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Lipoprotein Changes in HIV-Infected Antiretroviral-Naïve Individuals after Starting Antiretroviral Therapy: ACTG Study A5152s Stein: Lipoprotein Changes on Antiretroviral Therapy

James H. Stein, MD, FAHA[a], **Lauren Komarow, MS**[b], **Bruno R. Cotter, MD**[c], **Judith S. Currier, MD**[d], **Michael P. Dubé, MD**[e], **Carl J. Fichtenbaum, MD**[f], **Mariana Gerschenson, PhD**[g], **Carol K.C. Mitchell, PhD**[a], **Robert L. Murphy, MD**[h], **Kathleen Squires, MD**[i], **Robert A. Parker, ScD**[b], **Francesca J. Torriani, MD**[c], and **ACTG 5152s Study Team**

[a]University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin, USA

[b]Harvard School of Public Health, Boston, Massachusetts, USA

[c]University of California-San Diego, San Diego, San Diego, California, USA

[d]University of California-Los Angeles, Los Angeles, California, USA

[e]Indiana University School of Medicine, Indianapolis, Indiana, USA

[f]University of Cincinnati Medical Center, Cincinnati, Ohio, USA

[g]University of Hawaii, Honolulu, Hawaii, USA

[h]Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA

[i]University of Southern California, Los Angeles, USA

Abstract

Background—Dyslipidemia is a frequent complication of antiretroviral therapy (ART) for patients with human immunodeficiency virus infection (HIV). The effects of ART on lipoproteins are less well-understood, and have not been investigated in a prospective study where assignment to ART is randomized.

Objective—To evaluate the effects of three class-sparing ART regimens on lipids and lipoproteins.

Methods—This was a substudy of a prospective, multicenter study treatment-naïve HIV-infected individuals randomly assigned to receive a regimen of nucleoside reverse transcriptase inhibitors (NRTIs) + the non-nucleoside reverse transcriptase inhibitor efavirenz, NRTIs + the protease inhibitor lopinavir/ritonavir, or a NRTI-sparing regimen of efavirenz + lopinavir/ritonavir. Lipoproteins were measured by nuclear magnetic resonance spectroscopy.

Results—Among the 82 participants, total and small low-density lipoprotein concentrations increased (median, interquartile range) by 152 (-49 - +407, $p<0.01$) and 130 (-98 - +417, $p<0.01$) nmol/L, respectively, especially in the arms containing lopinavir/ritonavir ($p_{KW}<0.04$). Very low-density lipoproteins also increased ($p<0.01$), with a larger increase in the arms that contained

Address for Correspondence: James H. Stein, MD, FAHA, University of Wisconsin School of Medicine and Public Health, 600 Highland Avenue, G7/341 CSC (MC 3248), Madison, WI 53792, Phone: (608) 263-9648, Fax: (608) 263-0405, E-mail: jhs@medicine.wisc.edu.

lopinavir/ritonavir (p=0.022). High-density lipoproteins increased by 6.0 nmol/L (2.8 - 10.4, p<0.01), but differences between arms were not significant (p_{KW}=0.069). Changes were not related to changes in markers of insulin/glucose metabolism.

Conclusions—Total and small low-density lipoprotein concentrations increased, especially in the arms containing lopinavir/ritonavir, as did increases in total very low-density lipoproteins. Adverse changes were especially prominent in the arm with efavirenz + lopinavir/ritonavir.

Keywords

Antiretroviral therapy; Cardiovascular risk; Clinical trial; Human immunodeficiency virus; Lipids; Lipoproteins

Background

Dyslipidemia is a frequently observed complication of antiretroviral therapy (ART) for patients with human immunodeficiency virus infection (HIV).[1] The increased cardiovascular disease (CVD) risk associated with ART is related, at least in part, to changes in serum lipids.[2,3] Abnormalities of serum lipoproteins, as well as insulin resistance have been associated with endothelial dysfunction in patients on ART.[4,5,6] Because dyslipoproteinemia has been described in patients with HIV who are not receiving ART,[7,8] and the effects of ART on serum lipids differ both between and within different ART regimens[9,10,11,12,13] the pathogenesis and magnitude of lipoprotein changes associated with ART have been difficult to characterize. Most studies that evaluated the metabolic complications of ART measured lipids, rather than lipoproteins, thus providing incomplete information regarding the pathophysiology and CVD risk associated with the observed dyslipidemia, which frequently includes abnormal serum cholesterol and triglyceride levels. Furthermore, most studies evaluating the effects of ART on lipids have been observational, not randomized, and/or were of short duration, so the effects of ART on lipoprotein metabolism remain incompletely understood. This report describes the effects of three class-sparing ART regimens on lipoproteins, in the context of a randomized, prospective clinical trial in which assignment to ART was randomized and subjects were followed for six months.

