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Improvement in lipid profiles over 6 years of follow-up in adults with AIDS and immune reconstitution

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Abstract

Objectives—To evaluate long-term changes in lipids and assess other coronary heart disease (CHD) risk factors in highly-experienced AIDS patients with immune reconstitution, and examine their association with antiretroviral treatment (ART).

Methods—We evaluated 433 AIDS patients with prior severe immunosuppression and ART-based immune reconstitution, followed in a multicenter prospective observational study between 2000-2006. We estimated prevalence at entry of hypercholesterolemia, metabolic syndrome, and 10-year CHD risks. Trends in total cholesterol (TC), triglycerides (TG), and HDL cholesterol were evaluated over time and use of specific ART drugs at each study visit was assessed using mixed effect models, adjusting for CHD risk factors and use of lipid-lowering agents.

Results—At entry to observational follow-up, 28% of the 433 subjects had hypercholesterolemia and 15% had predicted 10-year CHD risk above 20%. Average TC and fasting TG levels declined over follow-up (median=5.8 years), associated with increased use of physician-prescribed lipid-lowering agents and changing ART regimens. After adjustment for CHD risk factors, TC and TG levels were significantly higher for those on ritonavir-boosted protease inhibitors and on NNRTIs, particularly efavirenz.

Conclusions—Abnormalities in serum lipids were common at baseline but improved over time, associated with increased use of lipid-lowering agents and selection of ART agents with less deleterious effects on lipids.

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Keywords

HAART; cardiovascular disease; metabolic syndrome; immune reconstitution; cholesterol

INTRODUCTION

Premature atherosclerosis (1,2) and metabolic complications (3-6) have been associated with HIV infection, and evidence continues to accumulate that antiretroviral therapy (ART) is associated with multiple cardiovascular risks (7-27). Hypertriglyceridemia and effects on LDL cholesterol have been associated with use of all three major ART drug classes: protease inhibitors (PIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and nucleoside analogues (NRTIs) (7-11). Specifically, treatment with ART may be associated with elevations in serum cholesterol and triglycerides (7,9,11), increases in trunk fat and insulin resistance (4-6,12), and with the development of hypertension (13), all of which are components of the metabolic syndrome and risk factors for coronary heart disease (CHD). Chronic HIV infection is also associated with reduced cholesterol levels (14,15). Effects of ART on risk of metabolic complications vary with stage of HIV disease (16), duration of ART use, and class of drugs. Protease inhibitors in particular have been implicated for effects on dyslipidemia (8,10,11,17-21). In addition, specific agents within the same drug class differ markedly in their effects on lipid abnormalities (18,22-27).

The specific contribution of ART to clinical CHD has been evaluated in two large prospective cohort studies that found an association between duration of use of combination ART and risk of myocardial infarction (MI). Both the large international D:A:D study and a multi-hospital French study found an association between duration of exposure to PIs and the risk of MI (28,29). Other case reports (30,31) and retrospective evaluations (32,33) also support an association of protease inhibitors with cardiovascular outcomes.

This manuscript describes the association of antiretroviral therapy with effects on total cholesterol, HDL, and triglycerides over almost 6 years of follow-up. Although numerous investigations have also addressed such associations, we feel that ours is unique in two respects: first, the cohort we consider consists of AIDS patients with advanced disease (median nadir CD4 count of 20 cells/mm³) who all experienced prolonged immune reconstitution on combination antiretroviral therapy. Second, we consider lipid measures collected over a median follow-up period of almost 6 years. In contrast, many other investigations of such associations between antiretroviral therapy and lipid measures have considered only antiretroviral naïve patients, typically with much less advanced disease, and have not had the extended duration of follow-up.

Patients with a history of severe immunosuppression and long-term ART were hypothesized to have high rates of dyslipidemia which would worsen with duration on ART. We addressed this hypothesis by examining changes in lipid profiles over almost 6 years of follow-up, and evaluating their association with specific ART drug classes and agents. Our evaluation adjusted for changes in regimens and other risk factors for dyslipidemia and CHD, including use of lipid-lowering agents. In addition, we evaluated the predicted incidence of CHD in a prospective evaluation of this highly ART-experienced cohort of AIDS patients with immune reconstitution.

PATIENTS AND METHODS

We examined CHD risk factors and trends in lipid measurements in subjects enrolled in a prospective observational study drawn from those initially participating in AIDS Clinical

Trials Group (ACTG) 362, a prospective trial of discontinuing *Mycobacterium avium* complex (MAC) prophylaxis (34). Between October 1997 and April 1999, we enrolled HIV-infected subjects without prior MAC and with documented immune reconstitution (CD4+ T cell counts <50 followed by CD4 >100 cells/mm³ on two separate occasions before study entry). The protocol and its successive amendments were approved by the institutional review boards at each participating ACTG site, and all participants provided written informed consent. Subjects were randomized to receive either azithromycin or blinded placebo; results of the randomized component of ACTG 362 have been previously reported (34). After randomized study treatment was discontinued in October 1999, participants were invited to continue observational follow-up to evaluate cardiovascular, metabolic, and neurological outcomes of HAART therapy. Of the 643 original subjects, 433 (77% of those still on study) continued in the observational study.

