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Impact of NRTIs on lipid levels among a large HIV-infected cohort initiating antiretroviral therapy in clinical care

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Abstract

Objective—To assess the associations between nucleoside reverse transcriptase inhibitors (NRTIs) and change in lipid levels among a large cohort of HIV-infected patients in routine clinical care initiating their first potent antiretroviral regimen.

Design—Longitudinal observational cohort study from the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort.

Methods—We used generalized estimating equations to examine the association between NRTIs and lipids accounting for within-patient correlations between repeated measures and key clinical and demographic characteristics including other antiretroviral medications.

Results—Among 2267 individuals who started their first antiretroviral regimen, tenofovir with emtricitabine or lamivudine was associated with lower levels for total cholesterol, low-density lipoprotein (LDL), triglycerides, non-high-density lipoprotein (HDL), and HDL, compared with other NRTI pairs in adjusted analyses. LDL levels were highest among patients receiving didanosine/lamivudine. Triglyceride levels were highest in stavudine/lamivudine users. HDL levels were highest among patients receiving didanosine/stavudine. Hepatitis C infection and younger age were also associated with lower lipid levels.

Conclusion—We found clinically important heterogeneity within the NRTI class of antiretroviral medications regarding their effect on lipid levels over time. Although the lipid profile of tenofovir with emtricitabine or lamivudine appeared to be less proatherogenic in this large longitudinal study of HIV-infected patients in routine clinical care, there was no association with beneficial HDL levels. In general, the change in lipid levels associated with most antiretroviral

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agents, particularly those NRTI combinations currently in common use, are relatively modest. Additional studies are needed to understand the long-term implications of these findings on cardiovascular disease risk.

Keywords

antiretroviral therapy; cholesterol; dyslipidemia; HIV; lipid levels; nucleoside reverse transcriptase inhibitors

Introduction

Dyslipidemia is an important risk factor for development of cardiovascular disease, the leading cause of death and morbidity in the general population in the US [1] and an important cause of death among HIV-infected individuals [2]. Abnormal lipid levels were evident among HIV-infected patients prior to the introduction of antiretroviral therapy (ART) [3,4]. After ART initiation, increases in total cholesterol (TC), low-density lipoprotein cholesterol (LDL), and triglyceride levels were noted among HIV-infected patients [5–8], possibly attributed in part to a return to preinfection levels [5].

Randomized controlled trials (RCTs) have examined the effect of a limited number of antiretroviral medications or regimens on lipids [9–20]; however, it is not feasible that any RCT will examine the effects of all antiretroviral medications in the context of combination therapy. Observational cohort studies can complement information from RCTs, yet many prior studies often included small samples [6,7,21–30], and were cross-sectional or had limited follow-up [22,23,25–28,31–34]. Furthermore, cohort studies often examined only class effects, and/or did not examine the contribution of each medication in a regimen, in particular not examining nucleoside reverse transcriptase inhibitors (NRTIs) [21–25,27,30,33–38].

We conducted this longitudinal study of a large cohort of HIV-infected patients in routine care initiating their first potent ART regimen to examine the associations between NRTI pairs and changes in lipid levels controlling for entire ART regimens.

Methods

Study setting

The observational cohort study was conducted among patients from the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort. CNICS is a longitudinal observational study of HIV-infected patients at eight clinical sites receiving primary care after 1 January 1995 to the present [39]. The CNICS cohort is a large and diverse population of HIV-infected patients [39]. Patients from four sites [University of Alabama at Birmingham (UAB), University of Washington, Johns Hopkins University (JHU), and Case Western Reserve University (CWRU)] were included in these analyses.

