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Changes in Lipids and Lipoprotein Particle Concentrations After Interruption of Antiretroviral Therapy

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Abstract

Background—The effect of interruption of antiretroviral therapy (ART) on lipoprotein particle subclasses has not been studied. We examined short-term changes in lipids and lipoprotein particles among 332 HIV-infected individuals randomized to interrupt or continue ART in the “Strategies for Management of Antiretroviral Therapy” trial.

Methods—Lipids and lipoprotein particles measured by nuclear magnetic resonance spectroscopy were compared between randomized groups at month 1; associations with inflammatory and coagulation markers (high sensitivity C-reactive protein; interleukin 6; amyloid A; amyloid P; D-dimer; prothrombin fragment 1 + 2) were assessed.

Results—Compared with continuation of ART, treatment interruption resulted in substantial declines in total, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, and triglyceride, at month 1 but had little net effect on total/HDL cholesterol ratio [baseline-adjusted mean difference [95% confidence interval (CI)] interruption versus continuation arms: −0.10 (−0.59 to 0.38); $P = 0.67$]. ART interruption resulted in declines in total, large, and medium very low density lipoprotein (VLDL) particle concentrations (VLDL-p) and total and medium HDL-p. However, there was no change in small HDL-p [baseline-adjusted percentage difference between arms: −4.6% (−13.1%, +5.1%); $P = 0.35$], small LDL-p [−5.0% (−16.9%, +8.6%); $P = 0.45$], or other LDL-p subclasses. Changes in lipid parameters on ART interruption did not differ according to baseline ART class (protease inhibitor versus non-nucleoside reverse transcriptase

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inhibitor) but were negatively associated both with changes in HIV viral load and with changes in inflammatory and coagulation markers, particularly D-dimer.

Conclusions—These results suggest that ART interruption does not favorably influence overall lipid profile: there was little net effect on total/HDL cholesterol ratio, and no change in small LDL-p or small HDL-p, the lipoprotein particle subclasses most consistently linked to coronary risk. Short-term declines in lipid parameters after ART interruption were not associated with class of ART and may be linked to increases in viral replication, inflammation and coagulation.

Keywords

antiretroviral therapy interruption; coagulation markers; inflammatory markers; lipids; lipoprotein particle subclasses

There is substantial evidence that HIV infection impacts on blood lipids, but the interplay between infection, treatment, and changes in various lipid parameters is complex. Seroconversion itself is associated with reductions in total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c) and low-density lipoprotein cholesterol (LDL-c),^{1,2} although initiation of multidrug antiretroviral therapy (ART) usually results in increases in lipids.^{3–7} Protease inhibitors tend to induce greater increases in TC, LDL-c, and triglyceride (TG) than nonnucleoside reverse transcriptase inhibitors,^{4,5} whereas the latter class has been linked to increases in HDL-c.^{6,7} Protease inhibitor-induced cholesterol changes at least partly explain the increased coronary heart disease risk observed in treated compared with untreated HIV-infected people.⁸

The extent to which lipid increases reverse when ART is stopped, and the rapidity with which any such changes take place is uncertain. In the “Strategies for Management of Antiretroviral Therapy” (SMART) randomized trial,⁹ compared with the ART continuation “viral suppression (VS)” strategy, the ART interruption “drug conservation (DC)” strategy resulted in a net increase in the TC/HDL-c ratio at year 1,¹⁰ due to a decline in both TC and HDL-c after treatment interruption. This has been suggested as a potential factor contributing to the raised cardiovascular disease risk that was associated with the interruption strategy.¹⁰ However, lipid changes at year 1 may not capture acute or short-term changes and may be substantially influenced by the fact that almost 40% of patients in the DC arm had resumed ART by this point.¹⁰ Furthermore, consideration of conventional lipid measures alone may be inadequate. There is evidence that lipoprotein particle size and density are related to atherogenicity,^{11–16} with predominance of small LDL particles believed to be particularly implicated in coronary risk in the general population. However, much less is known regarding the effect of ART on lipoprotein particles, and no previous studies have investigated changes in lipoprotein particles after ART interruption. In addition, the extent to which changes in lipid parameters after ART interruption are influenced by class of ART and/or linked to acute changes in systemic inflammation is uncertain.

In the SMART trial, lipoprotein particle subclasses and several inflammatory and coagulation markers were measured at baseline and month 1 in a subset of patients,¹⁷ providing a unique opportunity to investigate these issues within a randomized study. We assess: (1) the pattern of change in usual lipids in DC and VS arms over 8 months post randomization; (2) DC versus VS differences in lipids and lipoprotein particle subclasses at month one; (3) the effect of baseline demographic and treatment factors on DC versus VS differences in lipid parameters at month 1; (4) the associations of changes in lipid parameters with changes in inflammatory and coagulation markers and HIV plasma viral load.