Data Collection and Event Definitions

Subjects were initially examined at 8-16 week intervals and evaluated for new opportunistic infections or cardiovascular events, CD4 counts, plasma HIV-1 RNA measurements, clinical chemistry and hematology tests, signs and symptoms, alcohol and illicit drug use, medication adherence, and any changes in ART or other medications. HIV-1 RNA measurements were obtained using the Roche Amplicor standard assay (Roche Diagnostics, Branchburg, NJ), with a lower limit of quantification of 500 copies/mL. At initiation of observational follow-up, subjects reported history of hypertension and/or diabetes, family history of CHD, and smoking status. In addition, anthropometric measures (including height, weight, waist, and hip), new diagnoses and/or treatment of diabetes and hypertension, and lipid measures (including total cholesterol, TC; high density lipoprotein cholesterol, HDL; and triglycerides, TG) were collected at rollover to observational follow-up and every 32 weeks thereafter. Although the protocol specified that lipid measures should be collected in a fasting state, some participants arrived for study visits without fasting. Fasting status was documented and all available measurements were included in the analysis (only fasting measures were included in figures for TG). Collection of blood pressure (BP) and fasting glucose levels began in April 2002.

Atherosclerotic cardiovascular events (MI; angina; or coronary artery disease diagnosed by cardiac catheterization) reported after entry were reviewed and verified by the study chair (JSC). Metabolic syndrome was defined using published criteria (35) of at least 3 of the following: fasting TG >150 mg/dL, waist circumference >102 cm (male) or 88 cm (female), BP ≥130/85, fasting glucose ≥110 mg/dL, and HDL <40 mg/dL (male) or <50 mg/dL (female). Hypercholesterolemia was defined as TC ≥240 mg/dL.

Data was collected on the use of ART before and at randomization, and throughout the follow-up period. HAART was defined as: (1) use of ≥ 3 ART medications from ≥2 drug classes (NRTIs, NNRTIs, or PIs), (2) use of ≥3 NRTIs, or (3) ≥1 NNRTI combined with ≥1 PI, and duration on HAART reflected lifetime exposure in years including pre-entry use. Individual indicators for use of specific ART agents and overall ART drug classes were created at original study entry, at initiation of the observational phase, and at the time of each lipid measurement. PIs were classified as boosted (one or more PIs in addition to ritonavir) or non-boosted. Indicators of use of antihypertensive agents and lipid-lowering agents such as statins as prescribed by each patient's primary care physician were also evaluated for each study visit. Data collected from October 1997 through June 2006 are included in this analysis.

Statistical Methods

Trends in lipid measures (TC, non-HDL=TC-HDL, and TG) over time were summarized graphically by presenting the mean and 95% confidence interval at each scheduled visit week. A mixed effect repeated measures model was used to evaluate trends in lipid measures, allowing adjustment for the correlation among repeated measures on the same subject over time (36) under an equicorrelation assumption (any pair of lipid measurements of the same type was assumed to have the same within-subject correlation). The effect of each ART drug class (PIs, NNRTIs) and specific agents within drug classes were evaluated as time-dependent covariates, reflecting the difference at any visit for a subject receiving the particular antiretroviral drug at that time as compared to one not receiving it, holding all other factors constant. This modeling approach allows changes in exposure to occur at every time point. Because clinician-directed changes in regimens were often made at the same date at which lipid measurements were collected, we considered current use to reflect use since the prior visit.

Potential confounders evaluated included all demographic, health status, and CHD risk factors summarized in Tables 1 and 2. Interactions of each treatment indicator with follow-up time were also considered. Backwards selection and goodness-of-fit criteria (Akaike's Information Criterion) were used to reduce models to a parsimonious form. Final multivariate models were adjusted for any such factors which were at least marginally significant ($p < 0.10$). All initial models included an indicator of whether the lipid sample was taken fasting. Sensitivity analyses were conducted restricted to fasting measurements, which accounted for over 80% of all lipid measurements, and on log-transformed TG levels due to the right-skewed distribution of this lipid measure.

The cardiovascular health of the cohort was characterized using 10-year CHD risks, along with estimated prevalence of hypercholesterolemia and metabolic syndrome at entry to the observational phase. Estimates of 10-year CHD risk were based on the published Framingham scoring system (35). This approach uses age, sex, TC, HDL, smoking status, systolic BP, and treatment for hypertension to define risk scores and corresponding 10-year CHD risk estimates. Based on guideline recommendations (35), we also considered a history of diabetes as a CHD risk equivalent.