Study participants

All HIV-infected patients 18 years of age or older who were protease inhibitor and nonnucleoside reverse transcriptase inhibitor (NNRTI)-naïve when they enrolled in primary continuity HIV care at a participating site and initiated potent combination ART before 2 January 2008 were eligible for inclusion. Patients were required to have more than 2 months of follow-up after initiating ART, which was defined as regimens containing at least three drugs including either a protease inhibitor or NNRTI, and to have at least one set of serum lipid levels while receiving their initial potent regimen. Patients who started regimens with three or more NRTIs without a protease inhibitor or NNRTI, or whose regimen contained amprenavir, or included saquinavir or ritonavir as a single protease inhibitor were excluded due to small numbers. Patients were eligible if they had prior single or dual NRTI exposure; however, they must not have been receiving NRTIs in the 3 months prior to initiating their first potent regimen. Patients were followed until discontinuation or change in their initial potent regimen, loss to follow-up, or 4 January 2008, whichever occurred first. The study received Institutional Review Board approval.

Data sources

The CNICS data repository captures longitudinal data on the CNICS cohort and was the data source for this study. The data repository integrates comprehensive clinical data from all outpatient and inpatient encounters including standardized HIV-related information collected at enrollment (initial clinic visit) regarding a patient's prior ART history. Demographic, clinical, laboratory, and medication data are obtained from each site's electronic health record and other institutional data sources. Medication data are entered into the electronic health records by clinicians or prescription fill/refill data are uploaded directly from Pharmacy Systems and verified through medical record review.

Measurement of lipid levels

We examined serum lipid levels over time including TC, LDL, high-density lipoprotein cholesterol (HDL), triglycerides, and non-HDL values (calculated by subtracting HDL from TC values) [40]. Lipid values were measured as part of routine care, except LDL, which is either measured or calculated using the Friedewald equation [41].

Statistical analysis

We examined the association between lipid levels and antiretroviral medications categorized into mutually exclusive groups. A NRTI variable categorized patients by their pair of NRTIs. Patients receiving emtricitabine were grouped with patients taking lamivudine. Patients whose regimen contained more than two NRTIs were categorized by the pair of NRTIs other than lamivudine. A separate protease inhibitor/NNRTI variable categorized patients by their individual protease inhibitors and NNRTIs. Patients receiving boosted protease inhibitor regimens were grouped by their nonritonavir protease inhibitor. We also created a separate variable for boosting doses of ritonavir (400 mg/day). Nonpotent ART regimens (single or dual NRTIs in the prepotent ART era) were captured by a separate variable from potent ART regimens.

We also evaluated demographic characteristics (age, HIV transmission risk factor, race, sex, and site) and clinical characteristics [CD4⁺ cell count nadir, baseline HIV-1 RNA level, hepatitis C virus (HCV) infection indicated by either presence of HCV antibody or HCV RNA; hepatitis B virus (HBV) infection indicated by presence of HBV_e or surface antigen or HBV DNA, diabetes mellitus, smoking status, history of opportunistic infection at ART initiation, and body mass index (BMI)]. We examined secular trends in care using calendar period of ART initiation by year and as a binary variable (1999 and before vs. 2000 and after). For the small subset of individuals for whom baseline height was missing, we used an imputed height based on age, race, and sex. We calculated BMI using the traditional Quetelet index: weight divided by height squared (kg/m²) [42].

We used generalized estimating equations with an exchangeable correlation structure and robust standard errors to assess differences in lipid levels associated with antiretroviral medications accounting for within-patient correlations between repeated measures and confounding covariates [43]. Separate models were conducted for each outcome: TC, LDL, HDL, triglyceride, and non-HDL values. Final models were adjusted for age, race, sex, NRTI pairs, protease inhibitors/NNRTIs, boosted ritonavir, prior nonpotent ART (NRTI) exposure, HCV status, HBV status, CD4⁺ cell count nadir, smoking status, diabetes mellitus, history of opportunistic infection, time on ART, calendar period, and site. We conducted sensitivity analyses using natural log-transformed triglyceride values to address a skewed distribution.

We expected that patients would have lipid level changes associated with improvement in health status following ART initiation and these changes would be consistent across regimens. Nevertheless, we conducted sensitivity analyses that also incorporated change in CD4⁺ cell count and BMI in the initial 6 months of ART to evaluate if differences in lipid values associated with antiretroviral medications could be due to differential improvement in health status following ART initiation.