Methods

Study Design

AIDS Clinical Trials Group (ACTG) Study A5152s[14] was a sub-study (N=82) of ACTG A5142 (N=757),[15] a prospective, multicenter randomized clinical trial that investigated time to virologic failure among ART-naïve subjects who were randomly assigned to receive one of three ART-sparing regimens: (i) NRTIs plus the NNRTI efavirenz (a protease inhibitor [PI]-sparing regimen), (ii) NRTIs + the PI lopinavir/ritonavir (a NNRTI-sparing regimen), or (iii) efavirenz + lopinavir/ritonavir (a NRTI-sparing regimen). The NRTIs prescribed in this study were lamivudine plus extended-release stavudine, zidovudine, or tenofovir. NRTI use was investigator-selected prior to randomization and was a stratification factor. This study was approved by the institutional review boards at each institution. All subjects provided informed consent.

Major inclusion criteria included HIV-1 infection and plasma HIV RNA >2.0 $\log_{10}$ copies/mL. Major exclusion criteria included prior use of ART, known coronary artery disease, peripheral arterial disease, cerebrovascular disease, diabetes mellitus, significant kidney disease, and current use of lipid-lowering medications, insulin-sensitizing agents, antioxidant vitamin supplements, or hormones at greater than replacement doses. Pharmacological treatment of diabetes mellitus and dyslipidemia were not permitted during the study. Subjects

participating in A5142 from six sites in the United States were eligible, but not required, to enter this substudy. They were consecutively recruited and offered enrollment at participating sites. Study procedures were performed at baseline and then after 4 and 24 weeks. This paper describes the effects of three class-sparing ART regimens on lipoproteins.

Testing Procedures

Laboratory testing was performed using standard assays at the ACTG Central Metabolic Laboratory (Quest Diagnostics, Baltimore, MD) except as noted below. After at least an 8 hour fast, blood samples were drawn into 10 cc tubes containing EDTA and immediately centrifuged at 3000g for 10 minutes at 4°C. Aliquots were stored at -70°C until assays were performed. Advanced lipoprotein testing was performed by nuclear magnetic resonance spectroscopy at LipoScience, Inc (Raleigh, NC).[16] Low-density lipoprotein cholesterol (LDL-C) was measured directly by spectrophotometry (Genzyme Diagnostics, Cambridge, MA) on an Olympus AU600 (Olympus Europa GmbH, Hamberg, Germany).

Data Analysis

Evaluation of the relationships between levels of lipids, lipoproteins, and markers of insulin/glucose metabolism and their changes after 4 and 24 weeks were pre-specified goals of this study. The quantitative insulin sensitivity check index (QUICKI), a marker of insulin sensitivity, was calculated as $1 / \log_{10}$ (glucose in mg/dL) + $\log_{10}$ (insulin in μU/mL).

All values are reported as medians with interquartile ranges, unless noted otherwise. The Wilcoxon Signed Rank test was used to assess within-arm changes. Kruskal-Wallis (KW) or Fisher's Exact tests were used for between-arm comparisons. Throughout the paper p_{KW} denotes comparisons across all three groups. All other comparisons are within group or between two group comparisons. Spearman correlations (r_s) were used to evaluate relationships between pairs of continuous variables. Partial Spearman correlations adjusting for treatment regimen also were performed for variables with a difference between the treatment arms ($p_{KW}<0.10$). P values were not adjusted for multiple comparisons. Because several lipid and lipoprotein parameters would be expected to be intercorrelated, only those with $r_s>0.30$ are reported, unless otherwise noted. With 75 subjects, this study had over 80% power to detect this correlation with a $p = 0.05$.

Two participants randomized to efavirenz + lopinavir/ritonavir and two participants on NRTIs + lopinavir/ritonavir were excluded from week 24 because they started lipid-lowering medications between weeks 4 and 24. Additionally, one participant on efavirenz + lopinavir/ritonavir and one in the NRTIs + efavirenz arm were excluded from week 24 for non-adherence with ART. Data from the baseline and week 24 visits are presented.

Results

Baseline Characteristics

The 82 subjects were well-matched across groups at baseline (Table 1).[14] Of the 54 individuals who were randomized to NRTI-containing regimens, 9 (17%) received stavudine, 27 (50%) tenofovir, and 18 (33%) zidovudine with a similar distribution between the arms (p=0.46).

Baseline lipid and lipoprotein data are shown in Table 2. Serum lipids were similar in each arm ($p_{KW}>0.50$). Total cholesterol, high-density lipoprotein cholesterol (HDL-C), and LDL-C levels values were low; however, serum triglycerides were within the normal range. With the exception of very low-density lipoprotein (VLDL) size ($p_{KW}=0.009$) and large VLDL ($p_{KW}=0.064$), baseline lipoprotein concentrations and sizes also were similar in each arm ($p_{KW}>0.50$). The total VLDL concentration was low-normal; the large VLDL particle

concentration was normal.[16] The median VLDL particle size was low-normal. Intermediate-density lipoprotein (IDL) levels were elevated. Total LDL and small LDL concentrations were low; however, the median LDL particle size was normal. Total HDL particles were low, with a decreased number of large HDL particles; however, the median HDL size was normal.[16]

At baseline, the expected correlations between lipid and lipoprotein fractions were observed (data not shown). There were no significant correlations between CD4 cell counts and any of the lipid or lipoprotein fractions; however, the plasma HIV RNA concentration was inversely related to HDL-C (r_s=-0.37, p<0.001), total HDL (r_s=-0.41, p<0.001), large HDL (r_s=-0.35, p<0.001), and LDL-C (r_s=-0.30, p<0.001), but not total LDL, small LDL, or markers related to triglycerides. There was a significant inverse correlation between insulin levels and LDL size (r_s=-0.43, p<0.001), and significant positive correlations between insulin levels and large VLDL (r_s=0.39, p<0.001), glucose (r_s=0.37, p<0.002), and body-mass index (r_s=0.36, p<0.002).

