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Biomarkers and HIV-Associated Cardiovascular Disease

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Abstract

Purpose of Review—Our goal is to summarize recent literature on biomarkers of cardiovascular disease (CVD) in the setting of HIV infection with an emphasis on those associated with clinical events.

Recent Findings—Epidemiological data have demonstrated that HIV-infection is associated with increases in well-established markers of inflammation and thrombosis, and levels of hsCRP, IL-6, D-dimer and fibrinogen predict CVD and mortality risk in HIV cohorts. Levels of IL-6, D-dimer and endothelial adhesion molecules increase when antiretroviral therapy is interrupted, suggesting HIV replication may be driving CVD risk in this context. However, data on changes in many CVD biomarkers after starting ART are inconsistent or lacking. Finally, assessment of high-density lipoprotein particle concentration may provide important information specific to HIV-related CVD risk beyond that apparent from traditional measures of serum cholesterol.

Summary—Biomarkers of inflammation and thrombosis have the potential to improve CVD risk stratification beyond traditional and HIV-specific factors, and may prove useful for evaluating CVD prevention strategies for individuals with HIV infection.

Keywords

HIV infection; cardiovascular disease; biomarkers; inflammation; endothelial dysfunction; coagulation; thrombosis; lipoproteins

Introduction

Premature atherosclerotic cardiovascular disease (CVD) has become a leading cause of morbidity and mortality for patients with HIV infection in the era of effective antiretroviral therapy (ART).^{1–3} The pathogenesis of atherosclerotic vascular disease that culminates in morbid events begins with well-described mechanisms that include inflammation, endothelial dysfunction, plaque formation and thrombogenesis. Factors that amplify atherogenesis in HIV-infected persons include a greater prevalence of traditional risk factors (e.g., smoking, dyslipidemia), direct consequences of HIV infection itself, and exposure to specific antiretroviral drugs.^{4–7} Biomarkers may be used to study how HIV infection and

antiretroviral exposure influence the underlying CVD pathogenesis or evaluate treatments. Biomarkers that statistically related to clinical events may also have utility for improving CVD risk stratification. The focus of this article is to review recent biomarker studies in HIV-infected persons, with an emphasis on biomarkers that predict CVD risk or reflect HIV-associated CVD pathogenesis (table 1).

Markers of Inflammation

Inflammation is both a hallmark of HIV infection and a key element in the pathogenesis of CVD.^{30–32} In the general population, higher levels of high sensitivity C-reactive protein (hsCRP) and interleukin-6 (IL-6) are well-established risk markers for CVD events and death from any cause.^{33–37} IL-6 is a pro-inflammatory cytokine produced by monocytes, endothelial cells, and lymphocytes. IL-6 has a wide range of effects including antiviral properties, induction of acute-phase reactants, and promotion of hemostasis.^{38,39} High-sensitivity CRP is an acute phase protein produced and released by hepatocytes, largely in response to IL-6.³⁹ Multiple cross-sectional studies have shown that these two markers are elevated in HIV-infected compared to uninfected persons.^{8,9,15,16,18}

Chronic inflammation among persons with HIV infection may be a consequence of activation of lymphocytes and dendritic cells, damage to the mucosal barrier, injury to endothelial surfaces, metabolic changes, and/or other factors related to HIV replication.^{11,21,40–45} In the Strategic Management of Anti-Retroviral Therapy Study (SMART), it has been shown that hsCRP and IL-6 levels are associated with HIV viral replication and CVD and all-cause mortality risk.^{8,14,46} In SMART, higher levels of hsCRP and IL-6 at baseline were strongly associated with increased risk for mortality both over the short- and long-term (CVD and non-CVD related).^{14,46} A major limitation of these data is the ability to quantify the risk for a CVD event associated with absolute differences or changes in biomarker levels, since they involve case-control studies. In a separate data registry study of HIV-infected patients, higher CRP levels were associated with increased risk for myocardial infarction.¹⁵ Additional longitudinal studies of HIV-infected persons with suppressed HIV RNA levels are needed to validate and refine these risk associations.