Additional sensitivity analyses adjusted for lipid-lowering medication data were available from three sites (University of Washington, UAB, and CWRU). We categorized lipid-lowering medications into two categories: 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors ('statins') and other lipid-lowering medication (niacin, fibrates, fish oil, ezetimibe).

Results

There were 2267 patients who met study criteria and had lipid values measured while on their initial ART regimen with 10 641 TC values, 1341 patients with 4538 HDL values, 1332 patients with 4352 LDL values, 1872 patients with 8754 triglyceride values, and 1340 patients with 4530 non-HDL values. Mean age at ART initiation was 38 years (SD 9), 75% were men, mean CD4⁺ cell count was 173 cells/μl, and 54% had a peak viral load greater than 100 000 copies/ml (Table 1).

Antiretroviral therapy regimens were evenly divided between patients receiving protease inhibitor (*N* = 1082, 48%) and NNRTI-based regimens (*N* = 1185, 52%) (Tables 2 and 3).

Patients were on their initial regimen for a mean of 1.7 years (SD 1.7). There were 1706 patients (75%) on their ART regimen for more than 6 months, and 1223 (54%) for more than 12 months. Statin and other lipid-lowering medication use increased with ART duration; approximately half as many patients were receiving statins ($N=49$) or other lipid-lowering medication ($N=21$) after 1 year of ART vs. the number of patients on statins ($N=98$) or other lipid-lowering medication ($N=45$) after 3 years of ART (or end of the initial regimen, whichever came first).

Adjusted analyses

Women had higher mean TC, LDL, and HDL values, and lower triglyceride values compared with men in adjusted analyses (Table 4). African-American individuals had higher mean TC, LDL, triglyceride, and non-HDL values, and lower HDL values compared with white individuals. Older age was associated with higher TC, LDL, HDL, triglyceride, and non-HDL values. HCV was associated with lower TC, LDL, triglyceride, and non-HDL values (Table 4). $CD4^+$ nadir was associated with higher TC levels. There were no significant associations between patients with HBV, prior nonpotent ART (NRTIs), or opportunistic infections and lipid levels.

Mean lipid levels were higher at all follow-up time periods compared with baseline. In general, lipid levels increased most rapidly during the first 2 months and then either reached a plateau or continued to increase much more slowly (Table 5).

Patients receiving tenofovir/lamivudine (or tenofovir/emtricitabine) had lower lipid levels than other NRTI pairs. Specifically, TC levels were significantly higher among patients who received any other NRTI pair compared with tenofovir/lamivudine (+10–22 mg/dl, P values <0.001 – 0.002) (Table 6). Mean triglyceride values were higher among patients receiving any other NRTI pair compared with tenofovir/lamivudine in adjusted analyses; however, most of these increases did not reach statistical significance. Compared with patients on tenofovir/lamivudine, receiving stavudine/lamivudine, didanosine/lamivudine or zidovudine/lamivudine was associated with higher non-HDL levels. A similar effect cannot be ruled out for other NRTI pairs although they did not reach statistical significance. In comparison to tenofovir/lamivudine, patients receiving any other NRTI pair had higher HDL levels in adjusted analyses (+3–11 mg/dl, P values <0.001 – 0.02) (Table 6).

Regimens containing didanosine/lamivudine had the greatest impact on LDL levels (+12mg/dl, $P=0.03$). Didanosine/stavudine was associated with similarly higher LDL levels as didanosine/lamivudine (+14mg/dl), although this did not reach statistical significance in the main model, it was significant in sensitivity analyses (see below).

Triglyceride analyses were repeated using natural log-transformed values in order to address the skewed distribution. In addition to the findings in the main model (Table 6), elevated triglyceride values were also associated with zidovudine/lamivudine ($P=0.01$) compared with tenofovir/lamivudine.

We conducted sensitivity analyses that included change in $CD4^+$ cell count as a measure of health status improvement. There were 1533 patients (68%) with change in $CD4^+$ cell count

available at 6 months (± 3 months) on ART. Change in CD4 cell count was associated with higher TC, LDL, and non-HDL levels (0.2 mg/dl per 10 cells/ μ l, P values = 0.008–0.05) but not HDL or triglyceride levels. Associations between antiretroviral medications and change in lipid levels were essentially unchanged in models that also adjusted for change in CD4⁺ cell count over 6 months compared with the main models.

