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Lipoprotein Particle Subclasses, Cardiovascular Disease and HIV Infection

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Abstract

Both HIV and treatment for HIV have been associated with an increased risk of cardiovascular disease (CVD). Unfavorable lipid changes could offer a possible explanation for the increased risk of CVD. We examined the association of lipoprotein particles with CVD in HIV-infected patients.

The Strategies for Management of Anti-Retroviral Therapy (SMART) study was a trial of intermittent use of ART (drug conservation [DC]) versus continuous of ART (viral suppression [VS]). In a nested case-control study, lipoprotein particles (p) by nuclear magnetic resonance were measured at baseline and at the visit prior to the CVD event (latest levels) for the 248 patients who had a CVD event and for 480 matched controls. Odds ratios (OR) were estimated using conditional logistic models.

Total, large and small HDL-p, but not VLDL-p nor LDL-p, were significantly associated with CVD and its major component, non-fatal coronary heart disease. The HDL-p associations with CVD remained significant after adjustment for high sensitive C-reactive protein (hsCRP), interleukin-6 (IL-6) and D-dimer. Latest levels of total HDL-p were also significantly associated with CVD and treatment interruption led to decrease of total HDL-p; adjusting for latest HDL-p did not explain the greater risk of CVD that was observed in the DC vs VS group.

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Lipoprotein particles, especially small and large HDL-p identify HIV-infected patients at increased risk of CVD independent of other CVD risk factors.

Keywords

atherosclerosis; cardiovascular disease; cholesterol; ischemic heart disease; HDL- and LDL-cholesterol; HIV; lipids; lipoprotein particle size and number

Introduction

Advances in management of HIV disease and antiretroviral therapy (ART) during the last decade have led to a prolonged disease-free survival in a majority of individuals with HIV infection (1). Cardiovascular disease (CVD) is now a leading cause of death among HIV-infected patients; rates of heart disease appear to be increased in the HIV-infected versus uninfected population (2). Reasons for this increased CVD risk likely include alterations in metabolism, including lipids, both due to HIV and to ART for HIV (3).

In the Strategies for Management of Anti-Retroviral Therapy (SMART) study, intermittent ART was associated with an excess risk of AIDS, all-cause mortality, and serious non-AIDS diseases compared to continuous ART (4). Serious non-AIDS diseases were dominated by CVD. Both HDL-cholesterol (HDL-c) and LDL-cholesterol (LDL-c) declined following ART interruption, but the decrease in HDL-c was proportionally greater resulting in a more unfavorable lipid profile, as measured by total/HDL-c, for those in the intermittent compared to the continuous ART group (5). The HDL-c decline observed following ART interruption is consistent with studies showing that HDL-c is lower among untreated patients, and that increases with ART vary depending on the specific drugs used (6,7).

Few studies have been done on lipoprotein particle concentrations in HIV-infected individuals. In the Multicenter AIDS Cohort Study, total HDL particle concentration (HDL-p) was significantly lower among HIV-infected participants on and off ART compared to HIV-negative participants (8). In the general population, a number of studies have been done relating lipoprotein particle concentrations to ischemic heart disease. Although not conclusive, the data suggest that smaller LDL-p size, specifically a predominance of small dense LDL-p or a greater number of small LDL-p, is associated with an increased risk of coronary disease (9,10,11).

While the effect of HIV treatment and ART on lipoprotein particles has been studied, to our knowledge, the association of lipoproteins and CVD outcome has not. We investigated the relationship of lipoprotein particles with CVD morbidity and mortality.

METHODS

Study Design

Between January 2002 and January 2006, 5,472 HIV-infected patients with a CD4+ count >350 cells/mm³ were randomized to intermittent ART (drug conservation, DC) or continuous ART (viral suppression, VS) (4). VS patients taking ART at entry continued taking it, and those not taking it initiated ART after randomization. For the VS group, available ART was to be used in an uninterrupted manner with the goal of maximal and continuous suppression of HIV replication. The experimental DC strategy entailed intermittent use of ART for periods defined by CD4+ count (4). As previously reported on January 11, 2006, enrollment was stopped and participants in the DC group were advised to restart ART (this date is subsequently referred to as study modification). All participants were followed until July 11, 2007 (study closure). Patients were asked to consent to storing blood for future research, and only samples for

consenting patients were used. The SMART study was approved by the ethics committee of each clinical site and of the University of Minnesota.