METHODS

The methods and results of the SMART trial have been published.⁹ In brief, 5472 HIV-infected patients with CD4 cell count >350 cells per cubic millimeter (4591 of whom were on ART at trial entry) were randomized to 1 of 2 strategies. The VS strategy aimed to achieve maximal suppression of HIV viral load by continuous ART use. The DC strategy entailed interruption (or deferral) of ART until the CD4 cell count fell to <250 cells per cubic millimeter, at which time ART was (re)started until the CD4 cell count rose to >350 cells per cubic millimeter. On confirmation of CD4 cell count >350 cells per cubic millimeter, ART was interrupted again and resumed at CD4 cell count <250 cells per cubic millimeter. The DC strategy aimed to achieve maximal viral load suppression during periods of ART use. The trial was approved by the institutional review board at each site, and all participants gave written informed consent. Enrolment was stopped on January 11, 2006, due to poorer outcome in the DC arm. The hazard ratio (95% CI) for the primary endpoint (opportunistic disease or death) in the DC compared to VS group was 2.6 (1.9, 3.7).⁹

Usual lipids (TC, LDL-c, HDL-c, TG) were measured on serum at baseline and on plasma at months 1, 2, 4, and 8 by Quest Diagnostics, Inc. (Madison, NJ) using standard enzymatic methods. LDL-c was directly measured. Samples were not required to be fasting. HIV plasma viral load was measured at baseline, months 1, 2, and every 2 months thereafter for 12 months. All samples were obtained before the SMART protocol change on January 11, 2006, and laboratory analysis was performed blind to treatment arm.

Biomarker Sub-Study

A subgroup of 499 patients (249 from the DC arm; 250 from the VS arm) was selected randomly from SMART patients enrolled in the United States who were free of cardiovascular disease at entry and who had consented to storage of blood specimens for research purposes. Inflammatory and coagulation markers and lipoprotein particle subclasses were measured on plasma at baseline and month 1.¹⁷ Four inflammatory markers [high sensitivity C-reactive protein (hsCRP), interleukin 6 (IL-6), amyloid A, amyloid P], and 2 coagulation markers [D-dimer and prothrombin fragment 1 + 2 (F1.2)] were measured by the Laboratory for Clinical Biochemistry Research, University of Vermont. Lipoprotein subclasses were measured using nuclear magnetic resonance (NMR) spectroscopy at Liposcience Inc. (Raleigh, NC), and categorized according to particle diameter as large (60–200 nm), medium (35–60 nm), and small (27–35 nm) very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL) (23–27 nm) and large (21.3–23.0 nm) and small (18.3–21.2 nm) LDL; large (8.8–13.0 nm), medium (8.2–8.8 nm), and small (7.3–8.2 nm) HDL.¹⁸ For each subclass, particle concentrations (μmol/L for HDL and nmol/L for other measures) were determined and are denoted by ‘p’ (eg, Large VLDP p). Mean particle size was also determined for VLDL, LDL, and HDL particles. Reproducibility of the NMR technique, determined from replicate analysis of plasma pools, is indicated by the following coefficients of variation: <2% for VLDL size and <0.5% for LDL and HDL size, <10% for VLDL subclasses, <4% for total LDL-p, <8% for large and small LDL subclasses, and <5% for large and small HDL subclasses, with higher variation (<30%) for medium HDL and IDL (the latter due to their typically low concentrations).

The present analysis is based on 332 patients in the substudy who had measurements of usual lipids and lipoprotein particle subclasses at baseline and month 1 and who were taking ART at entry to SMART. The SMART study, including the consent for stored specimens, was approved by the institutional review board or ethics committee of each clinical site and the University of Minnesota, which served as the statistical and data management centre.

Statistical Methods

Values of TG and all lipoprotein particle measures were log transformed (base e) to normalize distributions and stabilize variance. For lipoprotein particle concentrations, values below the lower limit of detection were replaced with “minimum values” specified by the laboratory (see footnote to Table 3). Analysis of covariance was used to compare lipid parameters between DC and VS arms at month 1, adjusting for baseline values. For log-transformed parameters, percentage differences between DC and VS arms can be obtained by exponentiating the difference in means. Unpaired *t* tests were used to assess baseline differences in lipid parameters according to the following demographic and baseline treatment factors: gender, age group, ethnicity, type of ART (protease inhibitor or nonnucleoside reverse transcriptase inhibitor regimen; subjects taking both or neither class were excluded), and use of lipid-lowering drugs. Tests of interaction were used to assess whether DC versus VS differences in lipid parameters at month 1 varied according to these factors. Interaction tests were carried out only for those lipid parameters found to differ significantly between randomized arms in the analysis of covariance. Pearson correlation coefficients (*r*) were used to assess associations of lipids with inflammatory and coagulation markers and viral load in the DC arm, using changes from baseline to month 1.