For all 643 subjects originally enrolled in the MAC prophylaxis trial, we also estimated the overall incidence rate (IRs) for confirmed atherosclerotic CHD along with exact 95% confidence intervals under a Poisson distribution, and evaluated potential risk factors for development of CHD using a Cox proportional hazards model, including all follow-up time since randomization to the parent trial. All statistical analyses were conducted using Statistical Analysis System (SAS) version 9. A significance level of 0.05 was used, and all reported tests are 2-sided.

RESULTS

Characteristics of the Study Population

A total of 643 subjects with demonstrated immune reconstitution enrolled in the original randomized study to evaluate discontinuation of MAC prophylaxis. At randomization, the median CD4 count was 226 cells/mm³ and 64% had HIV-1 RNA <500 copies/mL. However, all eligible subjects were required to have a nadir CD4 <50 cells/mm³ (median nadir CD4=20) and 62% had a prior AIDS-defining infection, reflecting the history of severe immune suppression in this cohort. Additional details of baseline and immunological characteristics of this study population have been previously reported (34,37).

The demographic and health characteristics of the 433 subjects who continued in observational follow-up starting in 2000 were very similar to those of the original cohort (see Table 1). The observational cohort had a median follow-up time since the original enrollment of 7.5 years (interquartile range (IQR)=5.7-8.0 yrs) and the median time in observational follow-up was 5.8 years (IQR=4.1-6.0 yrs). These patients were highly ART-experienced, with a median time on treatment with HAART of 8.3 years (range 2.4–10.7 yrs). The median nadir CD4 count was 20 cells/mm³, and 60% had experienced an AIDS-defining infection prior to study entry. Despite past HIV disease severity, the loss to follow-up was only 3-5% per year, with a total of 83 subjects lost of 433 enrolled in the observational phase over a 7-year period.

Changes in Antiretroviral Treatment

At entry to the randomized parent study, 73% of subjects were on a NRTI+PI-based regimen (without NNRTIs), while 16% were on a NRTI+NNRTI+PI-based regimen, and 11% were on less standard regimens. From the time of study randomization in 1997-1999 until entry into the observational phase in early 2000, the use of PIs decreased from 96% to 85% of subjects, with slight decreases in use of non-boosted indinavir (36%), nelfinavir (24%), and saquinavir (18%) and increasing use of amprenavir (8%). At the same time, use of NNRTIs increased from 23% to 36% of subjects, particularly due to the increased use of efavirenz (22%). Thus, the percentage on a NRTI+PI-based regimen dropped to 57% while that on a NRTI+NNRTI+PI-based regimen increased to 24% (see Table 1). Tenofovir, atazanavir, fosamprenavir and lopinavir/ritonavir were not available at randomization, but were used as they became available during the course of follow-up.

Further changes in ART regimens occurred during the observational phase, as summarized in Figure 1. Overall, the percentage ever receiving an NNRTI during observational follow-up was 61%, ever receiving an NRTI was 98%, and ever receiving a PI was 91%. Use of ritonavir-boosted PIs increased (from 20% to 53%) while non-boosted PIs declined (from 61% to 21%). Among NNRTIs, efavirenz usage increased substantially (from 22% to 33%). Use of tenofovir also escalated rapidly from <1% at observational entry to 49% at the end of follow-up. The use of antihypertensives and lipid-lowering agents increased considerably over time, from 5% to 24% for antihypertensives, and from 1% to 42% for lipid-lowering agents. The substantial changes in use of ARV drugs and other relevant medications led to a clear need to adjust for time-varying indicators of current medication use at each time point in the statistical analysis of trends in lipid measures over time.

Cardiovascular Risk Factors

Traditional CHD risk characteristics and lipid levels at the initiation of observational follow-up are summarized in Table 2. Prevalence of CHD risk factors was high: 28% had TC $\geq$ 240 mg/dL, 11% had body mass index (BMI) $\geq$ 30, 9% had a history of diabetes, 17% had a history of hypertension, 31% were current smokers, and 20% had family history of CHD. Metabolic syndrome was identified in 100 of 433 subjects at entry (23%), with a significantly higher prevalence among females than males (40% vs 21%, $p=0.005$), primarily due to more abdominal obesity (66% vs 13%). A total of 266 (61%) were hypertensive at least once during follow-up.

Longitudinal Changes in Serum Lipids

Lipid values were measured at up to 11 study visits, with a median of 9 measurements each for TC, TG, and HDL measurements. TC and non-HDL cholesterol declined significantly over the six years of observational follow-up (Figure 2a, $p<0.001$), as did TG (Figure 2b, $p<0.001$), while HDL levels increased significantly by about 2.5 mg/dL ($p=0.001$, not shown).

