

Comparison of the Metabolic Effects of Ritonavir-Boosted Darunavir or Atazanavir Versus Raltegravir, and the Impact of Ritonavir Plasma Exposure: ACTG 5257

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Background. Metabolic effects following combination antiretroviral therapy (cART) vary by regimen type. Changes in metabolic effects were assessed following cART in the AIDS Clinical Trials Group (ACTG) A5257 study, and correlated with plasma ritonavir trough concentrations (C_{24}).

Methods. Treatment-naïve adult subjects were randomized to ritonavir-boosted atazanavir or darunavir, or raltegravir-based cART. Changes in lipids and other metabolic outcomes over time were estimated. Differences between arms were estimated with 97.5% confidence intervals and compared using pairwise Student *t* tests. Associations between ritonavir C_{24} and lipid changes at week 48 were evaluated via linear regression.

Results. Analyses included 1797 subjects with baseline fasting data. Baseline lipid profiles and metabolic syndrome rates (approximately 21%) were similar across arms. Comparable increases occurred in total cholesterol, triglycerides, and low-density lipoprotein cholesterol with the boosted protease inhibitors (PIs); each PI had greater increases relative to raltegravir (all $P \leq .001$ at week 96). Metabolic syndrome incident rates by week 96 (approximately 22%) were not different across arms. Ritonavir C_{24} was not different by arm ($P = .89$) (median, 69 ng/mL and 74 ng/mL in the atazanavir and darunavir arms, respectively) and were not associated with changes in lipid measures (all $P > .1$).

Conclusions. Raltegravir produced the most favorable lipid profile. Metabolic syndrome rates were high at baseline and increased to the same degree in all arms. Ritonavir C_{24} was not different in the PI arms and had no relationship with the modest but comparable increases in lipids observed with either atazanavir or darunavir. The long-term clinical significance of the lipid changes noted with the PIs relative to raltegravir deserves further evaluation.

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Keywords. HIV/AIDS; cART; lipids; metabolic syndrome.

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Contemporary antiretroviral therapy (ART) regimens have improved virologic efficacy compared with earlier therapies. However, less is known about how these regimens compare to each other with respect to metabolic outcomes. Given the need for lifelong therapy, data on metabolic outcomes from randomized clinical trials can provide useful information to guide the selection of

first-line therapy. Ritonavir-boosted protease inhibitor (PI)-containing therapy has been associated with the development of dyslipidemia and insulin resistance that may predispose to cardiovascular and cerebrovascular injuries [1–3]. On the contrary, raltegravir, an integrase strand inhibitor, has been shown to have milder lipid and metabolic effects relative to PI-based or nonnucleoside reverse transcriptase inhibitor-based therapy, producing minimal changes in plasma lipid levels, insulin resistance, or alteration of body habitus [4–6].

Furthermore, the extent of lipid and other metabolic changes in ritonavir-boosted PI regimens may vary by regimen type and by systemic ritonavir exposure [7]. Ritonavir is both a substrate and an inhibitor of the cytochrome P450 (CYP) 3A isoenzyme and, to a lesser extent, CYP2D6 [8]. All PIs vary in their affinity and impact on CYP3A4 isoenzyme [9]. As higher ritonavir exposure has been correlated with greater elevation in plasma lipids and the occurrence of other metabolic side effects [10, 11], the differential effect of coadministered PI on ritonavir plasma concentrations could impact the lipid profile of a given ritonavir-boosted PI regimen.

The AIDS Clinical Trials Group (ACTG) Study A5257 evaluated the virologic efficacy and tolerability of tenofovir disoproxil fumarate (TDF)/emtricitabine in combination with ritonavir-boosted atazanavir, raltegravir, or ritonavir-boosted darunavir in treatment-naïve human immunodeficiency virus (HIV)-infected adults in the United States and Puerto Rico [12]. In the current report, we examined the lipid and other metabolic effects of these 3 antiretroviral regimens, with the aim of evaluating differences between the 2 PI arms, and between each of the PI arms and the raltegravir arm. Additionally, in the 2 PI arms of the study, the effects of atazanavir and darunavir on plasma trough ritonavir concentrations (C_{24}) and the association between plasma ritonavir C_{24} and fasting lipid measures were evaluated.