RESULTS

Baseline Characteristics

Table 1 shows characteristics of the 332 patients who had measurements of lipids and lipoprotein particle concentrations and who were taking ART at entry to SMART. Approximately 70% of patients were male, and almost half were of black ethnicity. Baseline ART regimen included a protease inhibitor, nonnucleoside reverse transcriptase inhibitor, both of these classes, and neither class for 39.5%, 43.4%, 6.9%, and 10.2% of subjects, respectively. Median CD4 cell count was 581 cells per cubic millimeter and approximately 70% of subjects had viral load ≤ 400 copies per milliliter. About one fifth of patients were taking lipid-lowering drugs. Mean lipid values were 195.5 mg/dL for TC, 110.4 mg/dL for LDL-c, 43.7 mg/dL for HDL-c, 5.26 for TC/HDL-c ratio, and 5.17 log_e mg/dL for TG. The distribution of baseline characteristics was similar in the DC and VS arms (Tables 1 and 2).

Changes Over Time in Lipids

In the DC arm, the cumulative numbers of patients resuming ART were 1 (0.6%), 20 (12.8%), 40 (25.6%), and 61 (39.1%) by months 1, 2, 4, and 8, respectively. Figure 1 shows lipid changes over the first 8 months. Changes in lipids after interruption of ART were rapid. In the DC arm, TC, LDL-c, HDL-c, and TG fell substantially by month 1, with some further decline subsequently. Maximum declines were observed at month 1 for LDL-c, month 2 for TC and HDL-c, and month 4 for TG. There was little change over time in the TC/HDL-c ratio. In the VS arm, changes in lipids were smaller: moderate declines occurred in TC, LDL-c, and HDL-c, with little change in TC/HDL-c ratio and TG. At month 1, declines in TC, LDL-c, HDL-c, and TG were significantly greater in the DC compared with VS arm (Table 2): estimated DC versus VS mean differences (mg/dL) adjusted for baseline (95% CI) were -21.2 (-28.4 to -14.0) for TC, -7.1 (-12.5 to -1.7) for LDL-c, -3.4 (-5.0 to -1.7) for HDL-c; and the percentage difference (95% CI) for TG was -17.6% (-24.9% to -8.4%) ($P \leq 0.01$ for all). There was no significant difference in TC/HDL-c ratio [DC versus VS difference: -0.10 (95% CI: -0.59 to 0.38), $P = 0.67$].

Changes in Lipoprotein Particle Subclasses

Table 3 shows baseline values and changes at month 1 in lipoprotein particle subclasses. Compared with the VS arm, there were declines in total VLDL-p and in VLDL subclasses in

the DC arm at month 1; differences were significant for total, large, and medium VLDL-p ($P \leq 0.01$). The percentage difference (95% CI) for DC versus VS was -19.4% (-26.7% to -11.4%) for total VLDL-p, -27.3% (-44.3% to -5.1%) for large VLDL-p, and -28.7% (-39.6% to -15.9%) for medium VLDL-p. There were no significant differences between arms in total LDL-p [percentage difference (95% CI): -3.8% (-8.6% to $+1.3\%$)], small LDL-p [-5.0% (-16.5% to $+8.6\%$)], or other LDL-p subclasses. Total HDL-p and medium HDL-p declined in the DC arm relative to the VS arm [percentage differences (95% CI): -9.6% (-13.5% to -5.6%) for total and -39.9% (-59.3% to -11.3%) for medium HDL-p; $P \leq 0.01$]. There was no significant difference between arms for small HDL-p, (-4.6% [-13.4% to $+5.1\%$] $P = 0.35$), or for large HDL-p, VLDL-p, LDL-p, or HDL-p size.

Baseline and Changes in Lipids and Lipoprotein Particle Subclasses According to Demographic and Treatment Factors

Baseline lipids varied according to several demographic and treatment factors. Among the 332 subjects overall, mean HDL-c was lower among men (41.7 mg/dL) than women (48.2 mg/dL); TG levels were higher among men than women (5.24 versus 5.01 log mg/dL); and among subjects aged ≥ 45 years compared with < 45 years (5.28 versus 5.05 log mg/dL); LDL-c was higher among white subjects compared with others (115.5 versus 107.6 mg/dL). Subjects taking nonnucleoside reverse transcriptase inhibitor–based treatment had higher HDL-c than those taking protease inhibitor–based treatment (46.4 versus 40.8 mg/dL). Compared with others, subjects taking lipid-lowering drugs had considerably higher TC (218.8 and 189.4 mg/dL for subjects on and off lipid-lowering drugs, respectively), LDL-c (120.3 and 107.8 mg/dL) and TG (5.51 and 5.08 log mg/dL; $P < 0.05$ for all two sample t -tests).