At entry to the observational phase, 28% of subjects with TC measurements had hypercholesterolemia ($TC \geq 240$ mg/dL). Among the 284 without hypercholesterolemia at observational study entry and with follow-up measurements, 104 (37%) developed hypercholesterolemia, for an incidence rate of 10.8 events per 100 person-years (95% CI: 8.8-13.1). In addition, 109 of the 410 subjects with at least two TC measures (27%) had confirmed hypercholesterolemia (2 consecutive $TC > 240$ mg/dL). Importantly, 76% of subjects had either high cholesterol or hypertension during the course of the study, and 35% experienced both. Despite the continuing incidence of hypercholesterolemia, the prevalence declined from 28% at entry to 16% after almost 6 years of follow-up, due to subsequent improvement in the majority of subjects with high cholesterol (88%).

Age- and time-adjusted estimates of effects of ART classes, specific agents within class, and other medications are summarized in Table 3. Use of a ritonavir-boosted PI was associated with significantly higher levels of TC and TG. Other non-boosted PIs (indinavir, nelfinavir, and saquinavir) were associated with significantly lower mean TC or TG. Use of NNRTIs was also associated with higher lipid levels, primarily attributable to efavirenz for TG, and to nevirapine for HDL levels. In contrast, nevirapine was associated with significantly lower TG levels. Those who received NNRTIs or boosted PIs not only had significantly higher TC and TG levels, but also had significantly steeper declines over time in such levels. Use of a lipid-lowering agent at the time of lipid measurement was associated with lower levels of TC, TG, and HDL. Fasting did not appear to impact TC levels but was associated with lower values of TG and higher values of HDL. Exposure to weekly azithromycin prophylaxis in the original study was associated with higher TC after adjustment for age, time, and fasting, but not with other lipid measures.

The final multivariate models for TC, TG, and HDL adjusting for all covariates with $p < 0.10$ are summarized in Table 4. These models confirmed that, after adjustment for potential confounders, TC and TG levels were significantly higher for those on ritonavir-boosted PIs and on NNRTIs (specifically efavirenz for TG levels). For example, use of boosted PIs was associated with about 16 mg/dL higher TC and 109 mg/dL higher TG. For TG, the final model also included a significant interaction effect of both boosted PI use and NNRTI use with study week, reflecting the steeper decline in TG levels over time for those on these regimens, although they still did not resolve to normal levels over the course of the study. Use of tenofovir was associated with lower levels of TC, while HDL levels were higher for those on saquinavir, nevirapine, and stavudine. For all three lipid measures, there remained a residual effect of follow-up time after adjustment for the other covariates. Sensitivity analyses restricted to fasting samples (83-85% of lipid measurements) and applied to log-transformed TG levels resulted in selection of the same ART predictors for final multivariate models, with similar magnitude and significance of effects.

CHD Incidence and Estimated 10-year CHD Risk

A total of 23 of the 643 original subjects developed atherosclerotic CHD (IR=7.4 per 1000 person years, 95% CI: 4.7-11.1). Of these 23 subjects, 14 experienced an MI, 8 developed coronary artery disease, and 1 developed other CHD. All but one of the 23 subjects were on HAART at the time of the event (18 on HAART with a PI). There was no temporal trend in atherosclerotic CHD rates ($p=0.57$). Although the number of events was limited, we confirmed significant effects of age (HR=1.06, 95% CI: 1.01-1.11) and antihypertensive drug use (HR=4.33, 95% CI: 1.55-12.12) and a marginally significant effect of BMI (HR=1.08, 95% CI: 0.99-1.18) on the risk of CHD in a multivariate Cox proportional hazards model. Traditional CHD risk factors overall and for those with CHD events are shown in Table 2.

Using the Framingham model (35) to estimate the 10-year risk of serious cardiovascular events, $\geq 20\%$ risk of CHD within the next 10 years was predicted for 15% of subjects, and $\geq 10\%$ risk was predicted for 31% of subjects. The median predicted 10-year risk was 5% (IQR=1% to 12%). However, almost two-thirds of the CHD events were observed among those subjects predicted to be at low ($<10\%$) CHD risk.

DISCUSSION

Our study identified several important long-term trends in cardiovascular risk factors among severely immunocompromised AIDS patients who have had prolonged immune reconstitution with a median of over 8 years of treatment with HAART. CHD risk factors were very common in this population; only 24% of subjects had neither hypercholesterolemia nor hypertension during follow-up. Abnormalities in serum lipids were associated with the use of ritonavir-boosted protease inhibitors and with efavirenz, although lipid levels improved over time. Incidence of CHD was not substantially different from that in other large HIV-infected and HAART-treated cohorts and was associated with established risk factors such as age, hypertension, and BMI.