METHODS

Study Population and Design

ACTG A5257 was a phase 3, randomized, open-label trial in which participants were randomly assigned 1:1:1 to receive 1 of 3 regimens—(1) 300 mg of atazanavir (Reyataz, Bristol-Myers Squibb) plus 100 mg of ritonavir (Norvir, Abbott Laboratories) once daily (ritonavir-boosted atazanavir); (2) 400 mg of raltegravir (Isentress, Merck Inc) twice daily; or (3) 800 mg of darunavir (Prezista, Janssen Therapeutics) plus 100 mg of ritonavir once daily (ritonavir-boosted darunavir)—each with the fixed-dose combination of 300 mg of TDF plus 200 mg of emtricitabine (Truvada, Gilead Sciences). This study was approved by the biomedical investigational research committee at each site, and all participants gave written informed consent before study enrollment (ClinicalTrials.gov identifier NCT00811954).

The study population included ART-naïve, HIV-1-infected adults with plasma HIV-1 RNA level >1000 copies/mL. Study evaluations were completed before entry; at entry; at weeks 4, 8, 16, 24, and 32; and every 16 weeks thereafter. Participants were followed, regardless of meeting an endpoint, for 96 weeks after enrollment of the last participant. The primary objective of ACTG A5257 was to determine regimen equivalence with regard to virologic efficacy and tolerability over 96 weeks. Study A5257 had two important metabolic objectives. The first was to compare the impact of the study regimens on a variety of metabolic measures including fasting plasma lipid and glucose levels, prevalence of metabolic syndrome, and anthropometric measures. The study also aimed to detect an association between plasma ritonavir C_{24} at steady state and 48-week changes in fasting plasma lipid levels in the two ritonavir-boosted PI arms.

Fasting plasma lipid measurements evaluated included total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), calculated non-HDL-C (calculated as TC – HDL-C), and calculated low-density lipoprotein cholesterol (LDL-C) (calculated as TC – [HDL-C + (TG/5)], if TG ≤400 mg/dL). Per protocol, these parameters were assessed at weeks 0, 24, 48, 96, and 144. Fasting was defined as nothing to eat or drink for at least 8 hours except for water or decaffeinated black coffee, and required prescription medications. Fasting lipid profile levels were performed at any Clinical Laboratory Improvement Amendments-compliant laboratory. Steady-state plasma ritonavir concentrations were evaluated by ritonavir C_{24} assessed once at least two weeks after initiation of ritonavir-boosted atazanavir or ritonavir-boosted darunavir and obtained within 22–26 hours after the last self-reported dose of ritonavir. Sampling for ritonavir C_{24} continued until a target sample size of 258 participants with evaluable steady-state ritonavir C_{24} measures was reached. Concentrations were measured by liquid chromatography-tandem mass spectrometry (LC-MS/MS) as previously described [13] at the University of California, San Francisco, on batched plasma samples. Incident metabolic syndrome was assessed based on the National Cholesterol Education Program (NCEP) Adult Treatment Panel III criteria [14, 15].

Statistical Analysis

Unless otherwise specified, all analyses included all eligible participants with fasting lipid measures available at study entry but otherwise followed the intention-to-treat principle; as-treated analysis including participants who completed the study on randomized treatment and sensitivity analyses excluding participants on lipid-lowering medications (primarily aimed at reducing TC, TG, and LDL) and antihypertensive agents were also performed. Missing data were considered missing completely at random. Mean changes in fasting plasma lipid measures over time were estimated with 95% confidence intervals (CIs). Pairwise treatment differences at weeks 24, 48, 96, and

144 were estimated with 97.5% CIs and compared between the treatment arms using pairwise Student *t* tests. The cumulative probability of developing metabolic syndrome over time was estimated by Kaplan–Meier method. Participants not meeting criteria for metabolic syndrome prior to end of follow-up were censored at the time of their last visit requiring metabolic evaluation; participants meeting criteria for metabolic syndrome at study entry were excluded from this analysis. All treatment group comparisons were assessed at a 2.5% level of statistical significance to provide modest control of the type I error in the setting of multiple comparisons.