Table 4 shows baseline-adjusted DC versus VS differences in lipids at month 1, according to demographic and treatment factors. The declines in TC, LDL-c, and HDL-c in the DC arm relative to the VS arm tended to be greater among men compared with women, among older compared with younger subjects, and among white subjects compared with those of other ethnicity. Among the subgroup of 275 subjects taking either a protease inhibitor–based or nonnucleoside reverse transcriptase inhibitor–based ART regimen, there was no evidence that changes in lipids varied according to class of ART. However, changes in TC and LDL-c in the DC versus VS arm were much greater in subjects taking lipid-lowering drugs at baseline compared with those not taking these drugs. For TC, the baseline-adjusted DC versus VS differences in means (mg/dL) were -32.7 and -15.8 for subjects who were and were not taking lipid-lowering drugs, respectively; the corresponding differences in means for LDL-c were -18.0 and -3.6 ($P < 0.05$ for both interactions). Interaction tests were also performed for the following lipid particle measures: total, large, and medium VLDL-p and total and medium HDL-p, as significant differences between arms at month 1 had been found for these parameters. No significant interactions of randomized group with demographic factors, class of ART or lipid-lowering drug use were found ($P > 0.05$; data not shown).

Association of Changes in Lipids and Lipid Particle Subclasses With Changes in Inflammatory Markers, Coagulation Markers, and Viral Load After ART Interruption

Table 5 shows the association between 1-month changes in lipids and 1-month changes in inflammatory and coagulation markers and viral load, in the DC arm only. The strongest associations were with D-dimer and viral load: changes in TC, LDL-c, and HDL-c were negatively correlated with changes in D-dimer and viral load ($r = -0.40$ to $r = -0.24$). In other words, after ART interruption, decreases in lipids were associated with increases in viral load and D-dimer. Weak to moderate negative associations were apparent between changes in TC, LDL-c, and HDL-c and changes in IL-6 and amyloid A. There were similar

negative associations with lipoprotein particles in the DC arm: change in large VLDL-p was negatively associated with change in viral load ($r = -0.25$); change in total LDL-p was negatively associated with changes in amyloid A ($r = -0.24$) and viral load ($r = -0.21$); change in total HDL-p was negatively associated with change in D-dimer ($r = -0.41$), F1.2 ($r = -0.26$), amyloid A ($r = -0.37$), hsCRP ($r = -0.31$), IL-6 ($r = -0.41$), and viral load ($r = -0.34$); change in small HDL-p was negatively associated with change in amyloid A ($r = -0.23$) and IL-6 ($r = -0.30$).

DISCUSSION

We examined the effect of ART interruption on lipids and lipoprotein particle subclasses in a randomized comparison with subjects remaining on ART. ART interruption resulted in rapid and substantial declines in TC, LDL-c, HDL-c, and TG, but had little net effect on the TC/HDL-c ratio. There were no significant changes in LDL-p subclasses. There were declines in total, large, and medium VLDL-p and total and medium HDL-p, but no change in small HDL-p.

The major strengths of this study are the randomized nature of the comparison and the comprehensive ascertainment of lipid parameters. We focused on 1-month changes, which were not diluted by DC patients resuming ART. There are some limitations. Baseline TC, HDL-c, LDL-c, and TG were measured in serum, with subsequent measurements in plasma. Previous studies suggest that serum lipid values tend to be consistently higher than plasma values by about 2%–3% for TC and 3%–5% for TG.^{19,20} There is less evidence of a consistent serum/plasma difference for HDL-c. Therefore, in our study, declines in usual lipids from baseline to month 1 will tend to be slightly overestimated. Serum/plasma differences probably contribute to the declines in TC, LDL-c, and HDL-c observed at month 1 in the VS arm, although they do not seem to fully explain the declines (mean values declined by 6%–11%, Table 1). Our primary analysis involving comparisons between randomized groups should be unaffected by serum/plasma differences. Nonfasting lipid measurement may result in increased variability of TG and some underestimation of TG changes and associations with other factors but should have minimal impact on the other lipid measures.¹⁹

Previous randomized^{21–25} and nonrandomized studies^{26–31} have assessed changes in conventional lipids during a single ART interruption or during a strategy of repeated interruptions. Most were small (<50 individuals interrupting ART),^{21,22,26,27,29–31} some only reported on defined lipid abnormalities,^{27,29} few considered HDL-c,^{25,26,31} and none considered lipoprotein particle subclasses. Most previous studies suggested declines compared with baseline (of varying magnitudes) in TC^{21,22,24,25,27} (and/or LDL-c^{24,27}) and TG^{21,22,27} during ART interruption. Of 3 studies measuring HDL-c,^{25,26,31} only 1 found a significant decline on treatment interruption,³¹ but all were relatively small. Two of 4 trials failed to show significant differences in any lipid measure between interruption and continuation arms.^{22,23} The comparison between studies is complicated by their different interruption/resumption strategies, the differing time points for lipid endpoints and the ART status of patients at this time. Changes in conventional lipids at year 1 in the SMART trial have been reported previously,¹⁰ but 40% of DC subjects had resumed ART. The present results show that mean lipids declines were substantially greater at month 1 than year 1 (19%, 110%, and 130% greater for TC, LDL-c, and HDL-c, respectively among DC subjects on ART at baseline.) This is in part due to attenuation of lipid changes over time as patients resumed ART, but it also demonstrates that lipid changes were rapid, with much of the decline occurring within the first month.