The lipid levels at entry to the observational component of our study were similar to those reported in other ART-experienced cohorts (9), but higher than in antiretroviral naïve cohorts. For example, they were similar to ~7500 D:A:D subjects receiving PIs or dual PIs (9), but higher than ARV-naïve subjects in the D:A:D (7,9) and 2NN studies (25) or BMI-matched HIV-negative controls described by Hadigan et al (38).

Despite the high lipid levels at baseline, there were significant declines in the average levels of TC and TG over follow-up, partly attributable to increasing use of lipid-lowering agents and possible selection of antiretroviral agents with fewer adverse effects, similar to those noted by the D:A:D study (39). However, multivariate models suggested an improvement in lipid parameters over time that was not completely explained by changes in ART agents and or use of lipid-lowering agents, particularly for total cholesterol, suggesting that other unmeasured factors may contribute to this decline. Possible contributing factors include lipoatrophy or the amount of visceral fat, neither of which we were able to directly measure in this study. Previous studies have suggested that both lipoatrophy and visceral adipose tissue are associated with dyslipidemia (40). It is currently unknown whether improvements in these body shape changes are associated with improvement of lipids. However, as their prognosis improved, it is possible that our study subjects may have increased their activity levels, leading to weight loss and improved lipid levels; this is consistent with the favorable changes in TG and HDL cholesterol we observed for those with smaller waist-to-hip ratios.

Total cholesterol and TG levels were significantly higher for subjects on regimens including ritonavir-boosted PIs or NNRTIs (especially efavirenz), consistent with other reports (8,10,11,17-21,25). While such associations have been observed in other cohorts, they have been primarily seen in antiretroviral naïve subjects or healthier subjects with limited antiretroviral experience. For example, although Shlay et al (11) compared long-term changes in lipid levels across three randomized ART drug class strategies, their study focused on initial treatment strategy for antiretroviral naïve subjects using an intent-to-treat approach. Thus, their analysis addressed a different population and did not take into account any changes in ART over the follow-up period, despite the fact that the majority of subjects, including 78% of the participants on the NNRTI + PI arm, had at least one change in therapy. It is notable, therefore, that such associations of higher TC and TG with boosted PI and NNRTI-containing regimens also held in our ART-experienced cohort, even after adjustment for actual ART treatment and use of lipid lowering therapy and

antihypertensives. Our analysis also had the ability to evaluate individual ART agents within a class, which is crucial given the noted variability within drug classes (18,22-27).

During a median observation period of nearly 6 years, 643 subjects with HAART-induced immune restoration had a CHD incidence of 7.4 events per 1000 person-years (95% CI: 4.7-11.1). This rate is slightly although not significantly higher than that in D:A:D for patients with more than 5 years HAART exposure (5.5/1000 person-years) (28) and to the French study (29), which reported a rate of 6.6 events/1000 person-years. Differences in CHD event definitions and history of more severe immunosuppression of our participants as characterized by lower CD4 nadir may also have contributed to higher observed rates in our study.

Notably, the subjects in our study who developed CHD did not all present with traditional CHD risk factors; more than half were estimated to have low 10-year risk (<10%) of a CHD event based on traditional CHD risk factors. However, in our study population of AIDS patients with a history of severe immune suppression, the prevalence of such CHD risk factors was high. In addition, while changing treatment regimens appear to be associated with improved lipid profiles, it remains to be seen whether this will translate to reduced CHD rates. Thus, HIV-infected subjects with long-term exposure to HAART warrant future monitoring for cardiovascular complications and events. Development of a specific CHD risk prediction model for HIV-infected subjects may be warranted (41).

We recognize several limitations of our study. First, the overall size of our observational cohort (N=433) is smaller than other studies investigating dyslipidemia, and evaluation of lipids in our study was typically initiated after the most severe immunosuppression had been reverted. Thus, we were unable to observe changes in lipids during the initial period of immune reconstitution. Secondly, the small number of CHD events limited our ability to evaluate associations with predictors for CHD such as duration of HAART. In addition, the limited events also prevented a more in-depth evaluation of characteristics of those with CHD events but at low CHD risk versus high risk based on Framingham scoring.

However, our study had several strengths which distinguish it from other studies, including an extended duration of follow-up, repeated measurements of lipids, proper adjustment for changes in ART and lipid-lowering treatments, and assessment of other CHD risk factors over almost 6 years of follow-up. In addition, this study addressed a unique cohort of AIDS patients with a past history of severe immune suppression and subsequent prolonged immune-reconstitution, with a median ART exposure of over 8 years. Continued follow-up of this cohort who benefited from the earliest available triple combination regimens will provide insights into the long-term outcomes of treated HIV infection.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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List of Abbreviations

