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High-Density Lipoprotein Particles and Markers of Inflammation and Thrombotic Activity in Patients with Untreated HIV Infection

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Abstract

Background—Untreated HIV infection is associated with changes in blood lipids, inflammation, thrombotic activity, and increased risk for CVD.

Methods—We studied high-density lipoprotein particle (HDLp) concentrations and inflammatory (hsCRP, IL-6), endothelial activation (E-selectin, sICAM-1) and thrombotic (fibrinogen and D-dimer) biomarkers in 32 untreated HIV-infected and 29 uninfected persons. Differences in blood lipids and biomarkers by HIV status were examined before and after adjustment for: age, gender, race/ethnicity, smoking status, BMI, and hepatitis C.

Results—HIV-infected, versus uninfected, participants had lower HDLc (−26%) and total (−21%), large (−50%)and small HDLp (−20%; $p \leq 0.01$ for all), but not medium HDLp. A trend was present for higher total cholesterol ($p=0.15$) and triglycerides ($p=0.11$) with HIV infection. Levels of IL-6, sICAM-1 and D-dimer were 65–70% higher in HIV-infected participants ($p \leq 0.02$ for all). Covariate adjustment did not diminish these associations. For HIV-infected participants, total and small HDLp (respectively) tended to correlate inversely with levels of IL-6 ($p=0.08$ and $p=0.02$), sICAM-1 ($p<0.01$ for both) and D-dimer ($p=0.03$ and $p<0.01$).

Conclusions—Persons with untreated HIV infection have lower HDLp, primarily large and small HDLp, and higher IL-6, sICAM-1, and D-dimer levels, and the relationship of these markers with risk for HIV-mediated atherosclerotic risk requires further study.

Keywords

HIV-infection; inflammation; thrombosis; endothelial dysfunction; lipoprotein particles; HDL; cardiovascular disease

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Introduction

HIV infection, independent of anti-retroviral therapy (ART) use, may increase risk for atherosclerotic cardiovascular disease (CVD) via adverse changes in blood lipids, inflammation and thrombotic activity.[1] High-density lipoprotein cholesterol (HDLc) is inversely correlated with coronary heart disease in the general population, and HIV sero-conversion leads to decreases in HDLc that do not completely revert with ART initiation.[2–5] In addition to promoting cholesterol efflux from lipid-filled macrophages (foam cells), HDLc also possesses several anti-inflammatory and anti-thrombotic properties that may protect against injury to endothelial surfaces.[6]

Traditional measures of the amount of cholesterol in plasma from a particular class of lipoprotein, such as HDLc or low-density lipoprotein cholesterol (LDLc), are commonly used in clinical practice to assess CVD risk. Several studies have shown that new methods for assessing the size and number of lipoprotein particles provide additional information regarding CVD risk beyond assessment of total cholesterol (TC), HDLc and LDLc.[7–13] In the Veteran Affairs High-density lipoprotein Intervention Trial (VA-HIT) within the general population, estimates of HDL and LDL particle concentrations (HDLp and LDLp, respectively), not conventional HDLc and LDLc measures, were associated with CVD event risk before and after treatment with gemfibrozil.[8]

The Strategies for Management of AntiRetroviral Therapy (SMART) trial demonstrated a 60% increased relative risk for CVD events with a strategy of CD4-guided interruption of ART, and adverse changes in HDLc after stopping ART may explain some of the excess CVD risk.[14, 15] Further analyses of SMART data demonstrated markers of inflammation (IL-6) and thrombotic activity (D-dimer) at baseline were strongly associated with CVD and mortality risk.[16] Furthermore, IL-6 and D-dimer levels increased after stopping ART and this increase was associated with increases in HIV RNA levels.[16] In addition, baseline HDLp, but not LDLp, predicted CVD risk in SMART.[17] The relationship between HDLp and markers of inflammation and thrombotic activity has not been reported in HIV infected persons. We characterized differences in specific HDLp concentrations between HIV-infected participants not receiving ART and uninfected controls, and examine associations between HDLp with levels of IL-6, D-dimer and other biomarkers among HIV-infected participants.