Ritonavir C_{24} was analyzed on the natural logarithm scales and compared by treatment arms using Wilcoxon rank-sum tests. Associations between ritonavir C_{24} and change from baseline in levels of fasting TG, non-HDL-C, and calculated LDL-C at week 48 and week 96 were analyzed using linear regression; treatment-dependent associations were evaluated via 2-degrees of freedom tests for different intercept and slope. For analyses of these pharmacokinetic objectives, lipid values obtained following discontinuation of ritonavir-boosted PI or initiation of lipid-lowering agents were excluded, with values imputed with the last observations obtained prior to these events. The target sample size of 258 participants randomized to each of the ritonavir-boosted PI arms provided 90% power to detect an association between ritonavir C_{24} and 48-week change in fasting TG, equating to a 32 mg/dL lower change in fasting TG over 48 weeks per 12.6 ng/mL lower ritonavir C_{24} , and allowed for a 20% loss due to missing data (providing effective sample size of 103 participants per ritonavir-boosted PI arm).

RESULTS

A total of 1809 evaluable participants were enrolled from 57 sites into A5257 between 22 May 2009 and 9 June 2011. Of these, 1797 with confirmed baseline fasting samples and clinical measures were included in the current analyses. Baseline demographics, metabolic and lipid measures, and clinical characteristics of the study population were well balanced between treatment arms (Table 1). The study population comprised 24% of women, 34% of non-Hispanic white, 42% of non-Hispanic black, and 21% of Hispanic. Full demographic details have been previously presented [9].

Eighty-eight percent of participants had the NCEP target TC <200 mg/dL, 75% had TG <150 mg/dL, 89% had non-HDL-C <160 mg/dL, and 89% (of 1170 with TG ≤400 mg/dL) had calculated LDL <130 mg/dL, whereas only 43% had HDL-C ≥40 mg/dL. Median (Q1, Q3) fasting blood glucose level was 84 (78, 92) mg/dL; 89% had fasting blood glucose levels <100 mg/dL. Twenty-one percent of participants had evidence of metabolic syndrome at study entry. Fifty-eight percent of participants reported a history of smoking, 38% reported a smoking history

>10 years, and 39% were current smokers. At study entry, 106 (6%) were taking lipid-lowering agents, 273 (15%) were taking antihypertensive agents, and 64 (4%) were on hypoglycemic therapy at study entry (Table 1).

Changes from baseline and absolute values over time in lipid measures and other metabolic outcomes following therapy are summarized in Figure 1, Supplementary Figure 1, and Table 2, respectively. In pairwise comparisons, there were no differences in the mean change from baseline to all study weeks (24, 48, and 96) in any of the lipid measures between the ritonavir-boosted atazanavir and the ritonavir-boosted darunavir arms (all $P > .05$). However, each of the ritonavir-boosted PI arms had greater increases relative to the raltegravir arm in TC, TG, non-HDL-C, and LDL-C (all $P \leq .001$). HDL-C increased modestly in all 3 arms (an average increase of 6 mg/dL over 96 weeks), with no significant differences in mean change from baseline to all study weeks evaluated between treatment arms (all $P > .06$) (Figure 1A–C, Supplementary Figure 1A). From baseline to week 96, the percentage of participants who had taken lipid-lowering agents increased from 5% to 11% in the ritonavir-boosted atazanavir arm, 6%–9% in the raltegravir arm, and 6%–14% in the ritonavir-boosted darunavir arm. Sensitivity analyses of changes in lipid measures over time by treatment arms that included as-treated analyses with participants who completed the study on their original randomized treatment, or limited to participants not taking lipid-lowering agents, yielded findings that were consistent with the intention-to-treat analyses.

Fasting plasma glucose, waist circumference, and waist-to-height ratio increased following ART initiation in all 3 treatment arms (Figure 1D and 1E; Supplementary Figure 1B). In pairwise comparisons, larger increases in waist circumference were observed with the raltegravir arm compared with the ritonavir-boosted darunavir arm at weeks 48 and 96 (all $P \leq .023$) but not compared with the ritonavir-boosted atazanavir arm ($P \geq .07$); no other treatment group differences were apparent. The cumulative probability of incident of metabolic syndrome by week 96 was 21% (95% CI, 18%–26%) for the ritonavir-boosted atazanavir arm, 22% (95% CI, 18%–26%) for the raltegravir arm, and 22% (95% CI, 19%–27%) for the ritonavir-boosted darunavir arm, with no apparent difference between the treatment arms (all $P \geq .7$; Figure 2).

Of the 230 participants who had plasma obtained for evaluation of drug concentrations, 109 in the ritonavir-boosted atazanavir arm and 121 in the ritonavir-boosted darunavir arm had evaluable steady-state ritonavir C_{24} . Median (Q1, Q3) ritonavir C_{24} was 69 (40–105) ng/mL in the ritonavir-boosted atazanavir arm, and 74 (38–110) ng/mL in the ritonavir-boosted darunavir arm, with no apparent difference between the arms ($P = .89$). Associations between ritonavir C_{24} and changes in fasting plasma lipid measures were not apparent ($P \geq .4$) at either week 48 or week 96. While treatment group specific estimates of associations between ritonavir C_{24} and lipid change

Table 1. Baseline Characteristics and Metabolic Parameters Among Fasted Subjects

Characteristic	Total (N = 1797)	Treatment		
		ATV/r (n = 602)	RAL (n = 600)	DRV/r (n = 595)
Female sex	432 (24)	143 (24)	146 (24)	143 (24)
Age, y, mean (SD)	37.37 (11.02)	37.60 (10.84)	37.00 (10.81)	37.52 (11.40)
Race/ethnicity				
White non-Hispanic	612 (34)	212 (35)	212 (35)	188 (32)
Black non-Hispanic	753 (42)	250 (42)	253 (42)	250 (42)
Hispanic (regardless of race)	385 (21)	124 (21)	115 (19)	146 (25)
Other	43 (2)	15 (2)	18 (3)	10 (2)
Weight, kg, mean (SD)	78.64 (18.36)	78.97 (18.92)	78.84 (18.49)	78.11 (17.66)
BMI, kg/m ² , mean (SD)	26.14 (5.93)	26.22 (6.10)	26.26 (5.85)	25.94 (5.82)
Baseline HIV-1 RNA, log ₁₀ copies/mL, mean (SD)	4.63 (0.72)	4.63 (0.73)	4.65 (0.71)	4.60 (0.71)
Baseline CD4 ⁺ count, cells/μL, mean (SD)	308.45 (192.27)	309.16 (188.96)	306.07 (198.59)	310.15 (189.38)
Fasting TC, mg/dL				
Median (Q1, Q3)	154 (133, 178)	154 (134, 176)	155 (134, 181)	154 (133, 179)
<200 mg/dL	1,589 (88)	537 (89)	523 (87)	529 (89)
Fasting HDL-C, mg/dL				
Median (Q1, Q3)	38 (31, 46)	37 (30, 45)	38 (31, 46)	38 (31, 47)
≥40 mg/dL	780 (43)	249 (41)	272 (45)	259 (44)
Fasting TG, mg/dL				
Median (Q1, Q3)	103 (73, 148)	105 (74, 150)	103 (73, 146)	99 (73, 148)
<150 mg/dL	1,352 (75)	449 (75)	456 (76)	447 (75)
Fasting non-HDL-C, mg/dL				
Median (Q1, Q3)	114 (95, 138)	115 (96, 137)	115 (96, 140)	112 (93, 138)
<160 mg/dL	1,606 (89)	542 (90)	533 (89)	531 (89)
Fasting calculated LDL-C, mg/dL ^a				
Median (Q1, Q3)	92 (74, 112)	93 (75, 111)	93 (74, 115)	89 (73, 111)
<130 mg/dL	1,606 (89)	542 (90)	528 (88)	536 (90)
Fasting glucose, mg/dL				
Median (Q1, Q3)	84 (78, 92)	85 (79, 93)	85 (78, 92)	83 (77, 91)
<100 mg/dL	1602 (89)	529 (88)	539 (90)	534 (90)
Presence of metabolic syndrome	381 (21)	141 (23)	121 (20)	119 (20)
Smoking status				
History of smoking	1,044 (58)	358 (59)	349 (58)	337 (57)
Smoking history >10 y	678 (38)	249 (41)	225 (38)	204 (34)
Current smoker	706 (39)	251 (42)	241 (40)	214 (36)
On lipid-lowering treatment	106 (6)	33 (5)	35 (6)	38 (6)
On antihypertensive agents	273 (15)	95 (16)	89 (15)	89 (15)
Hypoglycemic agents	64 (4)	24 (4)	21 (3)	19 (3)

Data are presented as No. (%) unless otherwise specified.

Abbreviations: ATV/r, ritonavir-boosted atazanavir; BMI, body mass index; DRV/r, ritonavir-boosted darunavir; HDL-C, high-density lipoprotein cholesterol; HIV-1, human immunodeficiency virus type 1; LDL, low-density lipoprotein cholesterol; RAL, raltegravir; SD, standard deviation; TC, total cholesterol; TG, triglycerides.

^a Calculated as [fasting calculated LDL-C (mg/dL) = fasting TC – fasting HDL-C – (fasting TG/5)], only for subjects with fasting TG ≤400 mg/dL; subjects with fasting TG >400 mg/dL were excluded.

were in opposite directions (negative in the atazanavir group, positive in the darunavir group; [Supplementary Figure 2](#)), none of these associations were statistically significant ($P > .09$), and no evidence of PI-specific associations was apparent ($P \geq .09$) (Table 3).

DISCUSSION

In this prospective, randomized, open-label study evaluating raltegravir and the two ritonavir-boosted PI regimens as initial treatment of HIV infection, we identified differences in lipid changes

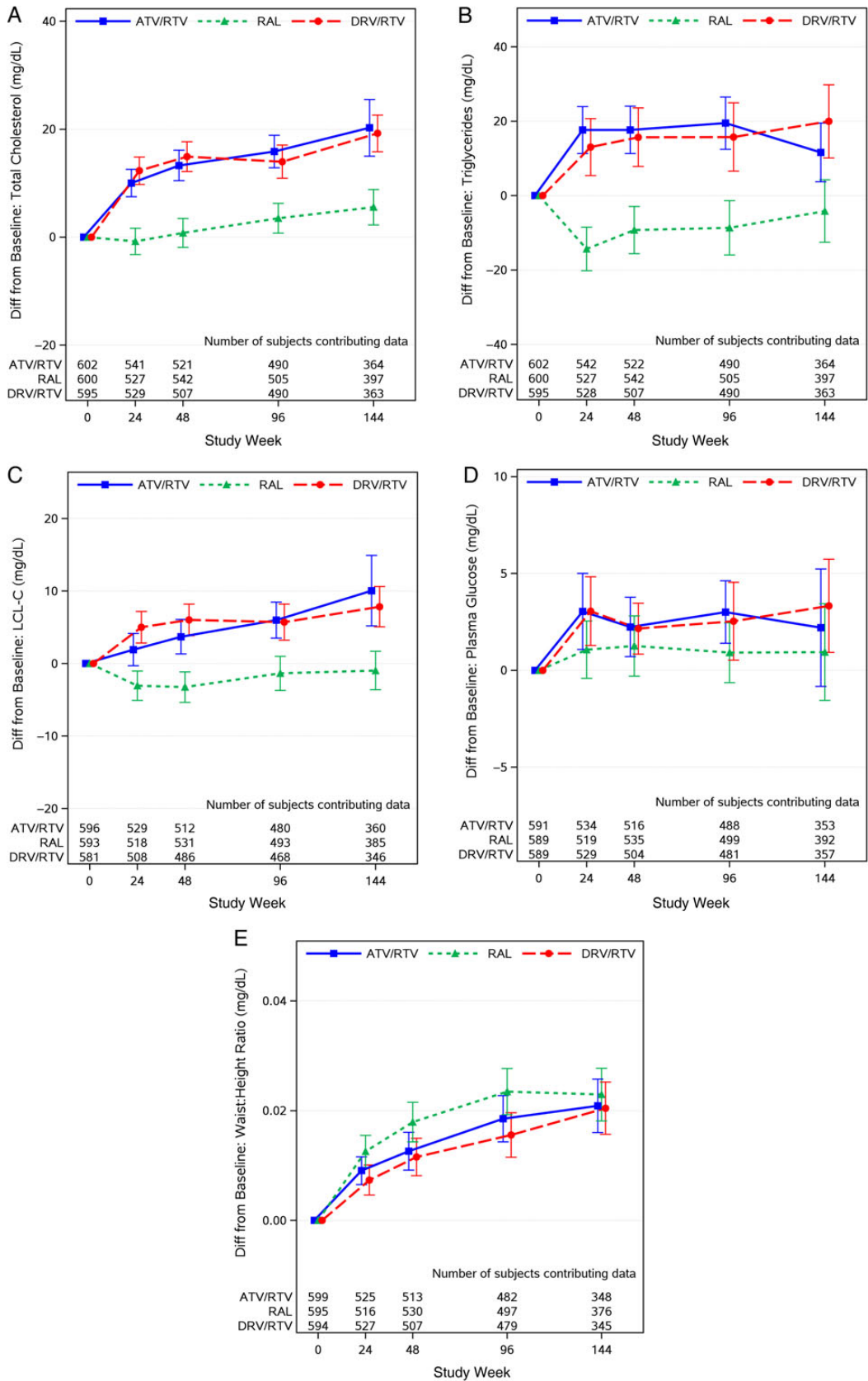


Figure 1. Mean changes from baseline in metabolic outcomes and anthropometric measures, over time, with 95% confidence interval. Abbreviations: ATV/RTV, ritonavir-boosted atazanavir; Diff, difference; DRV/RTV, ritonavir-boosted darunavir; LDL-C, low-density lipoprotein cholesterol; RAL, raltegravir.

Table 2. Summary of the Absolute Levels: Treatment Group Comparison of Lipids Over Time