ACTG	AIDS Clinical Trials Group
AIDS	Acquired Immune Deficiency Syndrome
ART	antiretroviral treatment
ARV	antiretroviral
BMI	body mass index
BP	blood pressure
CHD	coronary heart disease
CI	confidence interval
HAART	highly active antiretroviral treatment
HDL	high density lipoprotein
HIV	human immunodeficiency virus
HR	hazard ratio
IQR	interquartile range
IR	incidence rate
LDL	low density lipoprotein
MAC	<i>Mycobacterium avium</i> complex
MI	myocardial infarction
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
PI	protease inhibitor
RNA	ribosomal nucleic acid
TC	total cholesterol
TG	triglycerides

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Figure 1.
Changes in ART Use and other Medications During Observational Follow-up

Figure 2.
Trends in Lipid Measurements over Study Follow-up

Table 1
Demographic and Health Characteristics of Study Participants

Characteristic	At Entry to Original Randomized Trial (N=643)		At Entry to Long-term Observation Phase (N=433)	
	N	(%)	N	(%)
Male	559	(87%)	386	(89%)
Age (years), median (IQR)	40	(35-46)	43	(38-48)
Race/Ethnicity				
White	370	(58%)	273	(63%)
Black	131	(20%)	80	(18%)
Hispanic	117	(18%)	63	(15%)
Other	25	(4%)	17	(4%)
Previous/Current IV Drug Use	99	(15%)	62	(14%)
Prior Cocaine Use	253	(39%)	201	(46%)
Prior Heroin Use	65	(10%)	51	(12%)
Prior Amphetamine Use	154	(24%)	146	(34%)
CD4 Count (cells/mm ³)				
Median (IQR)	226	(172-315)	229	(170-318)
<200	241	(37%)	155	(36%)
200-299	208	(32%)	146	(34%)
300+	194	(31%)	132	(30%)
HIV-1 Viral Load (copies/ml)				
500 copies or less	417	(65%)	287	(66%)
500-20,000 copies	112	(17%)	71	(16%)
20,000+ copies	100	(16%)	65	(15%)
Unknown/missing	14	(2%)	10	(2%)
Nadir CD4 (cells/mm ³), median (IQR)	20	(10-33)	20	(10-33)
Antiretroviral regimen				
NRTI+NNRTI+PI-based regimen	105	(16%)	103	(24%)
NRTI+PI-based regimen	470	(73%)	246	(57%)
NNRTI+PI-based regimen	30	(5%)	15	(3%)
NRTI+NNRTI-based regimen	14	(2%)	40	(9%)
NRTI-only regimen	24	(4%)	15	(3%)
Not on ARVs	0	(0%)	14	(3%)
Pre-entry duration on HAART (yrs), median (IQR)	0.8	(0.4-1.4)	0.8	(0.4-1.3)
Total Duration on HAART (yrs), median (IQR)	6.6	(2.8-8.7)	8.3	(6.5-8.9)
Antihypertensive use	31	(5%)	44	(10%)
Lipid-lowering agent	9	(1%)	32	(7%)

IQR= Interquartile range, IV=intravenous, HAART=highly active antiretroviral therapy, PI=protease inhibitor, NRTI=nucleoside reverse transcriptase inhibitor, HIV=human immunodeficiency virus.

Table 2

Risk Factors for Coronary Heart Disease (CHD) among Subjects in Long-Term Observation and among those with CHD Events.

Characteristic	At Entry to Long-term Observation Phase (N=433)		Among those with CHD Event after start of Observation Phase (N=19)	
	N	(%)	N	(%)
Age >45 (Male), >55 (Female)	164	(38%)	11	(58%)
Current Smoker	135	(31%)	6	(32%)
History of Diabetes	39	(9%)	2	(11%)
History of Hypertension	73	(17%)	7	(37%)
Subject History of CHD	16	(4%)	6	(32%)
Family History of CHD event or death	85	(20%)	4	(21%)
Systolic Blood Pressure (mmHg) ¹				
Median (IQR)	122	(112-136)	122	(112-137)
≥ 140	66	(19%)	4	(22%)
Body Mass Index (kg/m ²) ²				
Median (IQR)	24.8	(22.8-27.6)	27.3	(23.8-28.7)
≥ 30	49	(11%)	3	(16%)
Waist/Hip Ratio ³				
Median (IQR)	0.95	(0.92-0.99)	0.93	(0.92-0.98)
≥ 1.0	90	(21%)	4	(21%)
Total cholesterol (TC), mg/dL ⁴				
Median (IQR)	211	(179-244)	230	(185-261)
≥ 240 mg/dL (approx 6.5mmol/L)	115	(28%)	7	(37%)
HDL cholesterol, mg/dL ⁵				
Median (IQR)	37	(30-45)	36	(32-48)
≤ 35 mg/dL (approx 0.9mmol/L)	173	(44%)	9	(47%)
TC:HDL Ratio ⁵				
Median (IQR)	5.6	(4.6-7.2)	6.7	(4.5-7.8)
≥ 6.5	136	(35%)	10	(53%)
Non-HDL Cholesterol, mg/dL ⁵				
Median (IQR)	173	(140-204)	194	(149-227)
≥ 200 mg/dL (approx 5.2 mmol/L)	111	(28%)	8	(42%)
Triglycerides, mg/dL ⁶				
Overall, Median (IQR)	238	(143-413)	227	(139-454)
Fasting, Median (IQR)	234	(139-397)	194	(136-454)
≥ 200 mg/dL (approx 2.3mmol/L)	233	(57%)	10	(53%)
Metabolic Syndrome	100	(23%)	---	---
Predicted 10-year CHD Risk ⁷				
Median (IQR)	5%	(1%-12%)	5%	(3%-20%)
< 5% Risk	211	(49%)	8	(42%)

Characteristic	At Entry to Long-term Observation Phase (N=433)		Among those with CHD Event after start of Observation Phase (N=19)	
	N	(%)	N	(%)
5-9% Risk	89	(21%)	4	(21%)
10-14% Risk	50	(12%)	1	(5%)
15-19% Risk	18	(4%)	1	(5%)
>20% Risk	65	(15%)	5	(26%)

Notes: CHD=Coronary heart disease, IQR=interquartile range, TC=total cholesterol.

Subjects with missing values were not included in calculation of percentages. Among the 433 subjects in long-term observation:

¹ 93 subjects were missing systolic BP

² 3 were missing BMI

³ 2 were missing waist-hip ratio

⁴ 25 were missing total cholesterol

⁵ 41 were missing HDL, TC:HDL ratio, and non-HDL cholesterol

⁶ 22 were missing triglycerides, and 73% of triglyceride values were taken fasting. One of the 19 subjects with CHD events was missing systolic BP.

⁷ Predicted 10-year CHD risk was based on Framingham scoring, as described in the NCEP ATP III Guidelines (35).

Table 3
Estimated Effects of Antiretroviral and Other Medications on Cholesterol and Triglyceride Levels based on Mixed Effect Models

Covariate	Total Cholesterol			Triglycerides			HDL Cholesterol		
	Estimate (mg/dL)/	95% Confidence Interval	p-value	Estimate (mg/dL)/	95% Confidence Interval	p-value	Estimate (mg/dL)/	95% Confidence Interval	p-value
Age at start of observation	0.46	(-0.09, 1.00)	0.10	-1.73	(-4.60, 1.15)	0.24	0.18	(0.05, 0.30)	0.006
Year of observation phase	-4.69	(-5.87, -3.48)	<0.001	-15.22	(-22.05, -8.38)	<0.001	0.39	(0.13, 0.64)	0.003
Fasting Status (yes vs no)	-0.23	(-5.43, 4.98)	0.93	-37.63	(-69.08, -6.18)	0.02	0.83	(-0.11, 1.77)	0.08
Age-, time, and fasting-adjusted estimates for antiretroviral and other medication predictors									
Placebo vs Azithromycin	10.33	(2.37, 18.28)	0.01	34.29	(-15.35, 83.94)	0.18	0.99	(-1.56, 3.55)	0.44
HAART with PI	12.84	(1.93, 23.75)	0.02	-45.91	(-154.6, 62.80)	0.41	3.86	(0.37, 7.36)	0.03
Duration on HAART (years)	1.20	(-3.85, 6.26)	0.64	-5.80	(-35.24, 23.63)	0.70	-0.18	(-1.95, 1.60)	0.84
Non-nucleoside reverse transcriptase inhibitor (NNRTI)-boosted PI	11.85	(5.91, 17.80)	<0.001	56.28	(25.31, 87.24)	<0.001	0.31	(-0.77, 1.40)	0.57
Isaquinavir (non-boosted)	-9.61	(-16.19, -3.03)	0.004	-24.81	(-61.92, 12.31)	0.19	-1.96	(-3.38, -0.54)	0.007
Nelfinavir (non-boosted)	-3.95	(-11.74, 3.85)	0.32	-57.75	(-107.6, -7.88)	0.02	1.01	(-1.98, 3.99)	0.51
Saquinavir (non-boosted)	4.76	(-6.74, 16.26)	0.42	-46.82	(-96.32, 2.68)	0.06	3.88	(-0.43, 8.19)	0.08
ABO NNRTI Use	9.23	(3.96, 14.50)	<0.001	7.68	(-21.52, 36.88)	0.61	3.12	(1.84, 4.40)	<0.001
Efavirenz	8.54	(2.33, 14.76)	0.007	40.04	(1.61, 78.47)	0.04	0.58	(-0.79, 1.94)	0.41
Nevirapine	6.16	(-3.16, 15.48)	0.20	-52.27	(-96.98, -7.55)	0.02	6.92	(4.55, 9.30)	<0.001
Stavudine	4.28	(-1.84, 10.39)	0.17	13.59	(-17.24, 44.42)	0.39	0.99	(-0.33, 2.30)	0.14
Tenofovir	-8.16	(-14.66, -1.66)	0.01	-2.68	(-39.10, 33.74)	0.89	-1.11	(-2.56, 0.35)	0.14
Antihypertensive	-3.33	(-9.91, 3.25)	0.32	6.26	(-55.63, 68.16)	0.84	0.80	(-1.00, 2.59)	0.39
Lipid-Lowering Agent	-8.18	(-14.74, -1.63)	0.01	-30.36	(-62.50, 1.79)	0.06	1.98	(0.75, 3.22)	0.002

HAART=highly active antiretroviral therapy, PI=protease inhibitor, NNRTI=non-nucleoside reverse transcriptase inhibitor

Estimated change in lipid measure for each covariate based on a mixed effect repeated measures model adjusting for correlation among repeated lipid measures over time within each subject. Top panel includes all three effects simultaneously, while bottom panel provides estimates for each individual medication use adjusted for age, week of follow-up, and fasting status.

Table 4
Final repeated measures models for longitudinal assessment of total cholesterol and triglyceride levels

Covariate	Total Cholesterol			Triglycerides			HDL Cholesterol		
	Estimate (mg/dL)/	95% Confidence Interval	p-value	Estimate (mg/dL)/	95% Confidence Interval	p-value	Estimate (mg/dL)/	95% Confidence Interval	p-value
Intercept	152.7	(114.6, 190.7)	<0.001	723.80	(346.7, 1100.9)	<0.001	8.64	(-6.74, 24.03)	0.27
Age at start of observation	0.53	(0.00, 1.06)	0.05	-2.64	(-5.38, 0.11)	0.06	0.23	(0.10, 0.35)	<0.001
Year of observation phase	-4.11	(-5.51, -2.72)	0.01	-5.86	(-12.67, 0.96)	0.09	0.28	(-0.01, 0.56)	0.06
Lipid-Lowering Agent	-10.59	(-17.05, -4.13)	0.001	-35.79	(-69.48, -2.09)	0.04	1.90	(0.71, 3.08)	0.002
Placebo vs Azithromycin	8.85	(1.08, 16.62)	0.03	---	---	---	---	---	---
Tenofovir	-10.93	(-17.48, -4.39)	0.001	---	---	---	---	---	---
Saquinavir	---	---	---	---	---	---	1.06	(-0.15, 2.27)	0.09
Regonavir-boosted PI	15.58	(9.42, 21.73)	<0.001	109.38	(-30.70, 2.63)	<0.001	---	---	---
Any NNRTI Use	11.51	(6.35, 16.68)	<0.001	---	---	---	---	---	---
Efavirenz	---	---	---	83.78	(8.47, 159.09)	0.03	---	---	---
Nevirapine	---	---	---	-40.14	(-80.75, 0.47)	0.07	6.67	(4.24, 9.11)	<0.001
Boosted PI* year on study	---	---	---	-16.67	(-30.70, -2.63)	0.02	---	---	---
Efavirenz* year on study	---	---	---	-16.77	(8.47, 159.09)	0.06	---	---	---
HAART with PI	---	---	---	---	---	---	4.01	(0.58, 7.44)	0.02
Intinavir (non-boosted)	---	---	---	---	---	---	-2.15	(-3.63, -0.68)	0.004
Saquinavir (non-boosted)	---	---	---	---	---	---	3.96	(0.16, 8.09)	0.06
Current smoking	-7.33	(-16.09, 1.42)	0.10	---	---	---	---	---	---
Body Mass Index	0.91	(-0.18, 2.01)	0.10	---	---	---	---	---	---
Female vs Male	---	---	---	-58.74	(-114.2, -3.27)	0.04	4.67	(1.61, 7.73)	0.003
Fasting Status (yes vs no)	---	---	---	-42.42	(-73.19, -11.66)	0.007	0.79	(-6.74, 24.03)	0.09
History of Diabetes	---	---	---	146.51	(38.27, 254.75)	0.008	-2.69	(-5.55, 0.16)	0.06
RNA>500 copies/mL	---	---	---	---	---	---	-3.97	(-6.22, -1.73)	<0.001
Nonwhite	---	---	---	---	---	---	3.58	(1.23, 5.94)	0.003
Karnofsky score	---	---	---	-2.57	(-5.63, 0.50)	0.10	0.12	(-0.03, 0.28)	0.10
Waist-hip ratio> 1	---	---	---	53.89	(-8.67, 116.44)	0.09	-3.16	(-5.93, -0.38)	0.03

HAAART=highly active antiretroviral therapy, PI=protease inhibitor, NNRTI=non-nucleoside reverse transcriptase inhibitor

/ Estimated change in lipid measure based on a mixed effect model including all covariates with parameter estimates presented.