Nested Case Control Study of Cardiovascular Outcomes

Criteria for CVD events have been previously described (5). For CVD cases that occurred through closure (248 patients) and for two controls ($n = 480$) (for some controls the sample was not sufficient) matched on country, age, gender, and approximate date of randomization lipoprotein particles using nuclear magnetic resonance were determined at Liposcience, Inc. in Raleigh, NC (9). Lipoprotein particle size and concentration were measured at baseline (study entry) and at the visit preceding the CVD event (latest levels). All samples were analyzed blinded to case and control status and to treatment group. Levels of HDL-c, LDL-c, total cholesterol and triglycerides were determined on the same samples using standard enzymatic methods by Quest Diagnostics, Inc. (Madison, NJ). LDL-c was directly measured.

As part of a separate investigation, two inflammatory markers, high sensitive C-reactive protein (hsCRP) and interleukin-6 (IL-6), and D-dimer were measured on the same samples by the Laboratory for Clinical Biochemistry Research at the University of Vermont (12).

Statistical Methods

Conditional logistic regression was used to study associations of study entry and latest levels of lipid levels, lipoprotein particle size and concentration with CVD. Selected analyses were also performed for non-fatal coronary heart disease (CHD) events (defined as clinical and silent myocardial infarction, coronary revascularization and coronary artery disease requiring drug treatment), non-fatal atherosclerotic non-CHD (defined as stroke and peripheral arterial disease), congestive heart failure and fatal CVD (defines as CV death and unwitnessed death). For these analyses events through study closure were used because there was no evidence of a difference in associations when analyses were restricted to events that occurred prior to study modification. Analyses by quartile of HDL-p size and concentration were performed and odds ratios (OR) for each of the three upper quartiles versus the lowest quartile (reference group) and for the upper three quartiles combined versus the lowest quartile are cited along with 95% confidence intervals (CIs). Quartiles were estimated from a random sample of 497 patients that has been previously described (12). Models that categorized lipid particles according to quartiles, models with continuous lipid levels after natural log transformation are also reported. In addition to the matching variables (age, gender, country and randomization date) that were considered in univariate analyses, the following additional baseline covariates were considered in multivariate models: race (black versus other), use of ART and HIV RNA level (no ART versus ART and ≤ 400 copies/ml versus ART and > 400 copies/mL), CD4+ cell count, smoking status, body mass index (BMI), prior CVD, diabetes, use of antihypertensive medication, use of lipid-lowering medication, presence of major resting ECG abnormalities, and co-infection with hepatitis B or C. Models that included triglycerides, LDL-c, hsCRP, IL-6 and D-dimer were also considered. When considering the association of large, medium and small HDL-p concentration with CVD, a model that included all three HDL particles sizes was considered.

Analyses which exclude participants on lipid-lowering medication were also carried out. Associations were considered for DC and VS participants separately. To assess whether associations between lipid particles and CVD varied by treatment, an interaction term (product of natural log transformed lipoprotein particle and treatment group) was included in the logistic models.

For analyses of latest levels of HDL-p size and concentration with CVD, the baseline level of the lipid particle that was the focus of the analysis was included as a covariate in some analyses. Other previously cited covariates were also considered.

To assess the effects of HDL-p differences between the DC and VS groups on the DC/VS odds ratio for CVD, conditional logistic models that included the latest level of HDL-p concentration as well as the treatment indicator were considered. These analyses are restricted to events that occurred prior to study modification. For cases and controls that did not have follow-up levels (largely patients who experienced events in the first year), baseline levels were used.

Statistical analyses were performed using SAS (Version 9.1). All reported p-values are 2-sided.

Results

Baseline Lipoprotein Levels in CVD Cases and Controls

Table 1 gives baseline characteristics for CVD cases and matched controls. In univariate analyses, prior AIDS, current smoking status, diabetes, prior CVD, major resting ECG abnormalities, and use of BP lowering drugs were associated with an increased risk of CVD. There was no significant difference in the lipid profile between the CVD cases and controls, except that HDL-cholesterol was lower and total/HDL was higher in CVD cases compared to controls. Baseline hsCRP, IL-6 and D-dimer were significantly higher in CVD cases than controls.