Metabolic Parameters	Study Week	ATV/r Mean (95% CI)	RAL Mean (95% CI)	DRV/r Mean (95% CI)
Fasting total cholesterol, mg/dL	0	156.7 (154.0–159.4)	158.3 (155.4–161.2)	157.0 (154.0–160.0)
	24	166.3 (163.1–169.4)	157.9 (154.9–160.9)	169.2 (166.1–172.3)
	48	169.8 (166.4–173.2)	159.5 (156.5–162.4)	172.3 (168.9–175.6)
	96	172.3 (169.0–175.6)	163.4 (160.3–166.4)	172.4 (169.0–175.8)
Fasting HDL-C, mg/dL	0	38.8 (37.8–39.8)	39.5 (38.3–40.6)	40.4 (39.2–41.5)
	24	43.4 (42.2–44.6)	43.9 (42.7–45.0)	44.4 (43.1–45.7)
	48	45.1 (43.8–46.5)	44.5 (43.3–45.7)	45.9 (44.6–47.1)
	96	45.2 (43.9–46.5)	45.4 (44.2–46.7)	45.6 (44.2–47.0)
Fasting triglycerides, mg/dL	0	123.8 (117.2–130.4)	123.4 (116.9–129.9)	124.3 (117.1–131.5)
	24	140.3 (133.0–147.6)	109.3 (103.4–115.2)	137.3 (129.7–144.9)
	48	139.7 (132.1–147.4)	115.3 (108.8–121.9)	139.5 (131.3–147.6)
	96	140.9 (133.0–148.8)	116.3 (109.6–122.9)	141.1 (131.1–151.1)
Fasting non-HDL-C, mg/dL	0	117.9 (115.4–120.4)	118.8 (116.2–121.5)	116.6 (113.9–119.3)
	24	122.9 (119.9–126.0)	114.0 (111.1–116.9)	124.8 (121.8–127.9)
	48	124.6 (121.4–127.9)	115.0 (112.1–117.8)	126.5 (123.2–129.7)
	96	127.1 (123.9–130.3)	118.0 (114.9–121.0)	126.9 (123.6–130.1)
Fasting calculated LDL, mg/dL	0	93.7 (91.4–96.0)	94.9 (92.4–97.5)	93.0 (90.5–95.4)
	24	95.4 (92.8–98.1)	92.2 (89.7–94.7)	98.0 (95.3–100.6)
	48	97.4 (94.5–100.2)	92.0 (89.6–94.3)	99.1 (96.3–101.9)
	96	99.4 (96.5–102.3)	95.1 (92.5–97.7)	99.9 (97.1–102.7)
Fasting plasma glucose, mg/dL	0	88.0 (86.2–89.8)	87.4 (85.6–89.2)	85.6 (84.0–87.1)
	24	90.3 (88.1–92.5)	89.2 (87.4–91.0)	88.9 (87.0–90.9)
	48	89.5 (87.9–91.2)	89.0 (86.8–91.3)	87.0 (85.6–88.5)
	96	90.2 (88.3–92.2)	88.6 (87.0–90.3)	88.9 (86.9–90.9)
Waist:height ratio, cm:cm	0	0.53 (.52–.53)	0.53 (.52–.53)	0.52 (.51–.53)
	24	0.54 (.53–.54)	0.54 (.53–.54)	0.53 (.52–.53)
	48	0.54 (.53–.55)	0.54 (.54–.55)	0.53 (.52–.54)
	96	0.55 (.54–.55)	0.55 (.54–.56)	0.53 (.52–.54)

Abbreviations: ATV/r, ritonavir-boosted atazanavir; CI, confidence interval; DRV/r, ritonavir-boosted darunavir; HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; RAL, raltegravir.