It is believed that information on lipoprotein particle subclasses measured by NMR may improve CHD risk assessment compared with standard lipid measures alone. Findings from non-HIV studies are inconclusive, but there is evidence that number of LDL particles, total LDL-p, small LDL-p, and smaller LDL size are positively associated with CHD,^{11–16} in some cases independently of chemically measured LDL-c.^{12–14,16} In addition, several studies have found an inverse association between small HDL-p and CHD.^{13,15} There is very little information from HIV-infected individuals. In cross-sectional analysis of the Multicenter AIDS Cohort Study, men on ART were judged to have an “atherogenic lipoprotein profile”: higher small LDL-p and total VLDL-p and lower large LDL-p and total HDL-p compared with HIV-negative men.³² In contrast, HIV-positive ART-naïve men had lower small LDL-p compared with HIV-negative men. The declines on treatment interruption observed in this present study in total VLDL-p and HDL-p would be consistent with results from Multicenter AIDS Cohort Study and with reversal of lipid changes induced by ART. However, although we observed a clear decline in chemically measured LDL-c in DC compared with VS arms, the difference between arms in NMR total LDL-p was not significant, and there were no differences in LDL-p subclasses. The association between lipoprotein particle subclasses and cardiovascular risk has recently been assessed in a nested case-control study within SMART; this analysis found that, of the NMR measures, small and large HDL-p had the strongest (inverse) associated with cardiovascular events.³³ Overall, the short-term changes in lipid parameters associated with interruption of ART in this analysis suggest little net effect on coronary risk. The reduction in LDL-c was offset by the decline in HDL-c; in addition, small LDL-p and small HDL-p, the NMR subclasses most consistently linked with CHD risk, did not differ between DC and VS arms.

We did not find greater reductions in TC and LDL-c in those stopping protease inhibitors or greater reductions in HDL-c among those stopping nonnucleoside reverse transcriptase inhibitors, as might be expected.^{3–7} As drugs within each class differ in their effect on different lipid fractions,^{3–7,34,35} this may be due to variations in specific drugs used, variations in duration of use, or differences in the nucleoside component of the regimen. Lipid changes on ART interruption tended to be greater among subgroups with higher baseline lipid levels (men, older subjects, white subjects and particularly those taking lipid-lowering drugs); differences were somewhat attenuated when assessed in terms of percentage change, using analysis on the log scale (data not shown). The considerably greater declines in TC and LDL-c among subjects on lipid-lowering drugs compared with other subjects may also be due to interactions between ART and lipid-lowering agents.³⁶ DC versus VS differences in lipids and lipoprotein particle subclasses were similar after exclusion of subjects taking lipid-lowering drugs at baseline (data not shown).

HIV replication is associated with endothelial dysfunction and activation of inflammatory and coagulation pathways.^{37,38} In the SMART trial, interruption of ART resulted in substantial increases in IL-6 and D-dimer at month 1.¹⁷ These present results show that, in the DC arm, greater increases in D-dimer, IL-6, and amyloid A were associated with greater declines in TC, LDL-c, and HDL-c, although there was no association with hsCRP. These correlations were strongest for D-dimer. Similar moderate negative associations were observed between changes in viral load and changes in TC, LDL-c, and HDL-c. Changes in various NMR lipid measures (particularly total and small HDL-p) were also negatively associated with changes in viral load and some inflammatory and coagulation markers. The associations with viral load were the most consistent. The pattern of rapid changes in lipids was similar to that observed for viral load: the percentage of subjects with viral load ≤ 400 copies per milliliter fell from 72% at baseline to 6% at 2 months in the DC arm overall.⁹ These results suggest that lipid declines may be closely linked to the sudden increase in viral replication and perhaps associated activation and inflammation, on interruption of ART.

Possibly it is these acute changes, rather than the specific antiretrovirals used, that are the dominating factors in determining short-term lipid changes when treatment is stopped.

Structured or CD4-guided treatment interruption strategies were once considered as a means of reducing toxicity associated with long-term ART—in particular, reversing drug-induced increases in TC. The SMART trial showed that CD4-guided treatment interruption resulted in increased risk of AIDS and severe non-AIDS morbidity. This assessment of short-term changes in lipids and lipoprotein particle concentrations among subjects on ART at baseline suggests that although TC changes associated with ART use seem to be rapidly reversed on treatment interruption, the overall lipid profile is not favorably influenced. Short-term changes in lipid parameters were not associated with class of ART and may be linked to increases in viral replication, inflammation, and coagulation.