Methods

Study Design

The protocol was pre-approved by the Hennepin County Medical Center (HCMC) Human Subjects Research Committee, and participants were enrolled between March 2007 and June 2008 after signing informed consent. Exclusion criteria included: ART use in the previous year, known atherosclerotic CVD, pregnancy, current/active bacterial infection, recent hospitalization (within 1 month), systemic vasculitis, and active/ongoing alcohol abuse or illicit drug use (excluding marijuana). Participants were recruited through informational flyers and referrals from patients and providers, at an urban HIV clinic (HCMC, Minneapolis, MN). The HIV-uninfected control group was recruited in the same way and efforts were made to enroll participants that were similar to the HIV-infected group with regard to age, gender, race/ethnicity, smoking status and the presence of diabetes mellitus (DM).

Study participants presented for a single visit at HCMC where a peripheral blood draw was performed, serum and plasma were isolated and frozen prior to laboratory analyses. Participants were instructed to fast and avoid alcohol during the 8-hour period before the visit. Framingham 10-year CVD risk score was calculated using an NHLBI online calculator (http://hp2010.nhlbihin.net/atpiii/calculator.asp).

Laboratory Markers

Blood samples were centrifuged within 1 hour of collection and frozen at −70°C until analysis. Specimens were tested at HCMC clinical lab for the following: HIV antibody (for HIV-uninfected participants), HIV RNA level (for HIV-infected participants), serologies for hepatitis B and C, serum TC, LDLc, HDLc, and triglycerides (TG). All samples were handled in a fully blinded fashion such that laboratory investigators had no knowledge of HIV status.

Lipoprotein particle size and concentration was estimated using an automated proton nuclear magnetic resonance (NMR) spectroscopic assay at LipoScience, Inc. (Raleigh, NC), as previously described.[7] HDL particle size (diameter in nm) was calculated from the weighted-average of subclass concentrations. HDL subclass concentrations in nanometer (nm) of particles per liter (nmol/L) were obtained from the measured amplitudes of distinct lipid methyl group NMR signals. HDLp subclasses were categorized by particle diameter as: large (8.8–13.0 nm), medium (8.2–8.8 nm) and small (7.3–8.2 nm).[7]

Two inflammatory markers (high sensitivity CRP [hsCRP] and interleukin-6 [IL-6], two endothelial activation markers (soluble intercellular adhesion molecule-1 [sICAM-1] and E-selectin), and two thrombotic markers (fibrinogen and D-dimer), were measured by the Laboratory for Clinical Biochemistry Research at the University of Vermont. These markers were chosen because they have a high degree of laboratory and biological reproducibility, have been associated with CVD and all-cause mortality in the general population, and to build on the findings from the SMART study.[16,18–27] IL-6 was measured with Chemiluminescent Sandwich ELISA (R&D Systems); hsCRP with a NB™II nephelometer, N Antiserum to Human CRP (Siemens Diagnostics); sICAM-1 with ELISA from Parameter Human sICAM-1 Immunoassay (R&D Systems); E-selectin with a Colorimetric Sandwich ELISA (R&D Systems); fibrinogen levels with a BN™II nephelometer, N Antiserum to Human Fibrinogen (Siemens Diagnostics); and D-dimer levels with immunoturbidometric methods on the Sta-R analyzer, Liatest D-DI (Diagnostica Stago).