Changes in Laboratory Tests

After 24 weeks of ART, plasma HIV RNA levels decreased and CD4 cell counts increased (p<0.001) to a similar extent in each arm (p_{KW}>0.60). Approximately 67% of participants had plasma HIV RNA levels <50 copies/mL. There was an increase in body-mass index (0.5 [-0.5 – +1.9] kg/m2, p<0.01) that was similar in each arm (p_{KW}=0.68). Waist circumference increased slightly (1.0 [-1.80 – 4.0] cm, p=0.04) without differences between arms (p_{KW}=0.910). Small but statistically significant increases in glucose levels were seen in the NRTI + efavirenz (+4, [0 – +9], p<0.05) and efavirenz + lopinavir/ritonavir (+5, [-3 – +12], p<0.05) arms (p_{KW}=0.04), but insulin levels were not different within or between arms (p_{KW}=0.24). Significant between-arms differences in changes QUICKI (p_{KW}=0.720) and high-sensitivity C-reactive protein (p_{KW}=0.234) were not observed after 24 weeks.

Changes in lipids and lipoproteins are described in table 3. Changes after 4 and 24 weeks were of similar magnitude, so only the 24 week data are reported. Total VLDL and large VLDL increased with ART (p<0.01). The VLDL particle size increased (p<0.01) without significant differences between arms. Large, statistically significant increases in total VLDL and large VLDL were observed in both arms that contained lopinavir/ritonavir (p<0.01), but not in the NRTIs + efavirenz arm. The increase in total VLDL was greater in the efavirenz + lopinavir/ritonavir arm than the NRTIs + efavirenz arm (p=0.008) and tended to be greater than in the NRTIs + lopinavir/ritonavir (p=0.085). Differences between arms in large VLDL were not statistically significant (p_{KW}>0.37). A large, significant increase in IDL was observed in the efavirenz + lopinavir/ritonavir arm (p=0.034) that was greater than observed in the other two arms (p≤0.036).

Total LDL and small LDL increased after 24 weeks of ART (p<0.01); however, the LDL particle size did not change significantly. Modest, statistically significant increases in total LDL were observed in the NRTIs + lopinavir/ritonavir arm (p<0.05). This increase was not statistically greater than observed in the NRTIs + efavirenz arm (p=0.316). In the efavirenz + lopinavir/ritonavir arm, large, statistically significant increases in total LDL were seen (p<0.01). These increases were greater than observed in the NRTIs + efavirenz (p=0.001) and in the NRTIs + lopinavir/ritonavir (p≤0.013) arms. Similar changes were seen for small LDL. In the efavirenz + lopinavir/ritonavir arm, large, statistically significant increases in small LDL were observed (p<0.01). These increases were greater than observed in the NRTIs + efavirenz arm (p≤0.014) and tended to be greater than in the NRTIs + lopinavir/ritonavir arm (p≤0.071). Changes in small LDL in the NRTIs + lopinavir/ritonavir and NRTIs + efavirenz arms were not statistically significant. There was a small but statistically significant increase in lipoprotein (a) (p≤0.01) that was similar in each arm.

Use of ART led to relatively large and statistically significant increases in total HDL in each arm ($p<0.01$). Participants in the efavirenz + lopinavir/ritonavir arm experienced the greatest numerical increase in total HDL. Although the overall test of significance between the arms had a p value of 0.069, the total HDL increase in the efavirenz + lopinavir/ritonavir arm was statistically higher than in the NRTIs + efavirenz arm ($p=0.036$) and tended to be higher than in the NRTIs + lopinavir/ritonavir arm ($p=0.056$). Large HDL increased ($p<0.01$); however, differences between arms were not significant. Changes in HDL size were not significant between or within groups. Changes in total LDL, small LDL, VLDL, and HDL did not differ by NRTI assignment.

Correlations between Changes in Laboratory Tests

Expected correlations between changes in lipids and lipoproteins were observed. For example, changes in LDL cholesterol were strongly correlated with changes in total LDL ($r_S=0.73$, $p<0.001$) and small LDL ($r_S=0.52$, $p<0.001$), as well as changes in large VLDL ($r_S=0.51$, $p<0.001$), IDL ($r_S=0.50$, $p<0.001$). Changes in triglycerides were strongly correlated with changes in total LDL ($r_S=0.55$, $p<0.001$) and small LDL ($r_S=0.58$, $p<0.001$), changes in total VLDL ($r_S=0.59$, $p<0.001$) and large VLDL ($r_S=0.82$, $p<0.001$), as well as VLDL size ($r_S=0.57$, $p<0.001$). In addition, changes in triglycerides were inversely associated with LDL size ($r_S=-0.43$, $p<0.001$) and large HDL ($r_S=-0.41$, $p<0.001$). Changes in HDL-C correlated positively with LDL size ($r_S=0.37$, $p=0.001$) as well as total ($r_S=0.59$, $p<0.001$) and large ($r_S=0.64$, $p<0.001$) HDL, but inversely with small LDL ($r_S=-0.33$, $p=0.005$) and large VLDL ($r_S=-0.36$, $p=0.002$). Partial correlations that considered treatment arm were not notably different in direction and level of statistical significance, indicating that the relationships between the changes in lipids and lipoproteins were not significantly influenced by the treatment arm.