Baseline Lipoprotein Levels and CVD Risk

Of the 248 CVD events, 124 were attributed to non-fatal CHD. Baseline lipoprotein particles for CHD events and matched controls are given with the unadjusted and adjusted ORs (4th/1st quartile) in Table 2. Total, large and small HDL-p were significantly associated with non-fatal CHD, while total LDL-p and VLDL-p were not after adjustment. There were 62 non-fatal atherosclerotic non-CHD cases, 26 cases of non-fatal congestive heart failure and 36 cases of fatal CVD. LDL-p and VLDL-p were not significantly associated with non-fatal atherosclerotic non-CHD. Total HDL-p was associated with non-fatal atherosclerotic non-CHD with OR 0.24 (0.09–0.64), $p=0.005$ and with fatal CVD 0.33 (0.10–1.12), $p=0.08$. No association was found for any lipoprotein particle and CHF.

The risk of CVD was significantly lower for those with total HDL-p levels above the lower quartile cut-point of 25.1 $\mu\text{mol/L}$ (Table 3). Adjustment for baseline risk factors and for LDL-c and triglycerides had little impact on this association. There was greater impact with additional adjustment for hsCRP (OR=0.50; $p=0.02$), IL-6 (OR=0.50; $p=0.02$) and D-dimer (OR=0.49; $p=0.02$). With simultaneous adjustment for all 3 markers as well as other factors, the OR was 0.57 ($p=0.07$). The correlations of total HDL-p with hsCRP, IL-6 and D-dimer were -0.07 , -0.25 and -0.26 , respectively.

In a model that considered total HDL-p as a continuous variable (last two columns in Table 3), a difference corresponding to the IQR (0.28 $\mu\text{mol/L}$) was associated with an OR of 0.72 ($p=0.0001$). For large HDL-p, like total HDL-p, each of the upper three quartiles was associated with a lower risk of CVD compared to the lowest quartile. For the upper three quartiles combined versus the lowest the OR was 0.68 (95% CI: 0.49–0.95; $p=0.02$). For small HDL-p, there was a similar pattern. For the three upper quartiles combined versus the lowest quartile the OR was 0.62 (95% CI: 0.42–0.91 $p=0.02$). In the model that considered small HDL-p as a continuous variable (last two columns of Table 3), a difference corresponding to the IQR (0.46 $\mu\text{mol/L}$) was associated with an OR of 0.84 ($p=0.01$).

The association of total HDL-p with CVD was similar for DC and VS participants ($p=0.18$ for interaction). Findings were also similar when the analyses were restricted to participants not taking lipid therapy at entry (72.2% of CVD cases and 77.3% of controls) (data not shown).

Models that included large, medium, and small HDL-p were also considered. ORs for the upper three quartiles combined versus the lowest quartile when all three HDL-p concentration sizes were considered in one model were 0.64 ($p=0.01$), 0.77 ($p=0.17$), and $p=0.62$ ($p=0.02$), for large, medium and small HDL-p, respectively.

Changes in HDL-p after 1 month

Compared to those in the VS group, total HDL-p, medium HDL-p and small HDL-p declined significantly in the DC group (Figure 1). The HDL-p decline in the DC group after one month was related to the HIV RNA increase ($P<0.0001$). This relationship between HDL-p and HIV RNA paralleled the previously reported IL-6 increase with HIV RNA ($P=0.0003$) (Fig 2) (12).

Latest Levels of HDL-p Concentrations and CVD Risk and Impact on DC/VS Odds Ratio

Latest levels of HDL-p were lower for cases than controls (Table 4). Latest levels of HDL-p were significantly related to CVD independent of baseline levels except for large and medium HDL-p. After adjustment for baseline covariates as well as baseline HDL-p concentration, the ORs associated with a difference in latest HDL-p levels corresponding to the IQR were 0.73 (95% CI: 0.54–0.97; $p=0.03$), 0.84 (95% CI: 0.63–1.12; $p=0.23$), 0.86 (95% CI: 0.68–1.09; $p=0.22$), and 0.87 (95% CI: 0.75–1.00; $p=0.06$) for total, large, medium and small HDL-p, respectively.