Statistical Analyses

Descriptive statistics are reported as means with standard deviation (SD) and medians with inter-quartile range (IQR). Student's t-test for independent groups and the chi square test for categorical variables were used to compare characteristics of the HIV-infected and HIV-uninfected groups. The summaries by group of lipids and biomarkers are presented as untransformed medians with IQR. For comparison of the lipids and biomarkers between the HIV-infected and HIV-uninfected groups, the relative percent difference (with 95% confidence internval) was obtained by exponentiating the mean difference on the natural log scale using generalized linear models. Those models were repeated with adjustment for age, gender, race/ethnicity, smoking status, body mass index (BMI), and hepatitis C. Hepatitis C infection was chosen over IDU in covariate models as 69% of persons with prior IDU had hepatitis C infection, current hepatitis C infection is more likely a confounder than IDU given potential implications for inflammation, and to limit the number of covariates in this small study. Regression coefficients were similar with and without inclusion of IDU in statistical models. Comparisons of IL-6, sICAM-1, and D-dimer levels with HDL measures were then restricted to HIV infected persons, and correlations were assessed using non-parametric rank tests due non-normal distribution of data. The level of significance for tests was defined as $p<0.05$, and all analyses were conducted with R statistical software (Version 2.8.1; http://www.cran.r-project.org).

Results

Study Sample

We enrolled 32 HIV-infected and 29 HIV-uninfected participants. The demographic and clinical characteristics of the participants are presented in Table 1. HIV-infected participants were similar to HIV-uninfected participants with respect to age, gender, race/ethnicity, and DM. A higher percentage of the HIV-infected group than controls had a history of IDU, and a trend existed for a greater presence of hepatitis C infection and smoking. Use of a statin or BP medication (beta-blocker, thiazide, calcium channel blocker or angiotensin converting enzyme inhibitor) was present in 1 and 6 HIV-infected, and 2 and 3 HIV-uninfected participants, respectively. The majority of HIV-infected participants had not taken ART (84%), and the 5 patients with prior ART use had a mean duration of HIV infection of 14 (median 13) years and had been off ART for at least 2 years. Most HIV-infected participants (56%) had CD4 counts above the threshold for initiating ART based on current guidelines (350 cells/mm^3). [28]

Lipid and Biomarker Differences by HIV Status

HIV-infected participants had lower HDLc and total cholesterol and higher triglycerides, compared to HIV-uninfected controls (Table 2). All HDLp measures, except medium HDLp, were lower in HIV-infected versus -uninfected participants. Levels of IL-6, sICAM-1, and D-dimer, but not hsCRP, E-selectin and fibrinogen, were significantly higher in HIV infected participants when compared with controls. The percent difference between HIV-infected and uninfected groups were most striking for HDL, large and small HDLp subclasses specifically, and for levels of IL-6, sICAM-1 and D-dimer. Adjusting for additional confounders did not have a large influence on estimated differences associated with untreated HIV infection (Figure 1). Thus, after adjustment HIV-infection was associated with lower levels of total and large HDLp with a trend present for lower small HDLp. In addition, HIV-infection remained independently associated with higher levels of IL-6, sICAM-1, and D-dimer.

HDL Measures and Biomarkers among HIV-infected Participants

Correlations between lipid levels (total cholesterol, TG, HDLc, and total, large and small HDLp) and biomarkers (hsCRP, IL-6, sICAM-1, and D-dimer) and HIV RNA levels were examined among HIV-infected participants (n=32; table 3). These comparisons were limited to measures that tended to differ between HIV-infected and –uninfected groups (figure 1). A trend exists for lower total cholesterol levels with higher HIV RNA levels, but no other lipid measures were clearly associated with HIV RNA level. Lipid levels did not demonstrate associations with hsCRP levels among HIV-infected participants. Inverse correlations were present between total and small HDLp with IL-6, sICAM-1 and D-dimer levels ($p<0.05$ for all except IL-6 and total HDLp). Overall, these associations were stronger for small HDLp. No significant associations were present between large HDLp with levels of IL-6, sICAM-1 or D-dimer. Finally, CD4+ counts, before and after square root transformation, were not correlated with any of the HDL measures or biomarker levels.