In addition, we conducted sensitivity analyses that included change in BMI among 823 patients with change in BMI available at 6 months (± 3 months). Change in BMI was associated with higher TC (1.9 mg/dl per kg/m², P = 0.02), LDL (1.5mg/dl per kg/m², P = 0.006), triglycerides (5.7 mg/dl per kg/m², P = 0.03), and non-HDL values (2.1mg/dl per kg/m², P = 0.009) but not HDL levels. Associations between antiretroviral medications and change in lipid levels were virtually unchanged in models that also adjusted for change in BMI over 6 months compared with the main models except didanosine/stavudine use was also associated with increased LDL (+14mg/dl, 95% CI 1–28, P = 0.04), triglyceride (+128 mg/dl, 95% CI 13–244, P = 0.03), and non-HDL values (+29 mg/dl, 95% CI 10–49, P = 0.003).

We examined the impact of statins and other lipid-lowering medications on our findings in sensitivity analyses among patients from three sites with information regarding these medications. Findings were similar to the main models after also adjusting for statins and other lipid-lowering medications.

Discussion

Findings from this large longitudinal study of HIV-infected patients in routine care demonstrated that patients whose initial regimen contained tenofovir/lamivudine (or tenofovir/emtricitabine) had the smallest increase in lipid levels for all lipid outcomes including not only pro-atherogenic lipids, but also HDL in adjusted analyses. Didanosine/lamivudine was associated with greater increases in LDL values. This study demonstrated the importance of comparing antiretroviral medications within classes and not just focusing on class effects. This study also demonstrated that HCV infection and younger age are associated with lower lipid levels among HIV-infected individuals following the initiation of ART.

Nucleoside reverse transcriptase inhibitors

We found smaller increases in lipids among patients who received tenofovir/lamivudine vs. other NRTI pairs in adjusted analyses. Prior studies on the association of NRTIs and lipids have had conflicting results. Whereas several studies have suggested there are differences associated with particular NRTIs [11,44–52], a few have not [9,28,53]. Switch studies have demonstrated decreases in lipid levels among those who changed other NRTIs to tenofovir [46–51,54,55]; however, these differences have sometimes waned over time [56], and did not necessarily include HDL [46,51,56,57]. In addition, switch studies are often small, and examine only one particular comparison. A meta-analysis of 48-week data from clinical trial patients found smaller increases in TC, LDL, and triglyceride levels among patients on tenofovir/emtricitabine than other NRTIs (stavudine, zidovudine, and abacavir with lamivudine); however, the other NRTIs were combined in one group and not compared

separately [12]. A large cross-sectional study suggested tenofovir was associated with lower triglyceride levels compared with those not receiving tenofovir [32]. Our findings differed from the Swiss cohort study results that found that increasing exposure to abacavir may be associated with a decline in triglyceride levels [58]. However, that study combined tenofovir with abacavir for analysis making interpretation of the impact of either drug difficult.

We found smaller increases in HDL levels among those who initiated tenofovir/lamivudine than those who started other NRTI pairs. This stands in contrast to a prior clinical trial that did not detect differences in HDL levels at 144 weeks among those on tenofovir/lamivudine vs. zidovudine/lamivudine [44]. This difference in findings may be due to the small absolute difference in HDL levels. Our findings also differ from those of another RCT conducted among treatment-naïve patients starting efavirenz, lamivudine, and either tenofovir or stavudine which found smaller increases in TC, LDL, and triglyceride values among patients on tenofovir, but larger increases in HDL [59]. A prior large cross-sectional study among HIV-infected women found that use of didanosine or lamivudine was associated with higher HDL levels; however, that study was not limited to individuals on their initial ART regimen [32]. A simplification trial of patients changed to abacavir/lamivudine vs. tenofovir/emtricitabine suggested that patients who received tenofovir/emtricitabine had lower lipid levels including HDL; however, they also were more ART-experienced and slightly more likely to be receiving lipid-lowering medication thereby complicating interpretation [60]. An RCT of patients on zidovudine or stavudine switched to abacavir or tenofovir found significantly greater decreases in mean TC, LDL, and triglycerides for patients switched to tenofovir than among those switched to abacavir, but differences in HDL levels were not significantly different [47]. Few large longitudinal studies have evaluated differences in HDL levels associated with particular NRTIs or NRTI pairs among naïve patients in routine care, which is addressed by the current study thereby providing complementary data to clinical trial results.