The unadjusted OR (DC/VS) for CVD was 1.6 (95%: 1.0 to 2.4). With adjustment for latest level of total HDL-p this OR was 1.5 (95% CI: 1.0 to 2.3). With adjustment for latest levels of large, medium, and small HDL-p, the OR was 1.5 (95% CI: 1.0 to 2.4).

Discussion

This is the first report of the relationship between lipoprotein particle concentrations and CVD outcomes in HIV patients. We found that lower baseline total, large and small HDL-p concentrations were associated with a higher risk of CVD. Neither VLDL-p nor LDL-p concentrations were associated with CVD. HDL-p was inversely related with IL-6 and D-dimer and remained significantly associated with CVD after adjustment for these markers. Like IL-6 and D-dimer (12), HDL-p was related to change in HIV RNA in the DC group.

This association between HDL-p and CVD is similar to studies of lipoprotein particles in chronic inflammatory conditions (13). This is in contrast with other studies in the general population where LDL-p, especially small LDL-p, is significantly associated with CHD (9, 14,15). An hypothesis is that lower HDL-p concentrations contribute to less anti-atherogenic protection than higher levels and this results in an increased risk of CVD, primarily non-fatal CHD (16).

In a small cross-sectional study, Rose et al. (17) demonstrated that HIV infection and the associated inflammatory process modifies HDL-c metabolism and redirects cholesterol to apo-B containing lipoproteins. Several epidemiological studies have suggested that the risk of CHD is higher in patients with infections and/or chronic inflammatory diseases (18). The decrease in HDL-p and the corresponding increase in IL-6 following ART interruption (and the increase in HIV RNA) is consistent with the hypothesis that an inflammatory process, namely HIV, alters the size and density of HDL-p.

There are some limitations of this study. Latest levels are missing for some CVD cases and controls prior to study modification, due to the fact that many patients had stored specimens collected annually. Second, a single measurement immediately prior to the event may not fully capture the effect of interrupting ART on these markers.

In conclusion, we demonstrated that total, large and small HDL-p are related to CVD in HIV-infected patients. The current findings may have implications for understanding proatherogenic mechanisms associated with CVD outcomes in HIV patients. It remains to be proven that raising HDL-c or improving its function will reduce the risk of CVD events (19). The long-term effects of each antiretroviral drug on HDL-p as well as other lipid parameters need to be further studied in randomized trials.

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References

1. Palella FJ Jr, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced immunodeficiency virus infection. N Engl J Med 1998;338:853–860. [PubMed: 9516219]
2. Obel N, Thomsen HF, Kronborg G, et al. Ischemic heart disease in HIV-infected and HIV-uninfected individuals: a population-based cohort study. Clin Infect Dis 2007;44:1625–1631. [PubMed: 17516408]
3. Grunfeld C, Kotler DP, Arnett DK, et al. Contribution of metabolic and anthropometric abnormalities to cardiovascular disease risk factors. Circulation 2008;118:e20–e28. [PubMed: 18566314]
4. El-Sadr WM, Lundgren JD, Neaton JD, et al. Strategies for Management of Antiretroviral Therapy (SMART) Study Group. CD4+ count-guided interruption of antiretroviral treatment. N Engl J Med 2006;355:2283–2296. [PubMed: 17135583]
5. Phillips AN, Carr A, Neuhaus J, et al. Interruption of antiretroviral therapy and risk of cardiovascular disease in persons with HIV-1 infection: exploratory analyses from the SMART trial. Antivir Ther 2008;13:177–187. [PubMed: 18505169]
6. Oh J, Hegele RA. HIV-associated dyslipidaemia: pathogenesis and treatment. Lancet Infect Dis 2007;7:787–796. [PubMed: 18045561]
7. Asztalos BF, Schaefer EJ, Horvath KV, et al. Protease inhibitor-based HAART, HDL, and CHD-risk in HIV-infected patients. Atherosclerosis 2006;184:72–77. [PubMed: 15935358]
8. Riddler SA, Li X, Otvos J, et al. Multicenter AIDS Cohort Study. Antiretroviral therapy is associated with an atherogenic lipoprotein phenotype among HIV-1-infected men in the Multicenter AIDS Cohort Study. J Acquir Immune Defic Syndr 2008;48:281–288. [PubMed: 18545156]
9. Jeyarajah EJ, Cromwell WC, Otvos JD. Lipoprotein particle analysis by nuclear magnetic resonance spectroscopy. Clin Lab Med 2006;26:847–870. [PubMed: 17110242]
10. Kuller L, Arnold A, Tracy R, et al. Nuclear magnetic resonance spectroscopy of lipoproteins and risk of coronary heart disease in the cardiovascular health study. Arterioscler Thromb Vasc Biol 2002;22:1175–1180. [PubMed: 12117734]
11. Otvos JD, Collins D, Freedman DS, et al. Low-density lipoprotein and high-density lipoprotein particle subclasses predict coronary events and are favorably changed by gemfibrozil therapy in the Veterans Affairs High-Density Lipoprotein Intervention Trial. Circulation 2006;113:1556–1563. [PubMed: 16534013]
12. Kuller LH, Tracy R, Belloso W, et al. INSIGHT SMART Study Group. Inflammatory and coagulation biomarkers and mortality in patients with HIV infection. PLoS Med 2008;5:e203. [PubMed: 18942885]
13. Kuller LH, Grandits G, Cohen JD, Neaton JD, Prineas R. Multiple Risk Factor Intervention Trial Research Group. Lipoprotein particles, insulin, adiponectin, C-reactive protein and risk of coronary heart disease among men with metabolic syndrome. Atherosclerosis 2007;195:122–128. [PubMed: 17011566]