Discussion

We compared HDLp and markers of inflammation, endothelial activation and thrombogenesis from HIV-infected participants with relatively preserved immune function who were not taking ART with HIV-uninfected controls, and characterized the relationship of these measures with one another among the HIV-infected participants. Persons with untreated HIV infection have lower levels of HDLc and HDLp, primarily large and small HDLp, and higher levels of inflammatory (IL-6), endothelial activation (sICAM-1), and thrombotic (D-dimer) biomarkers. Lower levels of HDLp, particularly small HDLp, were related to greater inflammation, endothelial activation and thrombotic activity. Whether HDLp measures represent another

marker of inflammation or a mediator of HIV-related premature atherosclerotic risk in this context requires further study.

Assessment of CVD risk related to blood lipids traditionally consists of measuring HDLc and LDLc. In the Multicenter AIDS Cohort Study (MACS), HIV sero-conversion led to reductions in TC, HDLc and LDLc.[5] While initiation of ART among participants in MACS led to substantial increases in TC and LDLc, HDLc remained 10mg/dL below pre-infection levels, which resulted in a lipid profile that resembled the metabolic syndrome.[5,29] NMR spectroscopy allows further characterization of HDLp size and concentration by 'counting' numbers of lipoprotein particle subclasses, which may be more informative with respect to CVD risk[7–13] Our finding that levels of total HDLp were lower in HIV-infected compared to HIV-uninfected participants is consistent with additional analyses performed on specimens from the MACS. Using these same methods, in the MACS total HDLp concentration was lower among 77 HIV-infected persons naïve to ART when compared to 609 uninfected controls. [30]

We built on the MACS findings by reporting that differences in total HDLp with HIV-infection are primarily due to lower levels of large and small HDLp. Small HDLp may be particularly protective in terms of atherosclerotic risk, given anti-inflammatory properties and their preference over larger HDL as initial acceptors of cholesterol, from peripheral cells, in reverse cholesterol transport.[31–33] Using these same NMR methods, analyses of lipoprotein particles from HIV-infected persons in SMART demonstrated that baseline levels of total and small HDLp, but not LDLp, were independently associated with subsequent risk for CVD events.[17] However, in longitudinal studies of participants from the general population, the clinical consequences of low levels of small HDLp, versus differences in other HDLp subclasses, for clinical CVD risk has been inconsistent.[8,[10],13]

Cohort data, from HIV-infected groups as well as the general population, have demonstrated increased risk for CVD events and all-cause mortality with elevations in the plasma markers we studied.[16,[20]–[22],[24],[26],27] In a comparison of HIV-infected participants from SMART with matched controls from the Coronary Artery Risk Development In Young Adults study (CARDIA) and Multi-Ethnic Study of Atherosclerosis (MESA), levels of hsCRP, IL-6 and D-dimer were 50 to over 100% higher with HIV infection.[34] In SMART, these changes were present for persons on and off ART at baseline and even among those with HIV RNA levels <400 copies/mL, suggesting that viral suppression alone may not be sufficient to counter the factors driving inflammation in this population. Endothelial activation markers, such as sICAM-1, have also been consistently elevated in cross-sectional comparisons of HIV-infected persons and the general population.[35] These data are consistent with our findings of higher IL-6, sICAM-1 and D-dimer levels in HIV infected persons. In contrast, we did not identify a significant difference in fibrinogen levels between groups. In the study of Fat Redistribution and Metabolic Change with HIV Infection (FRAM), fibrinogen levels were higher in HIV-infected participants receiving ART, and protease inhibitors specifically, when compared to participants from the general population in CARDIA.[36] Our findings and those from FRAM suggest that higher fibrinogen levels may be a consequence of ART drug effects rather than HIV-infection per se.