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FIGURE 1.

Mean changes from baseline in lipids according to randomized group, among 332 patients on antiretroviral therapy at baseline. (1) TC; (2) LDL cholesterol; (3) HDL cholesterol; (4) total/HDL cholesterol ratio (v) Log TG. DC arm represented by closed triangles; VS arm represented by open circles. Minimum denominators at months 0, 1, 2, 4, 8 are 156, 155, 142, 130, 107 for DC arm and 176, 175, 159, 149, 123 for VS arm.

TABLE 1

Baseline Characteristics of 332 Patients on Antiretroviral Therapy at Baseline and With Lipid and Lipid Particle Measurements, According to Randomized Group

n	Randomized Group		
	DC Arm 156	VS Arm 176	Total 332
n (%) unless otherwise stated			
Male	107 (68.6)	124 (70.5)	231 (69.9)
Age (years): mean (SD)	46.6 (10.0)	44.9 (8.9)	45.7 (9.5)
Race			
Black	80 (51.3)	83 (47.2)	163 (49.1)
White	52 (33.3)	66 (37.5)	118 (35.5)
Other	24 (15.4)	27 (15.3)	51 (15.4)
Antiretroviral regimen includes			
PI	59 (37.8)	72 (40.9)	131 (39.5)
NNRTI	71 (45.5)	73 (41.5)	144 (43.4)
PI and NNRTI	10 (6.4)	13 (7.4)	23 (6.9)
Neither PI nor NNRTI	16 (10.3)	18 (10.2)	34 (10.2)
History of PI and NNRTI use *	79 (50.6)	77 (43.8)	156 (47.0)
Viral load ≤ 400 copies/mL	111 (71.2)	121 (68.8)	232 (69.9)
CD4 cell count (/mm ³): median (IQR)	551 (449–725)	611 (478–799)	581 (466–755)
Previous AIDS-related illness	48 (30.8)	52 (29.6)	100 (30.1)
Hepatitis C coinfection	29 (18.6)	31 (17.6)	60 (18.1)
Use of lipid-lowering drug	31 (19.9)	38 (21.6)	69 (20.8)
Current smoker	64 (41.0)	73 (41.5)	137 (41.3)
Diabetes	11 (7.1)	21 (11.9)	32 (9.6)

* Used both drug classes (current or previous use).

NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

TABLE 2
One-Month Changes in Lipids in VS and DC Arms Among 332 Patients on Antiretroviral Therapy at Baseline

Baseline (BL)		Month 1 (M1)		M1-BL change		DC Versus VS; Difference in M1 Adjusted for BL (95% CI) *	P [†]	
N	Mean (SD)	N	Mean (SD)	N	Mean (SD)			
TC (mg/dL)								
DC	156	195.1 (74.7)	156	162.7 (39.8)	156	-32.3 (60.2)	-21.2 (-28.4 to -14.0)	<0.001
VS	176	195.9 (47.0)	176	184.3 (47.0)	176	-11.6 (32.2)		
LDL-c (mg/dL)								
DC	156	109.4 (35.8)	155	93.6 (31.4)	155	-16.2 (32.3)	-7.1 (-12.5 to -1.7)	0.011
VS	176	111.3 (34.0)	175	101.7 (34.5)	175	-9.7 (24.4)		
HDL-c (mg/dL)								
DC	156	42.4 (15.1)	156	34.6 (13.6)	156	-7.8 (9.1)	-3.4 (-5.0 to -1.7)	<0.001
VS	176	44.8 (16.5)	175	39.9 (14.9)	175	-5.0 (8.3)		
TC/HDL ratio								
DC	156	5.40 (5.21)	156	5.40 (2.77)	156	0.01 (4.38)	-0.10 (-0.59 to 0.38)	0.67
VS	176	5.14 (3.48)	175	5.39 (3.02)	175	0.27 (2.24)		
Log _e TG (log _e mg/dL)								
DC	156	5.16 (0.77)	156	5.01 (0.67)	156	-0.15 (0.57)	-0.19 (-0.29 to -0.09)	<0.001
VS	176	5.18 (0.69)	176	5.21 (0.66)	176	0.03 (0.49)		

* Using analysis of covariance.

[†] P value by likelihood ratio test.

