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Inflammatory Markers Associated with Coronary Heart Disease in Persons with HIV Infection

Carl J. Fichtenbaum
Division of Infectious Diseases, University of Cincinnati College of Medicine, 231 Albert Sabin Way, PO Box 670560, Cincinnati, OH 45267-0560, USA

Carl J. Fichtenbaum: Carl.fichtenbaum@uc.edu

Abstract

Coronary heart disease (CHD) is an inflammatory process that takes decades to develop. In HIV-seronegative persons, high-sensitivity C-reactive protein is a biologic marker of CHD risk. HIV infection induces chronic inflammation, despite adequate suppression of HIV replication with antiretroviral therapy, resulting in elevations of several biologic markers associated with CHD risk in HIV-seronegative persons. Indeed, the SMART study demonstrated that interruption in antiretroviral therapy is associated with higher mortality and CHD events postulated to be related to inflammatory mediators such as interleukin-6 and D-dimer. Specific antiretroviral agents (eg, abacavir) have been associated with higher rates of myocardial infarctions and elevations in markers of inflammation such as interleukin-6 and D-dimer in persons with CHD events. This article reviews the current understanding of biomarkers of inflammation associated with the development of CHD in the setting of HIV infection and the use of antiretroviral therapy.

Keywords

HIV; Inflammation; Coronary heart disease; Surrogate markers; High-sensitivity C-reactive protein; D-dimer; Interleukin-6; Atherosclerosis; Endothelial dysfunction

Introduction

Coronary heart disease (CHD) is the result of decades of progressive atherosclerosis. A number of risk factors and biologic mechanisms have been defined in HIV-seronegative persons. Among the most important mechanisms of the development and progression of atherosclerosis is inflammation [1••,2]. Several diseases, environmental factors, host factors, and biologic markers of CHD risk have been identified including diabetes mellitus, blood pressure, cholesterol, cigarette smoking, age, gender, and several inflammatory markers. Indeed, an elevated C-reactive protein (CRP) was recently demonstrated to define a group at higher risk benefitting from the use of rosuvastatin to prevent vascular disease events and improve survival in the JUPITER study (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) [3••]. Although inflammation is clearly involved in the development of atherosclerosis, and biologic markers of inflammation are associated with elevated CHD risk in HIV-seronegative persons, the

Correspondence to: Carl J. Fichtenbaum, Carl.fichtenbaum@uc.edu.

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situation in those with HIV infection is more complicated. Recent evidence has linked several inflammatory markers with elevated CHD risk in persons with HIV infection. This review outlines our current understanding of the relationship of HIV infection and antiretroviral therapy on chronic inflammation associated with the development and progression of CHD.

Inflammation and the Pathogenesis of CHD

Atherosclerosis is an inflammatory process that takes decades to develop into clinically evident disease. The pathogenesis includes vascular endothelial dysfunction, accumulation of lipids within macrophages, smooth muscle proliferation, and infiltration of inflammatory cells with release of various molecules leading to the production of atheromata [2]. Active symptomatic coronary artery lesions typically develop within nonobstructive, unstable atheromatous plaques that rupture, leading to activation of prothrombotic molecules with platelet activation and thrombin formation.