Didanosine/lamivudine use was associated with the greatest increase in LDL levels and didanosine/stavudine was associated with greater increases in lipid levels in sensitivity analyses that also accounted for BMI. Accounting for BMI may be particularly important in evaluating the association between lipids and NRTIs such as didanosine/stavudine, which have been shown to have a very different impact on body fat changes than other NRTIs such as abacavir/lamivudine [61]. Whether the increased LDL associated with didanosine/lamivudine contributes to the suggested association between recent didanosine and risk of myocardial infarction [62] has yet to be established.

Timing

We found the greatest lipid level increases in the first 2 months after starting ART and that individual lipid levels continued to increase for different time periods. Our findings expand on prior studies that found the largest increases in lipid levels during the first 6 months of ART but did not examine the time early after ART initiation [7] or look beyond 12 months [30,63,64]. Our findings differs from a Ugandan study of patients on NNRTI-based regimens which found TC and HDL levels increased during the first year and then plateaued, LDL increased over 2 years, and triglyceride levels dropped and then returned to baseline at 24

months [53]. We did not note an initial decline in triglyceride levels. These differences in triglyceride level results may be due to differences in health status among patients initiating ART in Uganda vs. the US.

Hepatitis C virus

Several prior studies have suggested an association between HCV and low TC [22,65–73] and LDL levels [22,67,69] among HIV-infected individuals. Conflicting results have been reported regarding a possible association between HCV and lower triglyceride levels among HIV-infected patients with some studies suggesting an association [65,69,74,75] and others not [22,66,67, 73,76]. We found that HCV is associated with lower TC, LDL, non-HDL and triglyceride levels in adjusted analyses. Notably, despite having more favorable proatherogenic lipid profiles, HCV co-infected patients recently were shown to have higher rates of cardiovascular events among a study of US veterans [77].

Health status

Improved immune status and restoration to good health may play a role in the changes in lipid levels seen with ART [8,22]. Part of the increase in lipid levels, particularly LDL, is likely a return to prebaseline levels with ART initiation and improvement in immune status [5,22,78]. It seems unlikely, however, that this would result in a differential impact on lipid levels by antiretroviral medications. We conducted sensitivity analyses that included changes in CD4⁺ cell count or BMI over 6 months to see if differential improvement in health status or weight could be affecting results. Increases in CD4⁺ cell count were associated with small increases in TC, LDL, and non-HDL values, whereas increases in BMI were associated with large increases in TC, LDL, triglyceride, and non-HDL values. Although more limited due to smaller sample size, these sensitivity analyses demonstrated that changes in CD4⁺ or BMI did not explain all of the differences in the impact of individual antiretroviral medications on lipid levels.

Lipid-lowering medication

We found that use of lipid-lowering medications increased over time, as has been seen previously [79]. This could confound the associations between lipid levels and antiretroviral medications; however, sensitivity analyses that included adjustment for statins and other lipid-lowering medication revealed similar findings as in the main model. The overall consistency of the various analyses provides additional reassurance of the robustness of the findings.

Limitations

Lipid values were measured in routine care so we could not confirm fasting status and there are different numbers of values for each lipid class. Patients were not randomized to their antiretroviral medications. As with any observational study, there may be confounding factors for which adjustment is not possible. Too few naive patients initiated ART with medications used less commonly in first regimens such as amprenavir, maraviroc, tipranavir, or darunavir to include patients on these regimens in the analyses; however, data continue to accrue. Due to small numbers, lipid-lowering medications were categorized into two classes,

rather than examined individually. Finally, the study lacks information regarding genetic factors, diet, and exercise; however, we would not expect these factors to vary by particular regimen.