TABLE 3

One-Month Changes in Lipoprotein Particle Concentrations in VS and DC Arms Among 332 Patients on Antiretroviral Therapy at Baseline

		Baseline (BL), Mean (SD)	Month 1 (M1), Mean (SD)	M1-BL Change, Mean (SD)	DC Versus VS; Difference in M1 Adjusted for BL (95% CI)*	P†
N						
	DC	156	154	154	—	—
	VS	174	175	174	—	—
	Log _e total VLDL-p					
	DC	4.25 (0.63)	4.06 (0.58)	-0.20 (0.53)	-0.22 (-0.31 to -0.12)	<0.001
	VS	4.24 (0.62)	4.27 (0.60)	0.02 (0.47)		
	Log _e large VLDL-p					
	DC	1.02 (1.76)	0.77 (1.61)	-0.28 (1.40)	-0.32 (-0.58 to -0.05)	0.019
	VS	1.06 (1.54)	1.11 (1.67)	0.04 (1.30)		
	Log _e medium VLDL-p					
	DC	3.26 (1.10)	3.03 (0.99)	-0.26 (0.98)	-0.34 (-0.50 to -0.17)	<0.001
	VS	3.30 (1.01)	3.38 (0.89)	0.07 (0.81)		
	Log _e small VLDL-p					
	DC	3.29 (1.09)	3.13 (1.19)	-0.18 (1.55)	-0.18 (-0.41 to 0.06)	0.14
	VS	3.37 (0.87)	3.31 (1.00)	-0.05 (1.10)		
	Log _e total LDL-p					
	DC	7.09 (0.38)	7.04 (0.33)	-0.05 (0.27)	-0.04 (-0.09 to 0.01)	0.14
	VS	7.15 (0.39)	7.12 (0.40)	-0.03 (0.25)		
	Log _e IDL-p					
	DC	2.83 (2.34)	2.62 (2.30)	-0.19 (2.63)	-0.09 (-0.56 to 0.39)	0.72
	VS	3.24 (2.03)	2.88 (2.37)	-0.37 (2.50)		
	Log _e large LDL-p					
	DC	5.38 (1.17)	5.33 (1.21)	-0.07 (1.22)	-0.05 (-0.28 to 0.18)	0.67
	VS	5.29 (1.20)	5.31 (1.21)	0.04 (1.24)		
	Log _e small LDL-p					
	DC	6.52 (1.02)	6.55 (0.87)	0.02 (0.76)	-0.05 (-0.18 to 0.08)	0.45
	VS	6.55 (1.38)	6.61 (0.97)	0.06 (0.86)		
	Log _e total HDL-p (μmol/L)					

	Baseline (BL), Mean (SD)	Month 1 (M1), Mean (SD)	M1-BL Change, Mean (SD)	DC Versus VS; Difference in M1 Adjusted for BL (95% CI)*	P†
DC	3.37 (0.26)	3.27 (0.27)	-0.12 (0.23)	-0.10 (-0.15 to -0.06)	<0.001
VS	3.38 (0.27)	3.36 (0.25)	-0.01 (0.21)		
Log _e large HDL-p (μmol/L)					
DC	1.44 (0.91)	1.47 (0.75)	0.03 (0.65)	-0.02 (-0.14 to 0.11)	0.81
VS	1.42 (1.06)	1.46 (0.96)	0.05 (0.70)		
Log _e medium HDL-p (μmol/L)					
DC	0.61 (2.19)	0.39 (2.20)	-0.21 (2.34)	-0.51 (-0.90 to -0.12)	0.011
VS	0.52 (2.36)	0.87 (1.97)	0.35 (2.04)		
Log _e small HDL-p (μmol/L)					
DC	2.84 (0.68)	2.78 (0.46)	-0.10 (0.61)	-0.05 (-0.14 to 0.05)	0.35
VS	2.86 (0.56)	2.81 (0.59)	-0.04 (0.42)		
VLDL size (nm)					
DC	4.01 (0.21)	4.03 (0.23)	0.03 (0.23)	0.00 (-0.04 to 0.04)	0.99
VS	4.01 (0.20)	4.04 (0.20)	0.02 (0.20)		
LDL size (nm)					
DC	3.03 (0.05)	3.03 (0.04)	0.00 (0.03)	0.00 (-0.01 to 0.00)	0.56
VS	3.02 (0.04)	3.02 (0.04)	0.00 (0.03)		
HDL size (nm)					
DC	2.17 (0.05)	2.18 (0.05)	0.00 (0.04)	0.00 (-0.01 to 0.00)	0.61
VS	2.18 (0.06)	2.18 (0.05)	0.00 (0.03)		

Minimum values used for values below limit of detection: 0.01 for large VLDL (0.6% and 1.5% of BL and M1 values respectively) and medium HDL (13.3% and 10.6%); 0.1 for medium VLDL (0.6% and 0%), small VLDL (1.2% and 2.1%), IDL (11.8% and 14.9%), large HDL (2.1% and 2.4%) and small HDL (0.9% and 0.3%); 1.0 for large LDL (2.1% and 2.4%), small LDL (1.5% and 0.6%); medium small LDL (1.5% and 0.6%) and very small HDL (1.8% and 0.6%).

* Using analysis of covariance.

† P values by likelihood ratio test.

p, particle concentrations measured in log_e nmol/L unless otherwise indicated.