The early events in the pathogenesis of coronary atherosclerosis revolve around endothelial vascular dysfunction that may be related to lipids that activate adhesion molecules [2]. Inflammatory monocytes with higher levels of P-selectin glycoprotein ligand begin to accumulate [1••]. Activation of vascular-cell adhesion molecule 1 (VCAM-1) by cholesterol allows for attraction and attachment of monocytes. These cells migrate via stimulation by various chemokines through interendothelial cell junctions into the subendothelial space [2]. Monocytes transformed into macrophages through growth factors and via scavenger receptors like CD36 are able to internalize several molecules such as oxidized low-density lipoproteins (LDL). A lipoprotein-associated phospholipase A2 (Lp-PLA 2) is involved in the generation of oxidized LDL [4]. These form early foam cells within the intima that have toll-like receptors, which, when activated, release inflammatory cytokines, proteases, nitrogen radicals, and cytotoxic oxygen radicals. Subsequently, T-cells migrate and differentiate into T-helper (Th)-1 effector cells producing activating cytokines such as interleukin-1 (IL-1), interferon (IFN)-γ, and tumor necrosis factor (TNF). The inflammation that ensues is reflected by higher levels of IL-6 and CRP that can be measured within the circulation [1••]. Other metabolic and inflammatory factors also play a role, including adipokines (eg, adiponectin and leptin) within inflamed adipose tissue. Ultimately, progression of atheroma development results from recurring waves of antigenic stimulation and inflammation with vascular endothelial dysfunction and formation of a mature atheromatous plaque.

Terminal events in the formation of an active unstable plaque typically involve rupture of the smooth muscle fibrous cap. Atheromata, rich in inflammatory molecules, are often stimulated to rupture by matrix metalloproteases (MMPs) and cysteine proteases. Release of proteases, inflammatory cytokines, and prothrombotic factors results in activation of platelets, cross-linking of thrombin, and clot formation within the lumen. Activated platelets shed CD40 ligand (CD154) and myeloid-related protein (MRP) 8/14, which are both proinflammatory. This ligand induces endothelial cell apoptosis, which is implicated in plaque thrombus generation. Clinically, this sequence of events terminates with the presentation of an acute coronary syndrome such as unstable angina or a myocardial infarction.

At the same time that the inflammatory process is ongoing, a counter-regulatory sequence of events ensues involving an array of cell types. Monocytes secreting transforming growth factor β (TGF-β) and responding to vascular endothelial growth factor (VEGF) are involved in tissue repair. Prostaglandin production also reduces inflammation and thrombosis.

Regulatory T cells, $CD8^+$ cells, and Th-2 cells are equally involved in down-regulating inflammation. Thus, there is ongoing attempt to counteract the ongoing inflammation.

Inflammatory Biomarkers of CHD Risk in HIV-Seronegative Persons

Atherogenesis is an active inflammatory process with constant remodeling of plaque and ongoing antigenic stimulation. A number of inflammatory molecules induce atheromata formation, are involved in counter-regulation, or are released into the circulation and may be measured at varying stages of the clinical process. Many of these biologic markers of inflammation have been associated with elevated CHD risk (Tables 1 and 2). Several have been proposed for diagnostic use, including MRP 8/14, Lp-PLA2, D-dimer, IL-6, MMP-9, and high-sensitivity CRP (hsCRP). Among these biomarkers, hsCRP has emerged as the most useful because it is relatively stable, has been proven to add risk to the other well-known factors described within the Framingham cohort, and decreases along with LDL in response to therapeutic interventions that reduce CHD mortality [1••]. For example, in the PROVE-IT TIMI 22 trial, clinical outcomes were best among those with an hsCRP less than 2.0 mg/L and an LDL less than 70 mg/dL [5]. In the JUPITER study, subjects with LDL less than 130 mg/dL and hsCRP ≥ 2.0 mg/L were randomly assigned to rosuvastatin, 20 mg daily, or placebo [3••]. The data safety monitoring committee recommended early termination of the study because of an observed 44% benefit in the primary endpoint of all vascular events with the use of rosuvastatin ($P<0.00001$).