Strengths

Strengths of this study include comprehensive clinical data and large patient numbers. Comprehensive data allowed us to censor lipid values after changes had been made to antiretroviral regimens. It has been suggested that excluding those on lipid-lowering medication would result in a biased estimate of lipid levels because these medications are most likely to be used in those with the highest serum lipid levels [8]. However, the comprehensive data allowed us to examine the impact of lipid-lowering medications rather than simply excluding those patients. Studies have provided information on individual protease inhibitor and NNRTI agents; however, many fewer studies have examined the impact of NRTI backbones. The large sample size facilitated inclusion of over 500 women allowing us to expand on prior studies, which focused only on men [5,7,8].

Additional strengths of this study are the longitudinal study design and inclusion of only patients naive to potent ART. This is not the first study to examine the association between medications and lipid levels; however, many of the prior studies were cross-sectional in nature [31,32], and did not limit patients to their initial regimen increasing concerns about confounding in comparisons between patients by antiretroviral medications. Although inclusion of only potent ART-naive patients may limit generalizability to all HIV-infected patients, it eliminates the potential confounding due to duration or number of prior regimens [31]. An additional strength is the inclusion of non-HDL which was not examined in many early studies and has been shown to be an important consideration in cardiovascular risk assessment, particularly in the setting of elevated triglycerides, a common problem in HIV-infected individuals.

Conclusion

The longitudinal study examined the association between different antiretroviral medications and lipids among a large cohort of ART-naive HIV-infected patients in routine care. Patients who initiated regimens containing tenofovir/lamivudine (or tenofovir/emtricitabine) had the smallest increases in lipid levels, including HDL. The long-term implications of these findings on cardiovascular disease risk are not yet known. Findings from this study demonstrate that comparisons of dyslipidemia and cardiovascular disease risk factors associated with antiretroviral medications should focus on individual agents rather than on class effects. This study provides additional evidence that the metabolic impact of most antiretroviral agents, particularly those used more commonly in initial regimens in the current ART era, are relatively modest.

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Table 1

Demographic and clinical characteristics of HIV-infected patients who initiated their first potent antiretroviral therapy regimen ($N = 2267$).

Characteristic	
Sex	
Men	1707 (75)
Women	560 (25)
Age (years)	
<30	329 (15)
30–39	904 (40)
40–49	764 (34)
50	270 (12)
Race	
White	876 (39)
African-American	1243 (55)
Other	148 (7)
CD4 cell count nadir cells/ μ l	
0–200	1428 (63)
201–350	552 (24)
>350	287 (13)
Initial HIV-1 RNA level copies/ml	
>100000	1224 (54)
50000–100000	316 (14)
<50000	727 (32)
Hepatitis C virus infection	
No	1794 (79)
Yes	473 (21)

Table 2

Patients receiving protease inhibitor and nonnucleoside reverse transcriptase inhibitor-based regimens in their initial antiretroviral therapy regimen ($N = 2267$).

Class	Medication	Number (%)
Protease inhibitors ($N = 1082$)	Atazanavir	202 (19)
	Indinavir	213 (20)
	Lopinavir/ritonavir	229 (21)
	Nelfinavir	386 (36)
	Saquinavir/ritonavir	52 (5)
NNRTI ($N = 1185$) ^a	Efavirenz	1052 (89)
	Nevirapine	133 (11)

Each patient is included once in the table. Boosting ritonavir not shown. However, 18% of the cohort, and 37% of those on PI-based regimens were also on boosting ritonavir. NNRTI, nonnucleoside reverse transcriptase inhibitor.

Table 3

Patients receiving NRTI pairs in their initial antiretroviral therapy regimen ($N = 2267$).

Class	Medication	Number (%)
NRTI pairs ($N = 2267$)	Abacavir/lamivudine	55 (2)
	Abacavir/zidovudine	110 (5)
	Didanosine/lamivudine	35 (2)
	Didanosine/stavudine	113 (5)
	Stavudine/lamivudine	372 (16)
	Tenofovir/lamivudine	579 (26)
	Zidovudine/lamivudine	897 (40)
	Other ^a	106 (5)

Each patient is included once in the table. Emtricitabine and lamivudine are combined. NRTIs, nucleoside (tide) reverse transcriptase inhibitors.