14. Rosenson RS, Otvos JD, Freedman DS. Relations of lipoprotein subclass levels and low-density lipoprotein size to progression of coronary artery disease in the pravastatin limitation of atherosclerosis in the coronary arteries (PLAC-1) trial. *Am J Cardiol* 2002;90:89–94. [PubMed: 12106834]
15. Blake GJ, Otvos JD, Rifai N, Ridker PM. Low-density lipoprotein particle concentration and size as determined by nuclear magnetic resonance spectroscopy as predictors of cardiovascular disease in women. *Circulation* 2002;106:1930–1937. [PubMed: 12370215]
16. Tabet F, Rye KA. High-density lipoproteins, inflammation and oxidative stress. *Clin Sci* 2009;116:87–98. [PubMed: 19076062]
17. Rose H, Hoy J, Woolley I, et al. HIV infection and high density lipoprotein metabolism. *Atherosclerosis* 2008;199:79–86. [PubMed: 18054941]
18. Wilson PWF. Evidence of Systemic Inflammation and Estimation of Coronary Artery Disease Risk: A Population Perspective. *Am J Med* 2008;121:S15–S20. [PubMed: 18926165]
19. Rader DJ. Molecular regulation of HDL metabolism and function: implications for novel therapies. *J Clin Invest* 2006;116:3090–3100. [PubMed: 17143322]

Figure 1.
Average change to 1 month in total, large, medium and small HDL-p ($\mu\text{mol/L}$) by treatment group.

* DC patients on ART at baseline with HIV RNA ≤ 400 copies/mL

Figure 2.

Average change to 1 month of IL-6 and total HDL-particle concentration in DC patients on ART at baseline with HIV RNA ≤ 400 copies/mL.

Table 1

Baseline Characteristics, CVD Risk Factors and Lipid Profile of CVD Cases and Matched Controls