Interruption of ART among patients with a suppressed viral load in SMART was associated with a rapid rise in IL-6 levels that correlated with HIV RNA levels.¹⁴ In a subgroup of SMART participants that were naïve to or off ART (for at least 6 months) at enrollment, biomarkers changes were examined for those starting ART compared with those randomized to defer ART.¹⁰ In this study, early versus delayed ART was not associated with significant improvements in IL-6 or hsCRP. In general, reports of changes in either hsCRP or IL-6 after starting ART have been inconsistent, and most studies have lacked a comparison group of participants not taking ART.^{12,17,20,21,26} Furthermore, levels of hsCRP and IL-6 among SMART participants with a suppressed viral load were approximately 40–60% higher than matched controls from the general population (from the Multi-Ethnic Study of Atherosclerosis [MESA] and the Coronary Artery Risk Development in Young Adults [CARDIA] study).⁸ Cumulatively, these data suggest any improvement in inflammatory markers with ART use is incomplete, and there is a need for adjunct anti-inflammatory treatments for individuals with HIV infection.

Finally, any potential anti-inflammatory benefits of ART may also differ by the specific antiretroviral components.^{47,48} In a baseline cross-sectional comparison of SMART participants, use of abacavir, versus other NRTIs, was associated with 27% and 16% higher levels of hsCRP and IL-6, respectively.⁴⁸ However, to date, longitudinal data have been unable to replicate a significant effect of abacavir exposure specifically for elevations in inflammatory markers.^{1749–51}

Markers of Thrombotic Activity

Higher levels of fibrinogen and D-dimer (a fibrin split product) have been associated with increased risk for all-cause mortality both in HIV-infected and uninfected populations.¹⁴¹⁹⁵²⁵³ In SMART, D-dimer levels at baseline were strongly associated with risk of death (OR for 4th/1st quartile 41.2; $p < 0.0001$) in adjusted models.¹⁴ In this analysis, associations were present for CVD and non-CVD death, and for persons on and off ART. Changes in D-dimer levels after stopping or starting ART are associated with the degree of HIV viral replication or suppression, respectively.¹⁰¹⁴²⁰²¹ Despite this, D-dimer levels remain 49% elevated in SMART participants with HIV suppression compared with uninfected controls from MESA.⁸ In FRAM (Study of Fat Redistribution and Metabolic Change in HIV infection), fibrinogen levels in men were 8% higher compared with uninfected controls from the CARDIA study.¹⁸ Follow-up analyses in FRAM have recently reported an increased risk of all cause mortality (OR 2.57 for 3rd/1st tertile; $p < 0.001$) independent of hsCRP levels, though the risk gradient declined with higher CD4 counts.¹⁹ When the influence of treatment was examined in FRAM, fibrinogen levels were 11% higher for participants taking a protease inhibitor (PI), and 10% lower for those taking a non-nucleoside reverse transcriptase inhibitor (NNRTI), when compared with uninfected controls.¹⁸ The influence of specific antiretrovirals on changes in fibrinogen and D-dimer levels requires further study.

It is worth noting that D-dimer and fibrinogen are non-specific markers, which primarily reflect increased activity in the thrombotic process and may be elevated in response to inflammatory stimuli. In terms of understanding the mechanisms driving thrombogenesis in this context, more research is needed to identify the specific steps in coagulation and fibrinolysis pathways that are most affected by HIV infection and/or its treatment. An increase in pro-coagulant factors (e.g. anti-phospholipid antibodies), decrease in anti-coagulant factors (e.g. deficiencies in protein C or S), and platelet activation have all been reported with HIV infection.^{54–60} Another possibility is that HIV-infection and/or immune activation increases expression of tissue factor on endothelial cells (reviewed below) or leukocytes, thereby up-regulating the ‘extrinsic’ coagulation pathway.^{61,62} In one recent report, HIV-infected persons were found to have more tissue factor expression on circulating blood mononuclear cells compared with uninfected controls.⁶² In this study, the expression of tissue factor correlated with HIV RNA levels, the proportion of CD8+ T cells expressing immune activation markers, and with D-dimer levels.⁶²