Evidence for the use of other biomarkers besides hsCRP is emerging, but is not as convincing. One such marker is the proinflammatory molecule MRP 8/14. In the PROVE-IT TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis in Myocardial Infarction 22) study, patients with CHD death or myocardial infarction after 30 days had higher median MRP 8/14 levels than patients who remained free of recurrent events (5.6 mg/L vs 4.0 mg/L, $P=.020$) [6]. Another marker is Lp-PLA2, which may also be a target for therapeutic intervention. In a collaborative analysis of 32 prospective studies, the relative risk, adjusted for conventional risk factors, was 1.10 (95% CI, 1.05–1.16) with Lp-PLA2 activity and 1.11 (1.07–1.16) with Lp-PLA2 mass for CHD [7]. Two other markers include fibrin D-dimer and IL-6. In a case-control study of 485 men with CHD events in the WSCOP (West of Scotland Coronary Prevention) study, on multivariate analyses, D-dimer had a significant association with coronary risk (RR, 1.86; 95% CI, 1.24–2.80), whereas IL-6 did not retain the significant association (RR, 1.47; 95% CI, 0.95–2.28) [8]. Proteases that can disrupt the smooth muscle fibrous cap on atheroma (eg, MMP-9) may also be diagnostic markers of CHD. However, Welsh et al. [9] reported that MMP-9 was of borderline value when adjusted for other known risk factors. Adjustment for conventional risk factors (smoking in particular) reduced the odds ratio of MMP-9 with CHD events to borderline significance (OR 1.28; 95% CI, 0.95–1.74) [9]. Thus, although several of these markers may be involved in the pathogenesis of atherosclerosis, the diagnostic utility in predicting CHD events varies depending on the marker chosen. Clearly, the strongest evidence exists for the use of hsCRP.

Coronary Heart Disease in HIV and Antiretroviral Therapy

Several studies have suggested that antiretroviral therapy and HIV are both associated with elevated risk of myocardial infarctions [10–13]. In a landmark article, the D:A:D study (Data Collection on Adverse Events of Anti-HIV Drugs) showed a relative risk of 1.26 per additional year of exposure to antiretroviral therapy [10]. In their follow-up analyses, researchers identified protease inhibitors as a class of antiretrovirals with greater risk (RR=1.16, 95% CI, 1.10–1.23 per year of additional use) [14]. There was no association with the use of non-nucleoside reverse transcriptase inhibitors and the occurrence of

myocardial infarctions. This work has since expanded with more recent analyses suggesting that a greater risk of myocardial infarction is associated with the use of lopinavir-ritonavir or indinavir [15]. Cumulative exposure to indinavir or lopinavir-ritonavir was associated with an increased risk of myocardial infarction (RR per year, 1.12 and 1.13, respectively). Although the majority of studies suggest there is added risk with the use of some types of antiretroviral therapy and HIV, Bozzette and colleagues [16] have not found added risk in their initial or follow-up studies. It is important to note that most studies also document the importance of traditional risk factors for CHD, including age, gender, cigarette smoking, hypertension, diabetes mellitus, and family history of premature coronary artery disease.

Over the past several years, several interesting and unexpected associations have been reported between CHD, HIV infection, and antiretroviral therapy. The D:A: D investigators reported that recent use of abacavir or didanosine-containing regimens have a greater risk for the development of CHD. The adjusted relative risk of CHD for ongoing use of abacavir was 1.89 and 1.49 for didanosine compared to those never using these agents or those who had stopped them for 6 months or greater [17••]. Interestingly, no cumulative effect was reported. Subsequently, investigators from the SMART study (Strategies for Management of Anti-Retroviral Therapy) confirmed similar findings with the use of abacavir and didanosine [18]. A combined analysis of subjects randomly assigned to abacavir was not able to confirm the findings of the prior studies [19•]. It may be that patients who are prescribed abacavir in cohort studies are more likely to develop CHD, representing what is called a “channeling bias.” A recent review by Costagliola and colleagues [20•] noted that it is not possible to eliminate confounding completely in the studies of abacavir: smoking was a potential confounder in two of the studies, renal insufficiency was a confounder in two others, and use of cocaine and/or injection drug abuse were potential confounders in others. Thus, it is difficult to determine whether abacavir is associated with a truly higher risk of myocardial infarction.