	CVD Cases (N=248)	Controls (N=480)	P-value *
Treatment group (% DC)	56.5	46.3	0.01
Demographics			
Age (median, IQR)	49 (44, 56)	49 (43, 55)	NA
Gender (% female)	19.4	19.4	NA
Black (%)	39.1	37.1	0.50
CD4+ (cells/mm ³) (median, IQR)	576 (457, 841)	620 (467, 802)	0.47
CD4+ nadir (cells/mm ³) (median, IQR)	235 (119, 345)	246 (150, 346)	0.81
HIV-RNA ≤ 400 copies/mL (%)	67.6	67.6	0.91
Prior AIDS-related illnesses (%)	37.1	24.8	0.0005
Hepatitis B (%)	2.0	1.3	0.40
Hepatitis C (%)	19.8	20.0	0.97
CVD Risk Factors			
Current smoker (%)	52.4	39.8	0.001
Diabetes (%)	16.9	8.3	0.0007
Prior CVD (%)	13.3	5.2	0.0004
Major ECG abnormality (%)	21.3	10.5	0.0001
Blood pressure lowering drugs (%)	45.2	30.6	<0.0001
Lipid lowering drugs (%)	27.8	22.7	0.15
Lipids			
Total cholesterol (mg/dl) (median, IQR)	196 (171, 233)	193 (168, 229)	0.29
HDL cholesterol (mg/dl) (median, IQR)	38 (31, 49)	42 (34, 52)	0.03
LDL cholesterol (mg/dl) (median, IQR)	111 (88, 141)	111 (89, 134)	0.76
Triglycerides (mg/dl) (median, IQR)	193 (134, 309)	178 (123, 288)	0.39
Total/HDL cholesterol (median, IQR)	5.2 (3.9, 6.8)	4.7 (3.6, 6.0)	0.05
Biomarkers			
hsCRP (μg/mL) (median, IQR)	3.62 (1.50, 7.51)	2.16 (0.90, 4.79)	<0.0001
IL-6 (pg/mL) (median, IQR)	3.10 (1.92, 4.88)	2.17 (1.37, 3.54)	<0.0001
D-dimer (μg/mL) (median, IQR)	0.31 (0.19, 0.59)	0.24 (0.15, 0.45)	0.0008
Lipoprotein Particles			
Total VLDL (nmol/L) (median, IQR)	85.7 (58.6, 121.9)	81.3 (54.1, 114.0)	0.38
Total LDL (nmol/L) (median, IQR)	1364 (1057, 1730)	1322 (1035, 1596)	0.30
Small LDL (nmol/L) (median, IQR)	1027 (609, 1455)	981 (613, 1260)	0.80

	CVD Cases (N=248)	Controls (N=480)	P-value[*]
Total HDL (μmol/L) (median, IQR)	28.4 (24.2, 32.7)	30.2 (26.1, 34.7)	0.0001
Large HDL (μmol/L) (median, IQR)	4.0 (2.1, 7.1)	4.7 (2.6, 7.7)	0.006
Medium HDL (μmol/L) (median, IQR)	3.9, (0.9, 8.4)	3.9 (1.2,7.7)	0.70
Small HDL (μmol/L) (median, IQR)	18.5 (14.2, 22.3)	20.1 (16.1, 23.9)	0.01

* P-value obtained from univariate conditional logistic model.
 Biomarkers and Lipoprotein particles are natural log transformed.

Table 2

Baseline Lipoprotein Particle Concentration Levels for Non-fatal CHD Events

Cases		Controls		Unadjusted OR (95% CI) for 4 th versus 1 st quartile		Adjusted ⁺ OR (95% CI) for 4 th versus 1 st quartile	
No.	Median (25 th , 75 th)	No.	Median (25 th , 75 th)	OR (95% CI)	P-value	OR (95% CI)	P-value
Non-fatal CHD ⁺⁺							
124	99 (67, 130)	240	82.0 (50.4, 109.4)	2.82 (1.33–5.99)	0.007	2.05 (0.83–5.06)	0.12
124	1440 (1087, 1878)	240	1320 (1037, 1588)	1.98 (1.00–3.92)	0.05	1.39 (0.58–3.35)	0.46
124	1142 (714, 1530)	240	963 (605, 1265)	2.16 (1.12–4.17)	0.02	1.98 (0.83–4.72)	0.12
124	28.9 (24.8, 33.2)	240	30.5 (26.5, 35.0)	0.43 (0.23–0.79)	0.006	0.30 (0.13–0.65)	0.003
124	3.6 (1.3, 6.6)	240	4.7 (2.6, 7.7)	0.44 (0.23–0.83)	0.01	0.37 (0.17–0.83)	0.01
124	5.0 (1.3, 8.7)	240	4.4 (1.3, 8.0)	0.97 (0.54–1.76)	0.92	0.79 (0.37–1.70)	0.55
124	18.6 (14.2, 22.8)	240	19.9 (16.1, 23.9)	0.60 (0.32–1.13)	0.11	0.47 (0.21–1.02)	0.06

⁺ Adjusted for baseline covariates: age, race, HIV-RNA and ART status, smoking, prior CVD, diabetes, use of BP-lowering drugs, use of lipid-lowering drugs, hepatitis co-infection, CD4⁺, BMI and major baseline ECG abnormalities.