Markers of Vascular Function

Vascular damage related to HIV replication and HIV therapy can be assessed via markers of endothelial function, injury and/or activation. Following injury, endothelial cells express various adhesion markers that may trigger an inflammatory response, adhesion and transmigration of leukocytes, platelet aggregation, and activate blood clotting.^{63–65} Endothelial biomarkers, such as soluble intercellular and vascular cell adhesion molecule (sICAM-1 and sVCAM-1), selectins (E-selectin and P-selectin), and molecules involved in coagulation and fibrinolysis (von Willebrand factor [vWF], thrombomodulin, and tissue-plasminogen activator [tPA], and plasminogen activator inhibitor-1 [PAI-1]), are associated with CVD risk and all-cause mortality in the general population.^{66–76} Endothelial biomarkers are consistently elevated in HIV-infected compared with uninfected individuals.¹⁶²³⁷⁷⁷⁸ In a cross-sectional study of 73 HIV-infected individuals, sVCAM-1 levels were associated with subclinical atherosclerosis assessed by ultrasound estimates of carotid intima-media thickness.⁷⁸

In the context of treatment interruption, endothelial adhesion markers (sICAM-1, sVCAM-1 and P-selectin) increase, and the change in sVCAM-1 specifically has been associated with increases in HIV viral replication.²⁰²⁵ In one of these treatment interruption studies, sVCAM-1 levels remained elevated despite HIV suppression 6 weeks after re-starting ART (n=21), compared with those randomized to persistent viral suppression (n=21) throughout the study period.²⁵ While many studies have demonstrated improvements in some endothelial biomarkers after starting ART, not all markers improve in all studies.¹²¹³²⁰²¹²⁵⁷⁷ Furthermore, a differential effect of specific antiretrovirals (e.g. PIs or abacavir versus other therapy) on endothelial biomarkers has not been a focus of clinical studies to date.^{132149–51} Cumulatively, these data emphasize that larger studies with longer follow-up are needed to validate which endothelial biomarkers can be used for early detection of CVD in HIV-infected patients.

Although more reflective of cardiac rather than endothelial dysfunction, a recent analysis from SMART demonstrated that higher baseline levels of N-terminal-pro-Brain-type natriuretic peptide (NT-proBNP) were independently associated with greater risk for CVD (OR 4th/1st quartile = 1.4), even after adjusting for hsCRP, IL-6 and D-dimer levels (OR 1.2).²⁷ NT-proBNP is released from myocytes and reflects increased ventricular stretch and wall tension. It remains unclear how HIV or ART independently influence NT-proBNP levels. Studies such as this, which consider novel markers, are important to better understand the physiology and pathogenesis of HIV-associated cardiovascular dysfunction.

Lipids and Lipoproteins

Both HIV and exposure to ART result in pro-atherogenic changes in blood lipids. Among men in the Multicenter AIDS Cohort (MACS) who were followed pre- and post-HIV infection, all serum lipid levels declined after HIV seroconversion.⁷⁹ Subsequently, initiation of ART among HIV-infected patients in MACS led to increases in total and low density lipoprotein cholesterol (LDL-C) above pre-infection levels, while high density lipoprotein cholesterol (HDL-C) remained approximately 10mg/dL below pre-infection

levels.⁷⁹ Furthermore, levels of HDL-C are inversely related to HIV viral load and increase more after starting NNRTI- versus PI-based.^{80,81} Thus, HIV-infection and ART exposure adversely influence the total cholesterol to HDL-C ratio, one of the strongest predictors of coronary heart disease risk in terms of serum lipid measures.^{82,83}