TABLE 4

Changes in Lipids According to Demographic and Treatment Factors

	DC Versus VS; Adjusted Difference at M1* (95% CI)			
	TC	LDL-c	HDL-c	Log _e TG
n = 332				
Gender				
Male	-26.0 (-34.6 to -17.4)	-10.9 (-17.5 to -4.2)	-4.2 (-6.0 to -2.3)	-0.19 (-0.31 to -0.07)
Female	-9.7 (-20.8 to 1.3)	0.5 (-8.5 to 9.5)	-1.8 (-5.3 to 1.7)	-0.17 (-0.35 to 0.0)
Interaction test	<i>P</i> = 0.052	<i>P</i> = 0.051	<i>P</i> = 0.22	<i>P</i> = 0.88
Age				
<45 years	-16.9 (-27.4 to -6.5)	-3.5 (-11.1 to 4.2)	-2.5 (-5.1 to 0.0)	-0.14 (-0.29 to 0.01)
≥45 years	-23.4 (-32.8 to -13.9)	-10.3 (-17.7 to -2.8)	-4.1 (-6.3 to -1.8)	-0.24 (-0.36 to -0.11)
Interaction test	<i>P</i> = 0.33	<i>P</i> = 0.19	<i>P</i> = 0.38	<i>P</i> = 0.36
Ethnicity				
White	-27.6 (-39.8 to -15.4)	-13.7 (-22.3 to -5.2)	-6.0 (-8.3 to -3.7)	-0.14 (-0.33 to 0.04)
Black/other	-17.1 (-26.0 to -8.3)	-3.3 (-10.1 to 3.6)	-2.1 (-4.4 to 0.1)	-0.20 (-0.31 to -0.09)
Interaction test	<i>P</i> = 0.16	<i>P</i> = 0.058	<i>P</i> = 0.037	<i>P</i> = 0.59
Antiretroviral-regimen [†]				
PI based	-20.8 (-32.0 to -9.5)	-6.6 (-15.0 to 1.9)	-3.7 (-6.1 to -1.3)	-0.23 (-0.37 to -0.08)
NNRTI based	-20.2 (-31.6 to -8.8)	-9.6 (-18.6 to -0.5)	-2.8 (-5.7 to 0.0)	-0.16 (-0.33 to 0.0)
Interaction test	<i>P</i> = 0.90	<i>P</i> = 0.68	<i>P</i> = 0.63	<i>P</i> = 0.56
Lipid-lowering drug at BL				
Yes	-32.7 (-52.9 to -12.6)	-18.0 (-33.2 to -2.9)	-3.0 (-6.5 to 0.4)	-0.20 (-0.44 to 0.03)
No	-15.8 (-22.6 to -8.9)	-3.6 (-9.1 to 1.9)	-3.5 (-5.4 to -1.6)	-0.18 (-0.29 to -0.07)
Interaction test	<i>P</i> = 0.026	<i>P</i> = 0.023	<i>P</i> = 0.83	<i>P</i> = 0.86

* Difference adjusted for baseline using analysis of covariance.

[†] Fifty-seven subjects taking both/neither PI and NNRTI excluded.

NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

TABLE 5

Association of Changes in Lipids With Changes in Viral Load, Inflammatory, and Coagulation Markers: DC Arm Only

N = 154 to 156				
Changes from BL to M1:	Changes from BL to M1			
	TC	LDL-c	HDL-c	Log _e TG
Log _e hsCRP	−0.11	−0.12	−0.16	−0.13
	<i>P</i> = 0.18	<i>P</i> = 0.15	<i>P</i> = 0.040	<i>P</i> = 0.11
Log _e IL-6	−0.19	−0.25	−0.17	0.01
	<i>P</i> = 0.017	<i>P</i> = 0.002	<i>P</i> = 0.037	<i>P</i> = 0.89
Log _e Amyloid A	−0.17	−0.23	−0.13	−0.08
	<i>P</i> = 0.039	<i>P</i> = 0.004	<i>P</i> = 0.099	<i>P</i> = 0.31
Log _e Amyloid P	0.04	0.09	0.13	−0.02
	<i>P</i> = 0.66	<i>P</i> = 0.26	<i>P</i> = 0.099	<i>P</i> = 0.83
Log _e D-dimer	−0.40	−0.27	−0.40	−0.12
	<i>P</i> < 0.001	<i>P</i> < 0.001	<i>P</i> < 0.001	<i>P</i> = 0.15
Log _e F1.2	0.04	0.02	−0.08	−0.09
	<i>P</i> = 0.63	<i>P</i> = 0.82	<i>P</i> = 0.35	<i>P</i> = 0.28
Log ₁₀ viral load*	−0.28	−0.30	−0.24	−0.20
	<i>P</i> < 0.001	<i>P</i> < 0.001	<i>P</i> = 0.003	<i>P</i> = 0.015

Values are Person correlation coefficients.

* For viral load changes, values <50 copies per milliliter were set to 50 copies per milliliter.