^a Other includes all NRTI pairs received by less than 35 individuals.

Table 4
Difference in mean lipid levels by demographic and clinical characteristics in adjusted analyses.

	Difference in mean HDL levels 95% CI, <i>P</i> value (N = 1341)	Difference in mean total cholesterol levels 95% CI, <i>P</i> value (N = 2267)	Difference in mean LDL levels 95% CI, <i>P</i> value (N = 1332)	Difference in mean triglyceride levels 95% CI, <i>P</i> value (N = 1872)	Difference in mean non-HDL levels 95% CI, <i>P</i> value (N = 1340)
Sex					
Men (reference)	0	0	0	0	0
Women	Ref	Ref	Ref	Ref	Ref
	10	9	8	-34	10
	8-12, <0.001	5-13, 0.001	4-12, <0.001	-46 to -23, 0.001	-5 to 5, 0.9
Race					
White	0	0	0	0	0
African-American	Ref	Ref	Ref	Ref	Ref
	-6	9	9	65	16
	-7 to -4, <0.001	5-12, <0.001	5-13, <0.001	50-80, <0.001	11-12, <0.001
Other	-4	7	7	43	11
	-6 to -1, 0.005	0-15, 0.05	0-13, 0.06	20-65, <0.001	2-20, 0.01
CD4⁺ cell count nadir					
<200	0	0	0	0	0
	Ref	Ref	Ref	Ref	Ref
200-350	1	5	4	-10	1
	0-3, 0.1	0-9, 0.03	0-7, 0.08	-26 to 5, 0.2	-4 to 6, 0.6
>350	1	6	2	-1	1
	-1 to 3, 0.3	1-12, 0.02	-4 to 8, 0.4	-20 to 20, 0.9	-5 to 8, 0.7
Age (per 10 years)	1	6	2	13	5
	0-2, 0.04	4-8, <0.001	0-4, 0.02	5-21, 0.001	3-8, <0.001
Diabetes mellitus					
No	0	0	0	0	0
	Ref	Ref	Ref	Ref	Ref
Yes	-3	9	5	90	14
	-6 to -1, 0.006	2-15, 0.01	-2 to 12, 0.1	54-126, <0.001	5-23, 0.003
Smoking					

	Difference in mean HDL levels 95% CI, P value (N = 1341)	Difference in mean total cholesterol levels 95% CI, P value (N = 2267)	Difference in mean LDL levels 95% CI, P value (N = 1332)	Difference in mean triglyceride levels 95% CI, P value (N = 1872)	Difference in mean non-HDL levels 95% CI, P value (N = 1340)
No	0	0	0	0	0
	Ref	Ref	Ref	Ref	Ref
Yes	-1	-6	-4	2	-3
	-2 to 0, 0.2	-10 to -1, 0.01	-8 to 0, 0.07	-17 to 19, 0.9	-8 to 2, 0.2
Hepatitis C co-infection					
No	0	0	0	0	0
	Ref	Ref	Ref	Ref	Ref
Yes	2	-15	-13	-27	-16
	0-2, 0.1	-19 to -10, <0.01	-18 to -7, <0.001	-43 to -11, -11, 0.001	-22 to -10, <0.001

All models use generalized estimating equations (GEEs) and are adjusted for age, sex, race, CD4⁺ cell count nadir, duration of ART, calendar time of ART initiation, hepatitis C virus status, hepatitis B virus status, history of opportunistic infection at ART initiation, diabetes mellitus, PI/NNRTIs, boosting ritonavir, all NRTI pairs, smoking status, and site. ART, antiretroviral therapy; CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

Table 5

Adjusted mean lipid levels at various time periods on initial antiretroviral therapy regimen.