Correlations between changes in lipoproteins after 24 weeks were as follows. Changes in total LDL correlated positively with changes in small LDL ($r_S=0.87$, $p<0.001$), IDL ($r_S=0.50$, $p<0.001$), total VLDL ($r_S=0.62$, $p<0.001$), and large VLDL ($r_S=0.35$, $p=0.002$), and inversely with changes in LDL size ($r_S=-0.51$, $p<0.001$), large HDL ($r_S=-0.38$, $p<0.001$), and HDL size ($r_S=-0.35$, $p=0.002$). Changes in large HDL was correlated significantly with changes in LDL size ($r_S=0.49$, $p<0.001$) and HDL size ($r_S=0.60$, $p<0.001$), and inversely with changes in total LDL ($r_S=-0.38$, $p<0.001$), small LDL ($r_S=-0.53$, $p<0.001$), total VLDL ($r_S=-0.35$, $p=0.002$), and large VLDL ($r_S=-0.33$, $p=0.004$). Significant correlations between changes in any of the lipoprotein parameters and changes in glucose, insulin, and body-mass index were not seen.

Discussion

This sub-study of a prospective clinical trial with randomized assignment to three distinct, modern, class-sparing ART regimens provided a unique opportunity to evaluate the effects of ART on lipids and lipoproteins. This is a matter of great clinical importance, since dyslipidemia occurs commonly in HIV-infected patients and serum lipids predict CVD risk among patients receiving ART.[2,3] Because ART-associated dyslipidemia involves abnormalities of several lipid fractions, and components of ART have differing effects on lipids that vary within and between ART classes, assessing the magnitude of CVD risk associated with ART has been challenging, as has understanding its pathophysiology and implications for therapy.[9,10,11,12,13] Furthermore, because lipoprotein abnormalities are seen in HIV-infected patients not on ART, including an increased prevalence of small LDL,[8,7] and because abnormalities of serum lipids may not reveal the qualitative and quantitative abnormalities in lipoproteins that underlie them,[17,18] characterization of ART-associated dyslipidemia requires longitudinal assessment of changes in lipoproteins, as in the current study.

In individuals without HIV Infection, concentrations of total and small LDL particles consistently are among the strongest predictors of CVD outcomes, independent of traditional lipids.[19,17,16,20,21] Increased total and small LDL have been observed in patients on ART.[4,22,23,24] In this study, total and small LDL particle concentrations increased, but there were notable differences between the treatment arms. Large, statistically significant increases in total and small LDL particles were seen with efavirenz + lopinavir/ritonavir. The magnitude of the median increase in these parameters approaches one standard deviation of the United States population, and crosses thresholds for increased levels of CVD risk based on current clinical interpretation of the advanced lipoprotein testing assay used in this study.[16] LDL particles also increased in the NRTIs + lopinavir/ritonavir arm, although the magnitude was less than on efavirenz + lopinavir/ritonavir, and the observed increase in small LDL was not statistically significant. The increase in LDL particles in the efavirenz + lopinavir/ritonavir arm was nearly twice as large as in the NRTIs + efavirenz arm, but this difference was not statistically significant. Of note, LDL size did not change significantly, despite the observed increases in triglycerides, as discussed below. Taken together, changes in LDL particles were greater in the arms that contained the PI lopinavir/ritonavir, and were especially high in regimens that included the NNRTI efavirenz. Importantly, the increases in the efavirenz + lopinavir/ritonavir arm could have been expected based on the direct LDL-C assay results, but the changes in the NRTIs + lopinavir/ritonavir arm would not have been elucidated without advanced lipoprotein testing. Because LDL-C is not calculated on a standard lipid panel when triglycerides are greater than 400 mg/dL, the increase in LDL particles observed in patients on ART may not have been recognized in studies that used the Friedewald equation to estimate LDL-C, or in clinical practices that do not perform direct measurements of LDL-C or advanced lipoprotein testing.