⁺⁺ Clinical MI, silent MI, coronary artery revascularization, coronary artery disease requiring drug treatment. Units: VLDL-p nmol/L; LDL-p nmol/L; HDL-p μ mol/L

Table 3
Risk of CVD Associated with HDL Particle Concentration Levels ($\mu\text{mol/L}$) at Baseline

	< 25 th Percentile (reference)	25 – 49 th Percentile		50 – 74 th Percentile		≥ 75 th Percentile		OR associated with diff. between lower and upper 25 th percentiles after natural log transformation	
		OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Total HDL									
no. cases/controls	76/91	52/116		66/121		54/152			
univariate	1.0 (ref.)	0.53 (0.3–0.8)	0.006	0.61 (0.4–0.9)	0.03	0.41 (0.3–0.6)	<0.0001	0.72 (0.6–0.9)	0.0001
adjusted ¹	1.0 (ref.)	0.47 (0.3–0.8)	0.006	0.65 (0.4–1.1)	0.11	0.41 (0.2–0.7)	0.001	0.72 (0.6–0.9)	0.002
adjusted ²	1.0 (ref.)	0.44 (0.3–0.8)	0.003	0.67 (0.4–1.1)	0.14	0.41 (0.2–0.7)	0.001	0.73 (0.6–0.9)	0.003
adjusted ³	1.0 (ref.)	0.45 (0.2–0.8)	0.01	0.79 (0.4–1.4)	0.42	0.57 (0.3–1.1)	0.07	0.85 (0.7–1.1)	0.15
Large HDL									
no. cases/controls	96/147	50/113		52/110		50/110			
univariate	1.0 (ref.)	0.65 (0.4–1.0)	0.05	0.70 (0.5–1.1)	0.11	0.69 (0.4–1.1)	0.09	0.81 (0.7–0.9)	0.006
adjusted ¹	1.0 (ref.)	0.52 (0.3–0.9)	0.01	0.63 (0.4–1.1)	0.08	0.68 (0.4–1.2)	0.16	0.77 (0.6–0.9)	0.006
adjusted ²	1.0 (ref.)	0.51 (0.3–0.8)	0.01	0.61 (0.4–1.0)	0.07	0.69 (0.4–1.2)	0.19	0.76 (0.6–0.9)	0.006
adjusted ³	1.0 (ref.)	0.57 (0.3–1.0)	0.05	0.65 (0.4–1.2)	0.15	0.77 (0.4–1.4)	0.40	0.79 (0.6–1.0)	0.03
Medium HDL									
no. cases/controls	61/105	58/127		54/110		75/138			
univariate	1.0 (ref.)	0.76 (0.5–1.2)	0.24	0.82 (0.5–1.3)	0.40	0.91 (0.6–1.4)	0.67	0.97 (0.8–1.1)	0.70
adjusted ¹	1.0 (ref.)	0.91 (0.5–1.6)	0.74	0.90 (0.5–1.6)	0.69	1.07 (0.6–1.8)	0.80	1.01 (0.8–1.2)	0.89
adjusted ²	1.0 (ref.)	0.90 (0.5–1.6)	0.71	0.84 (0.5–1.5)	0.55	1.08 (0.6–1.9)	0.78	1.01 (0.8–1.2)	0.96
adjusted ³	1.0 (ref.)	0.95 (0.5–1.7)	0.87	0.75 (0.4–1.4)	0.36	1.17 (0.6–2.2)	0.62	1.01 (0.8–1.3)	0.91
Medium HDL									
no. cases/controls	61/105	58/127		54/110		75/138			
univariate	1.0 (ref.)	0.76 (0.5–1.2)	0.24	0.82 (0.5–1.3)	0.40	0.91 (0.6–1.4)	0.67	0.97 (0.8–1.1)	0.70
adjusted ¹	1.0 (ref.)	0.91 (0.5–1.6)	0.74	0.90 (0.5–1.6)	0.69	1.07 (0.6–1.8)	0.80	1.01 (0.8–1.2)	0.89