	Baseline mg/dl (95% CI, <i>P</i>)	2 months mg/dl (95% CI, <i>P</i>)	6 months mg/dl (95% CI, <i>P</i>)	12 months mg/dl (95% CI, <i>P</i>)	18 months mg/dl (95% CI, <i>P</i>)	24 months mg/dl (95% CI, <i>P</i>)	36 months mg/dl (95% CI, <i>P</i>)
Total cholesterol	128	145	150	153	154	154	153
<i>N</i> = 2267	116–141, Ref	143–147, <0.001	148–152, <0.001	150–156, <0.001	151–157, <0.001	151–157, <0.001	150–157, <0.001
LDL	88	95	95	98	98	97	97
<i>N</i> = 1332	74–102, Ref	91–98, <0.001	92–98, <0.001	94–101, <0.001	95–102, <0.001	93–101, <0.001	93–101, <0.001
HDL	33	38	40	40	40	39	39
<i>N</i> = 1341	28–37, Ref	37–40, <0.001	39–41, <0.001	38–41, <0.001	39–41, <0.001	38–41, <0.001	38–41, <0.001
Triglycerides	120	132	138	145	145	146	149
<i>N</i> = 1872	79–161, Ref	124–141, 0.004	129–147, <0.001	135–155, <0.001	132–158, <0.001	133–159, <0.001	134–163, <0.001
Non-HDL	112	123	123	127	127	126	126
<i>N</i> = 1340	96–128, Ref	119–126, <0.001	120–127, <0.001	123–130, <0.001	122–132, <0.001	122–130, <0.001	121–131, <0.001

P values compare mean levels at each time period vs. at baseline. All models use generalized estimating equations (GEEs) and are adjusted for age, sex, race, CD4⁺ cell count nadir, duration of ART, calendar time of ART initiation, hepatitis C virus status, hepatitis B virus status, history of opportunistic infection at ART initiation, diabetes mellitus, PI/NNRTIs, boosting ritonavir, all NRTI pairs, smoking status, and site. ART, antiretroviral therapy; CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

Table 6

Difference in mean lipid levels by antiretroviral medications in adjusted analyses.

NRTI pair	Difference in mean HDL levels (95% CI, <i>P</i> value <i>N</i> = 1341)	Difference in mean total cholesterol levels (95% CI, <i>P</i> value <i>N</i> = 2267)	Difference in mean LDL levels (95% CI, <i>P</i> value <i>N</i> = 1332)	Difference in mean triglyceride levels (95% CI, <i>P</i> value <i>N</i> = 1872)	Difference in mean non-HDL levels (95% CI, <i>P</i> value <i>N</i> = 1340)
Tenofovir/lamivudine (reference)	0	0	0	0	0
	Ref	Ref	Ref	Ref	Ref
Abacavir/lamivudine	5	20	8	24	12
	1–9, 0.02	10–30, <0.001	–2 to 18, 0.1	–12 to 61, 0.2	–2 to 26, 0.09
Zidovudine/lamivudine	3	10	3	16	7
	1–5, <0.001	6–15, <0.001	–1 to 7, 0.1	–2 to 34, 0.08	2–13, 0.01
Stavudine/lamivudine	4	14	3	30	15
	1–7, 0.006	7–20, <0.001	–4 to 11, 0.4	5–56, 0.02	5–24, 0.003
Didanosine/lamivudine	5	22	12	8	13
	1–9, 0.02	9–35, 0.001	1–23, 0.03	–26 to 43, 0.6	4–23, 0.007
Didanosine/stavudine	11	14	14	20	9
	6–16, <0.001	5–23, 0.002	–5 to 33, 0.1	–15 to 55, 0.3	–8 to 25, 0.3

All models use generalized estimating equations (GEEs) and are adjusted for age, sex, race, CD4⁺ cell count nadir, duration of ART, calendar time of ART initiation, hepatitis C virus status, hepatitis B virus status, history of opportunistic infection at ART initiation, diabetes mellitus, PI/NNRTIs, boosting ritonavir, all NRTI pairs, smoking status, and site. Emtricitabine and lamivudine are combined Other NRTI pair categories containing small numbers of patients (*N* < 35) are not shown but were included in the model. ART, antiretroviral therapy; CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor.