Ex vivo studies have demonstrated greater platelet activation, chemokine release (e.g. regulated upon activation, normal T-cell expressed, and secreted), and reactivity to epinephrine, among HIV-infected vs. uninfected participants.\(^5\)\(^4\)\(^5\)\(^6\) Among participants with undetectable HIV RNA levels on ART and normal plasma platelet counts, levels of platelet microparticles (cell-membrane fragments released upon activation) were still over 80% elevated when compared with uninfected controls.\(^5\) Data on platelet toxicity related to ART are limited, though abacavir exposure has been shown to cause platelet hyper-reactivity in vitro.\(^5\)\(^6\) These studies support the need for additional research on the benefits of anti-platelet medications among HIV patients, given that they are generally safe, widely used as part of secondary CVD prevention strategies, and may be uniquely beneficial in the context of HIV infection.

### Vascular injury and atherosclerosis progression

Human immunodeficiency virus replication may activate endothelial surfaces both directly and/or via up-regulation of pro-inflammatory cytokines.\(^5\)\(^1\)\(^2\) Biomarkers of endothelial activation are elevated in HIV-infected compared with uninfected controls.\(^2\)\(^9\) In the context of stopping ART, soluble vascular cell adhesion molecule (sVCAM-1) levels increase and correlate with the increase in HIV viral replication.\(^4\)\(^3\)\(^5\)\(^8\) Levels of sVCAM-1 and von Willebrand factor specifically have been shown to decline after ART initiation consistent with a decrease in activation of endothelial surfaces.\(^4\)\(^2\)\(^3\)\(^9\) In cross-sectional studies, untreated HIV infection or detectable HIV RNA levels have been associated with impaired measures of vascular function.\(^6\)\(^0\)\(^1\)\(^1\)\(^2\) In a study of 82 patients starting ART, endothelial dysfunction [assessed via brachial flow-mediated dilation (FMD)] improved after 6 months and was associated with the decline in HIV RNA levels.\(^6\) However, among HIV-infected patients receiving ART for an average of >5 years, impaired FMD was associated with exposure to protease inhibitors (PIs) and alterations in lipoproteins and glucose.\(^6\)\(^3\) The complexity of these competing risks between HIV replication and antiretroviral toxicity is highlighted by another study reporting worsened femoral artery stiffness, but improved endothelial dysfunction plasma markers, after starting ART.\(^5\)\(^4\)

Atherosclerotic burden estimated by ultrasound measures of CIMT also highlight contributions of ART exposure and ART itself. Carotid artery intima–media thickness has been associated with vascular inflammation (e.g. sVCAM-1 levels) and duration of ART exposure among HIV-infected patients.\(^5\)\(^6\)\(^6\) In the FRAM Study, the largest comparison of HIV-infected and uninfected populations to date, HIV infection was independently associated with greater CIMT to a degree similar to having diabetes or being a smoker.\(^5\)\(^7\) In FRAM, the duration of tenofovir use was also associated with lower CIMT.\(^6\)\(^8\) Ultimately, HIV-infected individuals with undetectable viral loads, whether elite controllers or taking ART, still have greater CIMT when compared with uninfected controls in cross-sectional studies.\(^5\)\(^9\)

Longitudinal studies of atherosclerotic progression among HIV-infected persons are largely consistent with these findings. In the Study to Understand the Natural History of HIV and AIDS in the Era of Effective Therapy (SUN), maintaining HIV suppression (vs. a detectable HIV RNA level) was independently associated with less CIMT progression over 2 years.\(^7\)\(^0\) A single-site study also reported greater CIMT progression among HIV-infected vs. uninfected persons, and the magnitude of progression was associated with C-reactive protein levels after adjusting for traditional and HIV-specific factors.\(^7\) In this study, CIMT progression was most pronounced at the bifurcation of the internal and external carotid artery, both in the presence or absence of ART, but the clinical relevance of hypothesized differences in HIV-related atherosclerotic progression at different regions of the carotid artery is unclear.\(^7\) An important limitation of all these longitudinal CIMT studies remains the inability to disentangle the CVD consequences related to ART exposure and untreated HIV infection per se.

Data that HIV elite controllers also exhibited greater CIMT progression, when compared with uninfected controls, suggest that achieving a fully suppressed HIV RNA level will not fully mitigate accelerated atherosclerosis in this population.\(^7\)\(^1\) It also appears that progression of atherosclerosis may differ by the specific antiretroviral components of a patient’s ART regimen. In the SUN study, progression of CIMT was less for persons taking non-nucleoside reverse transcriptase inhibitor (NNRTI)- vs. PI-based ART regimens, independent of maintaining HIV suppression.\(^7\)\(^0\) In a separate study, the development and progression of carotid...
lesions was reportedly greater among patients treated with PIs when compared with those receiving NNRTIs.72

**Antiretroviral therapy to reduce cardiovascular disease events among individuals with human immunodeficiency virus infection**

Epidemiological studies have reported greater risk for myocardial infarctions and other CVD events among HIV-infected compared with uninfected individuals.73,74 SMART was the first clinical trial to demonstrate that untreated HIV infection increases the risk for CVD events, but the 60% increased risk associated with intermittent ART use was primarily due to stopping ART among participants who were already on treatment at enrolment and was of marginal statistical significance ($P = 0.05$).4 Subsequently, when the trial was stopped early and all participants were placed on ART, the CVD risk associated with intermittent ART use was reduced.75 These data, and additional observational cohort data, have motivated claims that HIV infection should be treated earlier (i.e. at higher CD4 counts) to reduce the CVD risk.76,77 However, there are currently no randomized data comparing the CVD risk between ART treatment and the state of untreated HIV infection to account for any relevant selection bias and unmeasured confounding.

The pro-atherogenic mechanisms of antiretroviral drugs, and PIs in particular, have classically been associated with lipodystrophy leading to metabolic disorders including insulin resistance and dyslipidaemia.78 Additional data have also highlighted CVD toxicity related to inflammation, immune activation, oxidative stress, vascular injury, mononuclear cell adhesion, and hyperhomocysteinaemia, with different PIs having different toxicity in this regard.63,78–82 The relationship between exposure to ART and risk for clinical CVD events has been previously reviewed.83 In the D:A:D Study, ART-associated risk for myocardial infarction was attributed to cumulative exposure to PIs but not NNRTIs.84 Some, but not all, of this risk is accounted for by the classic pro-atherogenic lipid changes associated with PI exposure.84 With additional follow-up in D:A:D, including over 1.78 million person-years, cumulative exposure to the NRTI abacavir, and the PIs indinavir and lopinavir-ritonavir has been specifically associated with increased risk for myocardial infarction.85 Minimizing the variable CVD, and non-CVD, toxicity related to individual antiretroviral drugs has become one of the greatest clinical challenges when managing contemporary HIV-infected patients who have achieved suppression of HIV replication.

**Summary**

Untreated HIV infection amplifies several pro-atherogenic mechanisms, and appears to accelerate atherosclerotic progression and...
the development of clinically overt CVD. While stopping ART among patients with HIV suppression is associated with inflammation (e.g. IL-6 increases), pro-coagulant changes, and declines in HDL that increase CVD risk, the compensatory improvement in these pathways after starting ART appears to be incomplete. Furthermore, exposure to specific antiretrovirals has been clearly shown to be associated with variable CVD-related toxicity. Thus, when the risk of AIDS is low and non-AIDS morbidity (such as CVD) dominates, the net benefit of starting ART, compared with untreated HIV infection, is unknown (Figure 3). The ongoing START (Strategic Timing of AntiRetroviral Therapy) trial is a randomized comparison of early vs. delayed treatment of HIV infection, and will provide much needed randomized data to address this pressing clinical question.

Treatments commonly used for CVD prevention in the general population may have increased utility for patients with HIV infection. In particular, vaso-protective agents and those with anti-inflammatory and anti-platelet activity [e.g. angiotensin-converting enzyme-inhibitors/angiotensin receptor blockers, 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors (‘statins’), and aspirin] may be uniquely beneficial for HIV-infected patients taking ART with undetectable HIV RNA, but who remain at an increased risk for CVD due to chronic inflammation and thrombogenesis. Indeed, trials from the general population suggest that statins are effective for CVD prevention among persons with elevated C-reactive protein and normal/low LDL levels, while aspirin may be more beneficial for CVD prevention among those with higher vs. lower C-reactive protein levels.16,87 Trials studying the unique effects of statins among HIV-infected patients are ongoing, though to date, data are lacking on anti-thrombotic strategies in this population.

In the coming decades, accelerated HIV-related CVD risk is likely to become even more prevalent. In the USA, over half of all HIV-infected individuals may be over the age of 50 years by 2015.3 In this context, prevention strategies that target traditional modifiable CVD risk factors (e.g. smoking cessation) should continue to be strongly emphasized in clinical practice. Ultimately, HIV-specific prevention strategies involving adjunct treatment given in addition to ART that target key inflammatory and coagulation pathways should be developed and studied to mitigate premature HIV-associated CVD.

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