NMR (nuclear magnetic resonance) spectroscopy allows characterization of the lipid fractions in blood beyond what is represented in traditional measures of cholesterol by 'counting' numbers of lipoprotein particles and assessing their size.⁸⁴ Changes in the number of HDL particles, or concentration, appear to be informative for CVD event risk but may not be apparent when measuring traditional HDL-C.^{85,86} In a cross-sectional study, total HDL particle concentration was 21% lower in patients with untreated HIV infection compared with uninfected controls, and this was primarily due to lower numbers of large and small HDL particles.¹⁶ In this same study, small HDL particle numbers were inversely correlated with levels of IL-6, D-dimer and sICAM-1.¹⁶ In SMART, lower total HDL particle concentration was independently associated with risk for CVD (OR for 4th/1st quartile 0.47; $p = 0.001$), even after additional adjustment for IL-6 (OR = 0.50; $p = 0.02$) or D-dimer (OR = 0.49; $p = 0.02$).²⁹ Furthermore, among SMART participants with suppressed viral load, the decline in total HDL particles was associated with HIV RNA level one month after stopping ART.²⁹ In a cross-sectional analysis of lipoprotein particles in MACS, total HDL particles remained lower in HIV-infected participants receiving ART compared with uninfected controls.²⁸ In summary, pro-atherogenic changes in HDL associated with HIV infection may not be fully corrected by ART, and assessment of HDL particle number provides clinically relevant information for CVD risk in HIV-infected patients.

Conclusion

CVD biomarkers previously validated in the general population, including CRP, IL-6, fibrinogen and D-dimer, are present at higher levels among HIV-infected compared to uninfected persons, and remain strongly predictive for CVD and mortality risk in HIV studies. Data from treatment interruption studies suggest that HIV replication may account for greater inflammation and thrombotic activity, in part, through damage to endothelial surfaces. Starting ART appears to be associated with an incomplete improvement in some, but not all, CVD biomarkers and this effect may vary by the specific antiretroviral.

In general, whether these plasma biomarkers are mediators of a disease process or simply clinical risk markers without direct causality, treatments that lead to lower levels may have a profound impact on mortality risk for persons with HIV infection. However, the clinical utility of each of these markers for HIV infected patients has yet to be established. Specifically, an important goal of future research should be to clarify whether CVD biomarkers improve risk stratification beyond HIV-related and traditional risk factors.

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Table 1

Summary of Biomarkers Predictive of CVD Events or Mortality in HIV Studies

BIOMARKER	Influence of HIV-infection (vs uninfected)	Associations with HIV Viral Load (VL)	Changes After Starting ART	Clinical Risk Predicted in HIV Studies
Inflammation				
CRP	50–82% higher ⁸⁹	Data are inconsistent ^{8–11}	Data are inconsistent ¹⁰¹²¹³	CVD and all-cause mortality ¹⁴¹⁵
IL-6	62–152% higher ⁸¹⁶	Correlated with VL after stopping ART ¹⁴	Data are inconsistent ¹⁰¹⁷	CVD and all-cause mortality ¹⁴
Thrombotic				
Fibrinogen	8% higher in men ¹⁸	Correlated with VL ¹⁹	No longitudinal data ¹⁸	All-cause mortality ¹⁹
D-dimer	71–94% higher ⁸¹⁶	Correlated with VL steady state and after stopping ART ⁸¹⁰¹⁴	Improved levels, but incomplete ⁸¹⁰²⁰²¹	CVD and all-cause mortality ¹⁴²²
Endothelial (dys)Function				
Endothelial adhesion molecules (sICAM-1/ sVCAM-1)	Typically > 40% higher ¹⁶²¹²³²⁴	Correlated with VL after stopping ART ²⁰²⁵	Improved levels reported ¹²²⁰²¹²⁶	CVD (sVCAM-1) ²²
Cardiac Function				
NT-proBNP	Unknown	Unknown	Unknown	CVD ²⁷
Lipids				
HDL particles	13–21% Lower ¹⁶²⁸	Inversely correlated with VL after stopping ART ²⁹	Unknown	CVD ²⁹

CVD = cardiovascular disease; VL = HIV viral load; ART = antiretroviral therapy; CRP = C-Reactive Protein; IL-6 = interleukin-6; sICAM-1 = soluble intercellular adhesion molecule-1; soluble vascular cell adhesion molecule-1; NT-proBNP = N-terminal-pro-Brain-type natriuretic peptide; HDL = high-density lipoprotein