The increases in HDL-C and HDL particles observed in this study were large and particularly striking, as they occurred despite increases in triglycerides, which would be expected to reduce HDL-C. Increases tended to be largest in the efavirenz + lopinavir/ritonavir arm, but differences in HDL particles between arms were small, not statistically significant, and were qualitatively similar to the changes in HDL-C. The mechanism of the increase in HDL particles is uncertain; however, in the ATLANTIC study, neither the addition of the NNRTI nevirapine nor the NRTI lamivudine significantly affected CETP mass, although a small increase in CETP mass was seen with the PI indinavir.[23] In that study, increases in HDL-C and apo A-I were greatest in patients that received nevirapine. In the recent Nevirapine Intensive Lipid Evaluation (NILE) Trial, nevirapine use was associated with increases in apo A-I and large HDL, without significant effects on CETP activity or HDL catabolism, suggesting an increase in apo AI synthesis.[25] It has been hypothesized that the greater increase in HDL-C observed in patients on NNRTIs should lead to cardiovascular benefits; however, in this study, arms with and without the NNRTI efavirenz had similar effects on HDL-related lipid and lipoprotein parameters. Direct comparisons between ATLANTIC, NILE, and the current study cannot be made because the ART regimens were so different. This study does not shed light on the mechanisms of HDL increases seen with ART or their effects on CVD risk.

As expected, triglycerides increased with ART, particularly in the arms that contained the PI, lopinavir/ritonavir. Large, statistically significant increases in total VLDL and large VLDL were observed in both lopinavir/ritonavir-containing arms, but not in the arm without PIs. Changes in total VLDL and large VLDL correlated positively with changes in LDL particles and inversely with changes in HDL particles. Furthermore, significant correlations between changes in any of the lipoprotein parameters and changes in glucose, insulin, and body-mass index were not seen.

Limitations

This study was designed to identify changes in endothelial function in each arm;[14] however, evaluation of lipoproteins and their changes were pre-specified endpoints of the study. The absence of significant differences between arms in lipoproteins may be due to a type II (false negative) error. Because multiple lipoprotein parameters were compared to one another, the magnitude of reported correlations and their consistency should be considered in their interpretation. Of note, partial correlations that considered treatment arm were not notably different in direction and level of statistical significance, indicating that the relationships between the changes in lipoproteins were not significantly influenced by the treatment arm. This study did not evaluate lipoprotein kinetics or the activity of enzymes involved in lipoprotein metabolism, so the mechanism(s) of the observed changes cannot be evaluated. Finally, because assignment to NRTIs was not randomized and only 9 patients received stavudine, the relative lipoprotein effects of tenofovir, zidovudine, and stavudine could not be evaluated.

Conclusions

In this prospective study with randomized assignment to three class-sparing ART regimens, significant lipoprotein changes were observed. Total and small LDL particle concentrations increased, especially in the arms containing the PI lopinavir/ritonavir, as did total VLDL particles. HDL particles increased to a similar extent in all arms. Adverse changes in LDL and IDL were especially prominent in the arm with efavirenz + lopinavir/ritonavir. These changes were not related to changes in markers of insulin/glucose metabolism.

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Reference List

1. Carr A, Samaras K, Burton S, Law M, Freund J, Chisholm DJ, Cooper DA. A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance in patients receiving HIV protease inhibitors. AIDS 1998;12:F51–F58. [PubMed: 9619798]
2. Friis-Moller N, Reiss P, Sabin CA, Weber R, Monforte A, El Sadr W, Thiebaut R, De Wit S, Kirk O, Fontas E, Law MG, Phillips A, Lundgren JD. Class of antiretroviral drugs and the risk of myocardial infarction. N Engl J Med 2007;356:1723–35. [PubMed: 17460226]
3. Triant VA, Lee H, Hadigan C, Grinspoon SK. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. J Clin Endocrinol Metab 2007;92:2506–12. [PubMed: 17456578]
4. Stein JH, Klein MA, Bellehumeur JL, McBride PE, Wiebe DA, Otvos JD, Sosman JM. Use of human immunodeficiency virus-1 protease inhibitors is associated with atherogenic lipoprotein changes and endothelial dysfunction. Circulation 2001;104:257–62. [PubMed: 11457741]
5. Solages A, Vita JA, Thornton DJ, Murray J, Heeren T, Craven DE, Horsburgh CR Jr. Endothelial function in HIV-infected persons. Clin Infect Dis 2006;42:1325–32. [PubMed: 16586393]
6. Shankar SS, Dube MP, Gorski JC, Klaunig JE, Steinberg HO. Indinavir impairs endothelial function in healthy HIV-negative men. Am Heart J 2005;150:933. [PubMed: 16290967]
7. Grunfeld C, Pang M, Doerrler W, Shigenaga JK, Jensen P, Feingold KR. Lipids, lipoproteins, triglyceride clearance, and cytokines in human immunodeficiency virus infection and the acquired immunodeficiency syndrome. J Clin Endocrinol Metab 1992;74:1045–52. [PubMed: 1373735]
8. Feingold KR, Krauss RM, Pang M, Doerrler W, Jensen P, Grunfeld C. The hypertriglyceridemia of acquired immunodeficiency syndrome is associated with an increased prevalence of low density lipoprotein subclass pattern B. J Clin Endocrinol Metab 1993;76:1423–7. [PubMed: 8501146]
9. Shlay JC, Bartsch G, Peng G, Wang J, Grunfeld C, Gibert CL, Visnegarwala F, Raghavan SS, Xiang Y, Farrough M, Perry HE, Kotler D, El Sadr WM. Long-term body composition and metabolic changes in antiretroviral naive persons randomized to protease inhibitor-, nonnucleoside reverse transcriptase inhibitor-, or protease inhibitor plus nonnucleoside reverse transcriptase inhibitor-based strategy. J Acquir Immune Defic Syndr 2007;44:506–17. [PubMed: 17325603]
10. Gatell J, Salmon-Ceron D, Lazzarin A, Van Wijngaerden E, Antunes F, Leen C, Horban A, Wirtz V, Odeshoo L, Van den DM, Gruber C, Ledesma E. Efficacy and safety of atazanavir-based highly active antiretroviral therapy in patients with virologic suppression switched from a stable, boosted or unboosted protease inhibitor treatment regimen: the SWAN Study (AI424-097) 48-week results. Clin Infect Dis 2007;44:1484–92. [PubMed: 17479947]
11. Haubrich, R.; Riddler, S.; DiRenzo, G.; Komarow, L.; Powderly, W.; Garren, K.; George, T.; Rooney, J.; Mellors, J.; Havlir, D. the AIDS Clinical Trials Group 5142 Study Team. Metabolic outcomes of ACTG 5142: A prospective, randomized, phase III trial of NRTI-, PI-, and NNRTI-sparing regimens for initial treatment of HIV-1 infection. Program and abstracts of the 14th Conference on Retroviruses and Opportunistic Infection; February 25-28, 2007; Los Angeles, CA. p. 38Abstract
12. Smith, K.; Weinberg, W.; DeJesus, E.; Fischl, M.; Liao, Q.; Ross, L.; Lancaster, T. Efficacy and Safety of Once-Daily Boosted Fosamprenavir (FPV/r) or Atazanavir (ATV/r) with Tenofovir (TDF)/emtrictabine (FTC) in Antiretroviral-Naive HIV-1 Infected Patients: 24-week Results from COL103952 (ALERT). Program and abstracts of the 46th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy; September 27-30, 2006; San Francisco, CA. p. H-1670a.Abstract
13. Shikuma CM, Yang Y, Glesby MJ, Meyer WA III, Tashima KT, Ribaudo HJ, Webb N, Bastow B, Kuritzkes DR, Gulick RM. Metabolic effects of protease inhibitor-sparing antiretroviral regimens given as initial treatment of HIV-1 Infection (AIDS Clinical Trials Group Study A5095). J Acquir Immune Defic Syndr 2007;44:540–50. [PubMed: 17245230]
14. Torriani FJ, Komarow L, Parker RA, Cotter BR, Currier JS, Dube MP, Fichtenbaum CJ, Gerschenson M, Mitchell CKC, Murphy RL, Squires K, Stein JH. for the ACTG 5152s Team. Endothelial function

in HIV-infected antiretroviral naive subjects before and after starting potent antiretroviral therapy: AIDS Clinical Trials Group Study 5152s. J Am Coll Cardiol. August 12;2008 in press

15. Riddler, SA.; Haubrich, R.; DiRienzo, G.; Peeples, L.; Powderly, WG.; Klingman, KL.; Garren, KW.; George, T.; Rooney, JF.; Brizz, B.; Havlir, D.; Mellors, JW. for the AIDS Clinical Trials Group 5142 Study Team. A prospective, randomized, phase III trial of NRTI-, PI-, and NNRTI-sparing regimens for initial treatment of HIV-1 infection. ACTG 5142. 16th International AIDS Conference; August 13-18, 2006; Toronto, Canada. p. THLB0204Abstract
16. Jeyarajah EJ, Cromwell WC, Otvos JD. Lipoprotein particle analysis by nuclear magnetic resonance spectroscopy. Clin Lab Med 2006;26:847–70. [PubMed: 17110242]
17. Cromwell WC, Otvos JD. Low-density lipoprotein particle number and risk for cardiovascular disease. Curr Atheroscler Rep 2004;6:381–7. [PubMed: 15296705]
18. Krauss RM. Heterogeneity of plasma low-density lipoproteins and atherosclerosis risk. Curr Opin Lipidol 1994;5:339–49. [PubMed: 7858908]
19. 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;106:1930–7. [PubMed: 12370215]
20. Kuller L, Arnold A, Tracy R, Otvos J, Burke G, Psaty B, Siscovick D, Freedman DS, Kronmal R. Nuclear magnetic resonance spectroscopy of lipoproteins and risk of coronary heart disease in the cardiovascular health study. Arterioscler Thromb Vasc Biol 2002;22:1175–80. [PubMed: 12117734]
21. Otvos JD, Collins D, Freedman DS, Shalaurova I, Schaefer EJ, McNamara JR, Bloomfield HE, Robins SJ. 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;113:1556–63. [PubMed: 16534013]
22. Schmitz M, Michl GM, Walli R, Bogner J, Bedynek A, Seidel D, Goebel FD, Demant T. Alterations of apolipoprotein B metabolism in HIV-infected patients with antiretroviral combination therapy. J Acquir Immune Defic Syndr 2001;26:225–35. [PubMed: 11242195]
23. van der Valk M, Kastelein JJ, Murphy RL, van Leth F, Katlama C, Horban A, Glesby M, Behrens G, Clotet B, Stellato RK, Molhuizen HO, Reiss P. Nevirapine-containing antiretroviral therapy in HIV-1 infected patients results in an anti-atherogenic lipid profile. AIDS 2001;15:2407–14. [PubMed: 11740191]
24. Badiou S, De Boever CM, Dupuy AM, Baillat V, Cristol JP, Reynes J. Small dense LDL and atherogenic lipid profile in HIV-positive adults: influence of lopinavir/ritonavir-containing regimen. AIDS 2003;17:772–4. [PubMed: 12646808]
25. Sankatsing, R.; Franssen, R.; Hassink, E.; Sauerwein, H.; Brinkman, K.; Oesterholt, R.; Arenas-Pinto, N.; Williams, I.; Storffer, S.; Kastelein, J.; Reiss, P.; Stroes, E. Nevirapine increases high density lipoprotein-cholesterol by stimulation of apolipoprotein A-I synthesis. 4th International AIDS Society Conference on HIV Pathogenesis, Treatment, and Prevention; Sydney, Australia. July 22-25, 2007; p. WEPEB120LBAbstract

Table 1

Baseline Subject Characteristics

	All	PI-Sparing	NNRTI-Sparing	NRTI-Sparing	P_{KW}
N	82	23	31	28	
Age, years	35 (30 – 40)	35 (31 – 40)	36 (30 – 41)	35 (29 – 42)	0.664
Male, %	91	91	94	89	0.887*
Systolic blood pressure, mmHg	119 (112 – 130)	115 (108 – 121)	120 (112 – 137)	120 (113 – 137)	0.119
Diastolic blood pressure, mmHg	74 (66 – 82)	71 (66 – 78)	74 (67 – 84)	78 (66 – 85)	0.459
Body-mass index, kg/m2	25.1 (22.8 – 27.7)	23.9 (22.0 – 26.7)	26.0 (23.8 – 28.5)	25.0 (22.7 – 27.7)	0.157
Waist circumference, cm	87 (80 – 94)	86 (77 – 93)	89 (80 – 95)	87 (80 – 95)	0.521
Current Smoker, %	44	43	39	50	0.694*
Glucose, mg/dL	86 (80 – 94)	88 (79 – 94)	84 (80 – 94)	86 (80 – 92)	0.981
Insulin, μU/mL	6 (4 – 10)	7 (5 – 10)	6 (3 – 11)	7 (5 – 13)	0.541
CD4, cells/μL	245 (119 – 356)	237 (97 – 413)	239 (150 – 333)	251 (127 – 369)	0.958
HIV RNA, log10copies/mL	4.82 (4.49 – 5.32)	4.72 (4.43 – 5.33)	4.89 (4.57 – 5.33)	4.83 (4.44 – 5.32)	0.684

All values are median (interquartile ranges), unless otherwise noted

* Fisher's Exact test

KW = Kruskal-Wallis test: comparison between arms, unless otherwise noted
NNRTI = non-nucleoside reverse transcriptase inhibitor
NRTI = nucleoside reverse transcriptase inhibitor
PI = protease inhibitor

Table 2

Baseline Lipid and Lipoprotein Values

	All	NRTIs + Efavirenz (PI-Sparing)	NRTIs + Lopinavir/ritonavir (NNRTI-Sparing)	Efavirenz + Lopinavir/ritonavir (NRTI-Sparing)	P_{KW}
Lipids					
Total cholesterol, mg/dL	144 (128 – 163)	145 (130 – 155)	144 (121 – 169)	144 (132 – 163)	0.979
Triglycerides, mg/dL	113 (90 – 178)	138 (89 – 240)	108 (88 – 145)	114 (90 – 187)	0.562
Direct LDL cholesterol, mg/dL	89 (75 – 103)	93 (75 – 100)	88 (75 – 111)	86 (73 – 106)	0.936
HDL cholesterol, mg/dL	31 (26 – 40)	29 (25 – 39)	32 (28 – 41)	36 (27 – 42)	0.565
Total/HDL cholesterol ratio	4.42 (3.79 –5.60)	4.84 (3.60 – 5.76)	4.35 (3.79 – 5.60)	4.34 (3.89 – 5.26)	0.645
Lipoproteins					
VLDL particles, nmol/L	58.3 (42.4 – 75.5)	65.5 (45.2 – 82.0)	57.2 (41.3 – 85.9)	57.8 (43.6 – 72.0)	0.622
Large VLDL particles, nmol/L	1.0 (0.4 – 3.4)	1.7 (0.6 – 6.5)	0.8 (0.2 – 2.2)	1.1 (0.3 – 3.2)	0.064
VLDL size, nm	46.3 (42.5 – 56.0)	48.6 (45.4 – 60.1)	44.1 (41.3 – 48.4)	46.9 (42.9 – 62.3)	0.009
IDL particles, nmol/L	29 (11 – 66)	21 (5 – 48)	41 (12 – 90)	27 (15 – 52)	0.105
LDL particles, nmol/L	1124 (874 – 1298)	1089 (941 – 1257)	1128 (869 – 1486)	1158 (861 – 1252)	0.700
Small LDL particles, nmol/L	831 (585 – 1061)	855 (584 – 1068)	855 (587 – 1102)	759 (575 – 960)	0.816
LDL size, nm	20.4 (19.8 – 21.0)	20.3 (19.8 – 20.8)	20.4 (20.0 – 20.7)	20.4 (19.8 – 21.1)	0.897
Lipoprotein (a), mg/dL	18 (12 – 74)	24 (13 – 79)	22 (13 – 50)	16 (12 – 38)	0.603
HDL particles, µmol/L	22.7 (20.0 – 26.1)	23.3 (21.2 – 27.6)	21.8 (18.6 – 26.1)	22.7 (19.1 – 26.9)	0.600
Large HDL particles, µmol/L	3.2 (2.1 – 4.9)	2.5 (1.9 – 4.9)	3.2 (2.2 – 4.8)	3.7 (2.1 – 5.6)	0.580
HDL size, nm	8.6 (8.4 – 9.0)	8.6 (8.4 – 8.8)	8.5 (8.4 –9.0)	8.7 (8.4 – 9.0)	0.713