HDL may reduce atherosclerotic disease risk via anti-inflammatory and anti-thrombotic properties, in addition to reverse cholesterol transport. HDL protects LDL from oxidation and decreases expression of adhesion molecules on endothelial cells (including E-selectin and sICAM-1).[6,37] HDL also improves endothelial function via stimulation of nitric oxide synthase activity, enhances endothelium-dependent vasodilation, increases prostacyclin production by endothelial cells, and inhibits endothelial tissue factor expression, all of which down-regulate thrombotic pathways.[33,[38],39] Small HDLp are primarily responsible for

HDL' s anti-inflammatory properties and inhibition of endothelial activation.[32,33] Among HIV-infected participants, we demonstrate that lower levels of HDLp, and small HDLp in particular, are inversely correlated with markers of endothelial activation and thromotic activity. Lower levels of HDLp may be a consequence of HIV infection and/or thrombotic activity, a mediator of endothelial injury and thrombogenesis, or both.[33,[38],[40],41] Low HDLc levels have been described in many chronic inflammatory states, and inflammation may also change HDLp qualitatively rendering them less atheroprotective.[37,[42],43]

Limitations of this study design include the cross-sectional study design and therefore our inability to describe associations for blood lipid and biomarker measures over time. Specifically, we are unable to account for biomarker variations over time, although participants were presumably at a steady state with respect to HIV viral replication. Although 5 HIV-infected participants were treatment experienced, they had been off ART for >2 years thereby minimizing influence to blood lipid and biomarker measures associated with recent or current ART use. Furthermore, data from SMART and the general population suggest levels of these markers measured at a single time point predict subsequent risk for future clinical events.[16, [19],[20],[44]–49] Also, comparisons were adjusted for HCV infection but not IDU due to the significant overlap in the presence of these variables, and accounting for IDU did not change results. Finally, as a consequence of the small sample size, confidence intervals are wide and important associations may have been missed.

In summary, untreated HIV infection is associated with lower levels of HDLp, particularly large and small HDLp. The relationship between small HDLp, inflammation, thrombogenesis and risk for premature atherosclerosis requires further examination in longitudinal studies of persons with HIV-infection.

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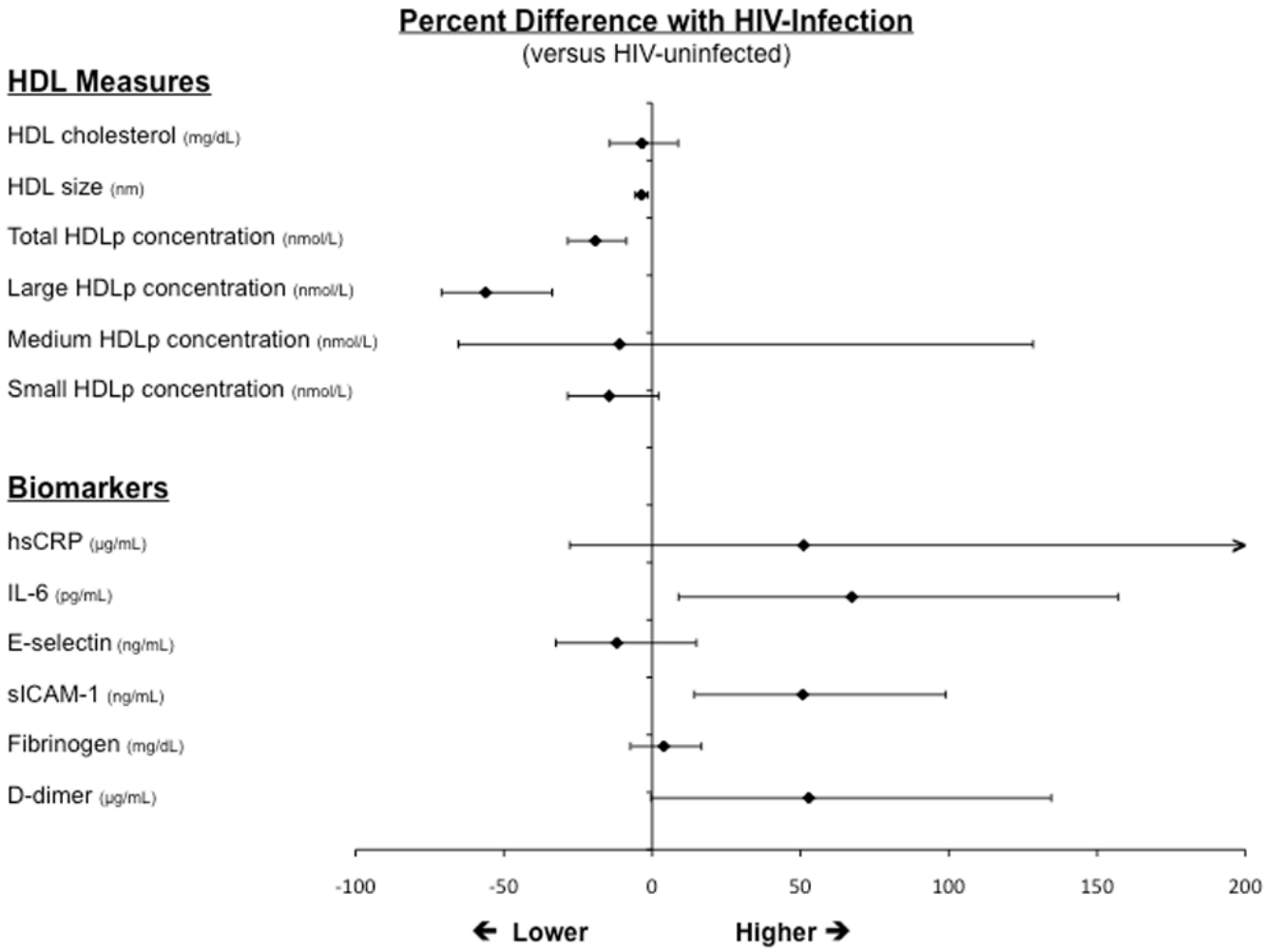