	< 25 th Percentile (reference)	25 – 49 th Percentile		50 – 74 th Percentile		≥ 75 th Percentile		OR associated with diff. between lower and upper 25 th percentiles after natural log transformation	
		OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
adjusted ²	1.0 (ref.)	0.90 (0.5–1.6)	0.71	0.84 (0.5–1.5)	0.55	1.08 (0.6–1.9)	0.78	1.01 (0.8–1.2)	0.96
adjusted ³	1.0 (ref.)	0.95 (0.5–1.7)	0.87	0.75 (0.4–1.4)	0.36	1.17 (0.6–2.2)	0.62	1.01 (0.8–1.3)	0.91
Small HDL									
no. cases/controls	61/84	68/116		58/127		61/153			
univariate	1.0 (ref.)	0.78 (0.5–1.2)	0.30	0.60 (0.4–1.0)	0.03	0.53 (0.3–0.8)	0.007	0.84 (0.7–1.0)	0.01
adjusted ¹	1.0 (ref.)	0.87 (0.5–1.5)	0.62	0.65 (0.4–1.1)	0.14	0.55 (0.3–0.9)	0.03	0.85 (0.7–1.0)	0.03
adjusted ²	1.0 (ref.)	0.88 (0.5–1.5)	0.64	0.65 (0.4–1.2)	0.14	0.54 (0.3–0.9)	0.02	0.84 (0.7–1.0)	0.03
adjusted ³	1.0 (ref.)	0.74 (0.4–1.3)	0.31	0.68 (0.4–1.3)	0.22	0.60 (0.3–1.1)	0.09	0.89 (0.8–1.0)	0.15
HDL size									
no. cases/controls	69/122	55/108		68/130		56/120			
univariate	1.0 (ref.)	0.88 (0.6–1.4)	0.59	0.92 (0.6–1.4)	0.70	0.84 (0.5–1.3)	0.44	0.99 (0.8–1.2)	0.95
adjusted ¹	1.0 (ref.)	0.74 (0.4–1.3)	0.27	0.78 (0.5–1.3)	0.33	0.75 (0.4–1.3)	0.31	0.97 (0.7–1.3)	0.82
adjusted ²	1.0 (ref.)	0.71 (0.4–1.2)	0.23	0.79 (0.5–1.3)	0.38	0.76 (0.4–1.3)	0.35	1.00 (0.8–1.3)	0.99
adjusted ³	1.0 (ref.)	0.65 (0.4–1.2)	0.15	0.84 (0.5–1.5)	0.54	0.69 (0.4–1.3)	0.24	1.00 (0.7–1.3)	0.99

¹ adjusted for baseline covariates: age, race, HIV-RNA and ART status, smoking, prior CVD, diabetes, use of blood-pressure lowering drugs, use of lipid-lowering drugs, hepatitis co-infection, CD4+, BMI and major baseline ECG abnormalities.

² adjusted for baseline covariates plus LDL and triglycerides

³ adjusted for baseline covariates, LDL and triglycerides, plus loge D-dimer, IL-6 and hsCRP

Percentile definitions (average difference between lower 25th and upper 25th percentiles on natural log scale):

Total: <25.1, 25.1–28.9, 29.0–33.1, ≥33.2 (0.28)

Large: <3.0, 3.0–5.1, 5.2–7.8, ≥ 7.9 (1.00)

Medium: <0.9, 0.9–3.5, 3.6–7.1, ≥ 7.2 (2.08)

Small: <14.2, 14.2–18.6, 18.7–22.3, ≥22.4 (0.46)

Table 4

Latest Levels of HDL Particle Concentrations for Cardiovascular Cases and Matched Controls Cases Controls

CVD events and controls ⁺	Cases	Controls	P-value ⁺⁺	P-value ⁺⁺⁺
	Median (25 th , 75 th %)	Median (25 th , 75 th %)		
Total HDL particles (μmol/L)	27.1 (22.9, 32.0)	29.6 (25.5, 33.8)	<0.0001	0.001
Large HDL particles (μmol/L)	4.3 (2.2, 7.1)	4.7 (2.4, 7.8)	0.02	0.15
Medium HDL particles (μmol/L)	3.5 (0.8, 6.9)	4.1 (1.5, 8.0)	0.04	0.06
Small HDL particles (μmol/L)	17.3 (13.4, 21.7)	19.2 (15.3, 23.3)	0.006	0.02

⁺ 195 CVD cases and 368 controls.⁺⁺ P-value obtained from univariate conditional logistic model with natural log transformed latest level.⁺⁺⁺ P-value obtained from conditional logistic model with natural log transformed latest level, adjusted for natural log transformed baseline level.