Much of the evidence of HIV infection’s role in the development of CHD comes from a single treatment-interruption study. Studying the natural history of HIV infection in the development of atherosclerosis is challenging because it is unethical to withhold antiretroviral therapy. However, investigators from the SMART trial demonstrated a higher risk of CHD with discontinuation of antiretroviral therapy (relative hazard=1.6, 95% CI, 1.0 to 2.5, P=0.05) [13].

It is important to note that there are no randomized clinical trials demonstrating a clear association with anti-retroviral therapy and CHD endpoints such as myocardial infarctions or proven coronary artery disease. It may be that the risk associations merely reflect the occurrence of CHD in a population that is aging with other known risk factors and chronic inflammation associated with HIV infection. Furthermore, traditional CHD risk factors like cigarette smoking, age, gender, diabetes mellitus, hypertension, and lipids remain important in explaining CHD events in persons with HIV.

Inflammatory Markers, HIV Progression, and Mortality

Inflammation is a key process in HIV infection. The association of inflammatory markers and mortality was recently examined in the SMART study in persons who discontinued their antiretroviral therapy. Kuller et al. [21••] studied six biomarkers to determine the association between higher mortality in the treatment interruption (drug conservation [DC]) group: hsCRP, D-dimer, IL-6, amyloidal A, amyloidal P, and prothrombin fragment 1+2. They studied 85 deaths, of which 55 occurred in the arm that stopped treatment. Compared to controls matched by age, gender, and country of origin, subjects in the DC group had higher median levels of hsCRP (4.49 vs 1.78 μg/mL); IL-6 (3.85 vs 2.24 pg/mL); and D-dimer

(0.66 vs 0.22 μg/mL). There were 21 CHD or unwitnessed deaths. In that group, biomarkers were also higher than matched controls with higher odds ratios corresponding to clinical outcomes with 2.3 (95% CI, 1.0–5.0; *P*=0.04) for hsCRP, 3.2 (95% CI, 1.2–8.4; *P*=0.02) for IL-6, and 3.2 (95% CI, 1.1–9.3; *P*=0.04) for D-dimer. The risk of death was also higher comparing the latest level of these three biomarkers proximate to the time of death. Calmy et al. [22] also reported somewhat similar findings measuring 11 different biomarkers in the STACCATO (Swiss-Thai-Australia Treatment Interruption) trial. In this study, 490 subjects with HIV suppression for ≥6 months were randomly assigned 1:2 to continue antiretrovirals or interrupt them. Their analysis was restricted to the 145 subjects from Thailand, 97 of whom underwent a treatment interruption. Initiation of antiretroviral therapy resulted in significant declines in s-VCAM-1, P-selectin, leptin, and D-dimer, whereas mediators with anti-inflammatory properties (eg, adiponectin and IL-10) increased. At 12 weeks after treatment interruption, there were positive associations between levels of s-VCAM-1 and monocyte chemoattractant protein (MCP)-1 with an increase in plasma HIV-RNA (*r*= 0.271, *P*=0.001 and *r*=0.24, *P*=0.005, respectively), whereas levels of adiponectin decreased for each 1-log increase in plasma HIV-RNA (*r*=0.24, *P*=0.002). Detectable IL-10 was less likely (OR=0.64, 95% CI, 0.43–0.96) for each 1−log increase in plasma HIV-RNA. Thus, independent of treatment, HIV had profound effects on biomarkers. Tien et al. [23••] also studied the relationship between biomarkers and mortality in the FRAM cohort, a study of 1183 subjects at 16 sites in the United States. In this study, those in the highest tertile of fibrinogen had an unadjusted mortality rate of 24.7% compared to 9.7% and 7.4% in the lower tertiles. HIV-infected participants with high CRP (>3.0 mg/L) also had a higher unadjusted mortality rate of 19.3%, compared with 14.4% in those with CRP 1 to 3 mg/L and 7.3% in those with CRP less than 1 mg/dL. Many of these subjects were on treatment and the investigators were not able to adjust analyses for the effects of antiretrovirals independent of those of HIV infection.