Figure 1. Adjusted Percent Difference in HDL Measures and Biomarkers by HIV status

For each measure, the percent difference between the HIV-infected and HIV-uninfected group is plotted with error bars reflecting 95% confidence intervals. The percent difference was calculated after adjustment for age, gender, race/ethnicity, smoking status, BMI, and hepatitis C infection. Results indicate that HIV infection is associated with a decrease in HDL measures, and higher levels of IL-6, sICAM-1 and D-dimer levels.

TABLE 1

Baseline Characteristics

Characteristic	HIV Infected (n=32)	HIV Uninfected* (n=29)	*p*-value
Age, mean years (SD)	40.0 (9.6)	40.6 (10.8)	0.78
Gender (male)	88% (28)	90% (26)	0.79
Race/Ethnicity			0.32
White	44% (14)	48% (14)	
African American	31% (10)	41% (12)	
Other	25% (8)	10% (3)	
Smoker	59% (19)	41% (12)	0.16
Injection Drug Use	38% (12)	14% (4)	0.04
Hepatitis C	34% (11)	14% (4)	0.06
Diabetes Mellitus	6% (2)	7% (2)	0.92
Body Mass Index, mean kg/m^2 (SD)	26.0 (5.1)	27.8 (4.5)	0.15
Systolic Blood Pressure, mean mmHg (SD)	127.7 (13.9)	126.7 (12.5)	0.77
Diastolic Blood Pressure, mean mmHg (SD)	77.0 (11.3)	74.5 (7.8)	0.31
Framingham 10yr CVD risk, mean % (SD)	4.8 (4.6)	3.5 (4.7)	0.27
Number with score <10%	27	25	
Percent (#) with score 10–20%	5	4	
Duration of Infection, mean years (SD)	6.5 (6.6)	--	
Prior AIDS	7% (2)	--	
Prior ART Use	16%(5)	--	
HIV RNA, mean $\log_{10}$ copies/mL(SD)	4.15 (0.73)	--	
CD4 Count ($cells/mm^3$)			
Mean (SD)	391 (182)	--	
Median (IQR)	382 (255–514)	--	