All values are medians (interquartile ranges)

HDL = high-density lipoprotein
IDL = intermediate-density lipoproteins
LDL = low-density lipoprotein
KW = Kruskal-Wallis test: comparison between arms
NNRTIs = non-nucleoside reverse transcriptase inhibitors
NRTIs = nucleoside reverse transcriptase inhibitors
PIs = protease inhibitor
VLDL = very low-density lipoproteins

Table 3

Changes in Lipids and Lipoproteins after 24 weeks of Antiretroviral Therapy

	All	NRTIs + Efavirenz (PI-Sparing)	NRTIs + Lopinavir/ritonavir (NNRTI-Sparing)	Efavirenz + Lopinavir/ritonavir (NRTI-Sparing)	P_{KW}
Lipids					
Total cholesterol, mg/dL	27* (8 – 67)	18* (3 – 29)	21* (6 – 57)	65* (32 – 108)	<0.001
Triglycerides, mg/dL	44* (-4 – 126)	22 (-49 – 79)	72* (-1 – 186)	83* (11 – 164)	0.051
Direct LDL cholesterol, mg/dL	10* (-3 – 31)	6 (-5 – 24)	7 (-8 – 19)	26* (11 – 54)	<0.001
HDL cholesterol, mg/dL	9* (2 – 14)	9* (5 – 15)	3# (-1 – 13)	11* (7 – 17)	0.053
Total/HDL cholesterol ratio	-0.28 (-0.75 – 0.88)	-0.58* (-1.64 – -0.02)	0.02 (-0.99 – 1.29)	0.01 (-0.51 – 1.43)	0.017
Lipoproteins					
VLDL particles, nmol/L	29.6* (1.2 - 60.4)	13 (-16.6 - 33.4)	26.3* (2.8 - 60.3)	48.3* (14.2 - 84.4)	0.022
Large VLDL particles, nmol/L	1.1* (-0.2 - 6.7)	0.3 (-0.7 - 2.2)	3.2* (0.0 - 10.3)	1.2* (-0.1 - 11.3)	0.063
VLDL size, nm	3.2# (-5.2 - 11.1)	-0.2 (-5.2 - 7.4)	5.4# (-1.8 - 12.3)	2.6 (-10.4 - 12.4)	0.372
IDL particles, nmol/L	2 (-28 - 40)	-3 (-28 - 11)	-8 (-39 - 36)	18# (-5 - 76)	0.036
LDL particles, nmol/L	152* (-49 - 407)	64 (-65 - 167)	135# (-115 – 312)	414* (120 - 740)	0.003
Small LDL particles, nmol/L	130* (-98 - 417)	101 (-162 - 207)	127 (-162 – 357)	371* (-9 - 720)	0.039
LDL size, nm	-0.1 (-0.5 - 0.4)	0 (-0.3 - 0.6)	-0.1 (-0.6 - 0.4)	-0.3 (-0.5 - 0.1)	0.134
Lipoprotein (a), mg/dL	5* (0-33)	3# (0-20)	4* (0 – 28)	7* (2 – 41)	0.309
HDL particles, µmol/L	6.0* (2.8 - 10.4)	5.3* (2.4 - 9.3)	5.1* (1.6 - 9.7)	8.3* (5.9 - 10.8)	0.069
Large HDL particles, µmol/L	0.5* (-0.9 - 2.8)	1.1 (-0.5 - 2.5)	0.1 (-1.1 - 2.6)	1.3# (-0.8 - 3.0)	0.663
HDL size, nm	0.1 (-0.2 - 0.3)	0.1 (-0.1 - 0.3)	0 (-0.2 - 0.4)	0.1 (-0.2 - 0.4)	0.799

All values are medians (interquartile ranges)

* p<0.01 compared to baseline, Wilcoxon signed rank probability test

0.01≤p<0.05 compared to baseline, Wilcoxon signed rank probability test

Abbreviations as in Table 2.