Several other groups have also investigated the role of CRP in HIV progression and mortality [24,25]. In each of these studies, CRP correlated with progression of HIV and mortality, even when adjusting for other important variables, including CD4 count and HIV RNA levels. Finally, Kalayjian et al. [26••] reported higher pretreatment concentrations of soluble TNF-1, soluble CD27, soluble CD40L, and plasma IL-6 were associated with a new AIDS-defining illness or death in separate models adjusted for age, sex, hemoglobin, and the latest CD4 cell counts.

Thus, it appears that several biologic markers are associated with progression of HIV infection and mortality, but they are not necessarily specific indicators of CHD or atherosclerosis progression. Several plausible alternate biologic mechanisms may explain elevations in a broad array of inflammatory markers in persons with HIV infection. For example, many persons with HIV have comorbid infections, including hepatitis B, hepatitis C, and cytomegalovirus infection, as well as ongoing translocation of microbial pathogens that may affect biologic markers of inflammation. Consequently, it is important to analyze newer studies in the context of the direct effects of ongoing HIV replication as well as other pathogens and conditions that can lead to inflammation.

Inflammatory Markers, Antiretroviral Therapy, and CHD Risk

If it were not already complicated enough to differentiate the effects of HIV and other comorbid inflammatory conditions, recent studies have implicated antiretroviral therapy as a specific risk factor for CHD events. Several authors have postulated that some agents may induce inflammation, leading to higher CHD event rates. This concept was first proposed by the D:A:D investigators in association with a counterintuitive observation that abacavir and didanosine were associated with a higher risk of myocardial infarction [17••]. These

investigators had hypothesized that thymidine analogs (eg, zidovudine or stavudine) would be more likely to be associated with a higher risk of myocardial infarction. Since their report, several other groups have attempted to replicate these findings. Palella et al. [27] reported the results of biomarker studies from a combined analysis of the Women's Interagency HIV Study and the Multicenter AIDS Cohort Study. In the combined group analysis, from pre-antiretroviral treatment to post-therapy, HIV RNA reductions in response to antiretroviral therapy correlated with D-dimer (r=0.14, P<0.01) and IL-6 (r=0.12, P<0.01) reductions but not hsCRP. There were no significant differences in changes in any biomarker when comparing those on abacavir-containing regimens to those without abacavir. Similarly, investigators from the AIDS Clinical Trials Group found no association between subjects randomly assigned to abacavir compared to regimens containing other nucleoside reverse transcriptase and CHD events, although the study was underpowered [28].

In search of a potential mechanism to explain the association of abacavir with CHD events, several other groups assessed biologic markers. In the BiCombo study, 80 subjects who were randomized to switch to abacavir/lamivudine or tenofovir/emtricitabine were evaluated for an array of 12 biologic markers [29]. Despite an increase in total cholesterol and LDL in the abacavir group relative to the tenofovir group, there were no significant changes in CRP (−3.9 vs 0.0%), MCP-1 (5.9 vs 4.0%), osteoprotegerin (5.1 vs −2.8%), IL-6 (0.0 vs 0.0%), IL-10 (0.0 vs 0.0%), TNF-α (0.0 vs 0.0%), intercellular adhesion molecule-1 (ICAM-1) (6.6 vs 5.2%), VCAM-1 (0.02 vs −0.01%), selectin E (−0.4 vs7.8%), selectin P (4.6 vs 12.6%), adiponectin (−2.2 vs 15.4%), and D-dimer (0.0 vs 0.0%) between groups (P>0.12 for all comparisons). In a retrospective case-control study of persons taking abacavir compared to other nucleoside reverse transcriptase containing regimens, no difference was found in several inflammatory and prothrombotic biologic markers [30]. The authors noted that compared to the reference ranges for the general population, increased activated protein C sensitivity ratio was found in 79% and lower protein C and VEGF levels in 40% and 43%, respectively. Patients in the high-risk category for CHD with hsCRP levels greater than 3 mg/L had significantly higher fibrinogen and D-dimer compared to patients from the low-risk category with hsCRP levels less than 1 mg/L. Finally, in the STEAL study, a randomized, controlled switch study to an abacavir-based versus tenofovir-based regimen, no differences were observed after 48 weeks in levels of hsCRP, amyloid-P, amyloid-A, IL-6, IL-10, IFN-α, and macrophage migration inhibitory factor; coagulation—D-dimer and fibrinogen; platelet function—soluble P-selectin; endothelial function—VCAM-1 and ICAM-1; renal function—cystatin C [31].

Inflammatory Markers and Surrogate Measures of Atherosclerosis Progression

Another way to demonstrate that biologic markers predict risk is to evaluate their relationship to other surrogate measures of atherosclerosis, such as carotid intima medial thickness (cIMT). In 2006, Hsue et al. [32] demonstrated that HIV-infected persons with cytomegalovirus coinfection had increased cIMT compared to HIV-seronegative controls (0.95 mm vs 0.68 mm, P<0.001). Although HIV-infected subjects had higher median levels of hsCRP (P<0.05) than controls, this increased level was not independently associated with increased cIMT. However, Ross et al. [33] reported a positive association with hsCRP and cIMT thickness in 27 children with HIV infection compared to matched controls. Interestingly, several other biologic markers were not independently associated with cIMT in that study, including TNF, IL-6, sVCAM, sICAM, and myeloperoxidase. In a small study of initiation of anti-retroviral therapy with lopinavir/ritonavir combined with either zidovudine/lamivudine or nevirapine, cIMT increased significant in both arms after 24 months (0.061 mm and 0.044 mm, respectively, P<0.05) [34]. Once again, hsCRP did not

change and adhesion molecules sVCAM and sICAM both improved significantly despite increases in cIMT. In contradistinction, Ross et al. [35••] demonstrated that hsCRP and sVCAM both correlated with cIMT in 73 HIV-infected patients and 21 matched controls. Thus, cIMT that correlates with atherosclerosis progression and predicts those at higher risk for CHD events is consistently abnormal in persons with HIV, but is inconsistently associated with biomarkers of inflammation, endothelial function, and thrombosis.

Conclusions

In the absence of large, randomized, clinical endpoint studies demonstrating that HIV infection or antiretroviral therapy are definitively associated with the development of CHD endpoints, we are left with trying to sift through the complex interactions of biologic markers of inflammation, endothelial function, and thrombosis. Although it is clear that inflammation and vascular endothelial dysfunction are critical steps in the development and progression of atherosclerosis, it is not easy to understand the interrelationships of these processes with ongoing HIV infection. Because of multiple other stimuli that induce inflammation in persons with HIV infection, it has not been consistently proven that these biologic markers predict progression of CHD in persons with HIV. Mechanistically, it is tempting to hypothesize that the inflammatory events associated with HIV replication may worsen or accelerate the process of atherogenesis. What is most important is determining whether some individuals with HIV are at higher risk of CHD events or more rapid progression of atherosclerosis to develop interventions that might retard or reverse this process. And although recent evidence suggests that abacavir is associated with a higher risk of CHD events, the data on a clear mechanism are inconsistent and, in fact, many of these individuals appear to have significant inflammation that may be unrelated to the particular selection of antiretroviral agents. For the time being, the meaning of biologic markers like hsCRP which predict risk in the HIV-seronegative population cannot be relied upon in the same manner in those with HIV infection. Much work remains to be done to understand the role of inflammation in HIV and the progression of atherosclerosis, and how we can predict this process using biologic markers.

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Table 1

Selected biologic markers associated with coronary heart disease pathogenesis and risk

Marker	Function	Effects in HIV infection
CRP	Acute-phase reactant generated in the liver with proinflammatory activities	Higher levels associated with CHD events and mortality
Fibrinogen	Converted by thrombin into fibrin; involved in active clot formation over an unstable plaque.	Higher levels associated with mortality
D-dimer	Fibrin degradation product and marker of increased turnover of intravascular cross-linked fibrin	Higher levels associated with CHD events, endothelial dysfunction, and mortality
Soluble vascular cell adhesion molecule-1	Adhesion molecule released in endothelial dysfunction and activation	Higher levels in HIV; levels decrease with antiretroviral therapy
Lipoprotein-associated phospholipase A2	Proinflammatory molecule that hydrolyzes oxidized phospholipids and is involved in endothelial dysfunction, plaque inflammation, and plaque core necrosis	Insufficient data
P-Selectin	Adhesion molecule promoting leukocyte adherence to endothelium and a marker of platelet activation	No change with antiretroviral therapy
Monocyte chemoattractant protein-1	Proinflammatory chemokine regulating monocytes in inflammatory sites	Higher concentrations associated with greater degree of atherosclerosis
Matrix metalloprotease 9	Involved in turnover of normal and injury-induced extracellular matrix; associated with atherosclerotic plaque destabilization.	Insufficient data
IL-6	Proinflammatory cytokine	Higher levels associated with endothelial dysfunction, HIV progression, and mortality
Myeloid related protein 8/14	Proinflammatory molecule secreted by platelets	Insufficient data

CHD coronary heart disease; *CRP* C-reactive protein; *IL* interleukin

Table 2

Summary of recent important developments in inflammatory markers of CHD in HIV

Outcome	Study	Major new findings	Summary of results
Mortality and HIV disease progression	SMART study [21••] (*N*=5472)	D-dimer and IL-6 levels associated with HIV progression and mortality	In an expanded case-control analysis (four controls per case), the OR (DC/VS) for mortality was 1.5 (95% CI, 0.8–2.8) and 1.4 (95% CI, 0.8–2.5) after adjustment for latest levels of IL-6 and D-dimer, respectively.
Mortality and HIV disease progression	FRAM [23••] (*N*=922)	Fibrinogen and hsCRP associated with a higher risk of all-cause mortality	Higher adjusted odds of death with: 2.6-fold higher with fibrinogen levels in the highest tertile (>406 mg/dL) and, 2.7-fold higher with higher CRP (>3 mg/L).
Subclinical atherosclerosis	Prospective cross-sectional study [36] (*N*=187)	Framingham risk score under predicts subclinical atherosclerosis	56% with low-risk Framingham risk scores had subclinical atherosclerosis associated with: MCP-1 (OR 1.027; 95% CI 1.004–1.050; *P*=0.020) oxidized LDL (OR 1.026; 95% CI 1.001–1.051; *P*=0.041).
cIMT and arterial stiffness	Prospective cross-sectional study [34] (37 subjects)	cIMT and femoral artery stiffness increased after initiation of antiretroviral therapy, but no correlation with biologic markers of inflammation	cIMT increased by 0.061±0.016 mm (*P*<0.001) in the ZDV/3TC/LPV/r arm and by 0.044±0.018 mm (*P*=0.012) in the NVP/LPV/r arm
cIMT, inflammation, endothelial activation	Prospective cross-sectional study [35••] (73 subjects; 21 controls)	Enhanced endothelial activation, inflammation, and increased cIMT occur in HIV-infected patients despite antiretroviral therapy	hsCRP, mg/L 5.43 (0.13–84.6) vs 1.53 (0.05–24.4) *P*<0.001 cIMT, 1.25 mm (0.75–3.23) vs 1.05 mm (0.75–1.35) *P*<0.001 IL-6, pg/mL 6.0 (0.8–270) vs 2.8 (1.0–8.2) *P*=0.008

CHD coronary heart disease; *cIMT* carotid intima media thickness; *CRP* C-reactive protein; *hsCRP* high-sensitivity CRP; *IL* interleukin; *MCP*-1 monocyte chemoattractant protein-1