Data presented are percent (no.) unless otherwise specified

* Attempt was made to match HIV uninfected group on age, gender, race/ethnicity, smoking status and diabetes

Table 2

Lipid Measures and Biomarkers

	HIV-infected (n=32)	HIV-uninfected (n=29)	Percent Difference (95% CI)*	*p*-value
	Median (IQR)			
Traditional Lipid Panel				
Total Cholesterol (mg/dL)	168 (148–186)	191 (161–221)	−8 (−19, 3)	0.15
HDLc (mg/dL)	34.5 (30.0–44.5)	47.0 (42.0–56.0)	−26 (−37, −13)	<0.01
LDLc (mg/dL)	108 (81–114)	108 (93–145)	−5 (−21, 15)	0.61
Triglycerides (mg/dL)	126 (90–178)	112 (77–143)	23 (−5, 59)	0.11
High-Density Lipoprotein				
HDL Size (nm)	8.50 (8.38–9.03)	8.90 (8.60–9.10)	−2 (−5, 1)	0.12
Total HDLp (nmol/L)	23.9 (20.2–27.8)	30.4 (25.5–33.1)	−21 (−30, −11)	<0.01
Large HDLp (nmol/L)	3.80 (2.50–6.78)	6.40 (4.20–8.80)	−50 (−67, −23)	<0.01
Medium HDLp (nmol/L)	1.05 (0.27–2.97)	0.90 (0.30–3.30)	−6 (−61, 127)	0.90
Small HDLp (nmol/L)	18.4 (13.9–21.0)	21.5 (17.1–24.4)	−20 (−33, −5)	0.01
Inflammatory, Endothelial and Thrombotic Markers				
hsCRP (μg/mL)	1.94 (0.82–5.84)	1.46 (0.68–5.04)	27 (37, 156)	0.49
IL-6 (pg/mL)	1.79 (1.32–5.35)	1.26 (0.72–2.14)	71 (11, 162)	0.01
E-selectin (ng/mL)	40.8(26.6–56.6)	46.4 (35.8–56.4)	−7 (−28, 19)	0.54
sICAM-1 (ng/mL)	312 (251–488)	225 (168–279)	65 (25, 117)	<0.01
Fibrinogen (mg/dL)	409 (334–479)	413 (340–447)	2 (−9, 14)	0.76
D-dimer (μg/mL)	0.39 (0.19–0.67)	0.19 (0.13–0.38)	71 (10, 165)	0.02

* Comparisons between HIV infected and uninfected (% difference) reflect differences in mean values after natural log transformation

Table 3

Correlation of Lipid Measures with HIV RNA and Biomarkers within HIV-infected Participants

Lipid Measurements	Spearman Rank Correlation Coefficient (*p*-value)				
	HIV RNA (log_{10} copies/mL)	hsCRP (μg/mL)	IL-6 (pg/mL)	sICAM-1 (ng/mL)	D-dimer (μg/mL)
Total Cholesterol (mg/dL)	−0.34 (0.06)	0.08 (0.66)	−0.02 (0.93)	−0.37 (0.04)*	−0.46 (0.01)*
Triglycerides (mg/dL)	0.09 (0.64)	−0.10 (0.58)	−0.29 (0.11)	0.20 (0.27)	−0.27 (0.14)
HDLc (mg/dL)	−0.21 (0.26)	−0.01 (0.98)	−0.01(0.97)	−0.45 (0.01)*	−0.10 (0.59)
Total HDL Particles (nmol/L)	−0.24 (0.19)	−0.04 (0.85)	−0.32 (0.08)	−0.52 (<0.01)*	−0.38 (0.03)*
Large HDL Particles (nmol/L)	−0.15 (0.43)	−0.07 (0.70)	0.16 (0.38)	−0.16 (0.37)	−0.25 (0.18)
Small HDL Particles (nmol/L)	−0.22 (0.23)	0.11 (0.56)	−0.41 (0.02)*	−0.50 (<0.01)*	−0.57 (<0.01)*

*denotes a significant correlation