and anthropometric changes between treatment regimens. As expected based on prior small studies, we found increases in fasting lipid measures including TC, TG, non-HDL-C, and LDL-C following therapy with the two ritonavir-boosted PI arms but not with the raltegravir arm. These lipid changes were similar at every study evaluation point between the two ritonavir-boosted PI arms, confirming previously reported equivalence in the lipid effects of these two widely used PI regimens in clinical practice [16]. Of note, the mean HDL-C level was low in the majority of participants at entry, as expected for ART-naive subjects [17]. However, small increases were observed for this lipid measure in all 3 arms with no apparent differences between arms, also consistent with prior data suggesting that initiation of ART modestly improves HDL-C levels [17].

Metabolic syndrome is a term that describes a cluster of clinical, anthropometric, and laboratory measures that confer heightened risk of cardiovascular disease and type 2 diabetes [18]. There

is a relatively high prevalence of metabolic disorders among HIV-infected individuals [19], which has been attributed to lipid abnormalities, particularly high plasma TG and low HDL-C commonly seen in untreated HIV disease [20], and to antiretroviral-induced metabolic and body shape changes [21, 22]. At baseline, the fasting lipid profile was below NCEP lipid thresholds for individuals with one or more cardiovascular risk factors for a large proportion of participants, fasting blood glucose levels were <100 mg/dL in 89%, and the use of hypoglycemic agents was modest. The presence of pretherapy metabolic syndrome was high (21%), and similar to that previously reported for HIV-infected individuals [23, 24]. In contrast to the general population, among whom metabolic syndrome is primarily driven by hypertension, hyperglycemia, and abdominal obesity [25], baseline metabolic syndrome in this study was driven largely by a combination of low plasma HDL-C levels and hypertriglyceridemia—two lipid parameters directly affected by HIV infection [17].

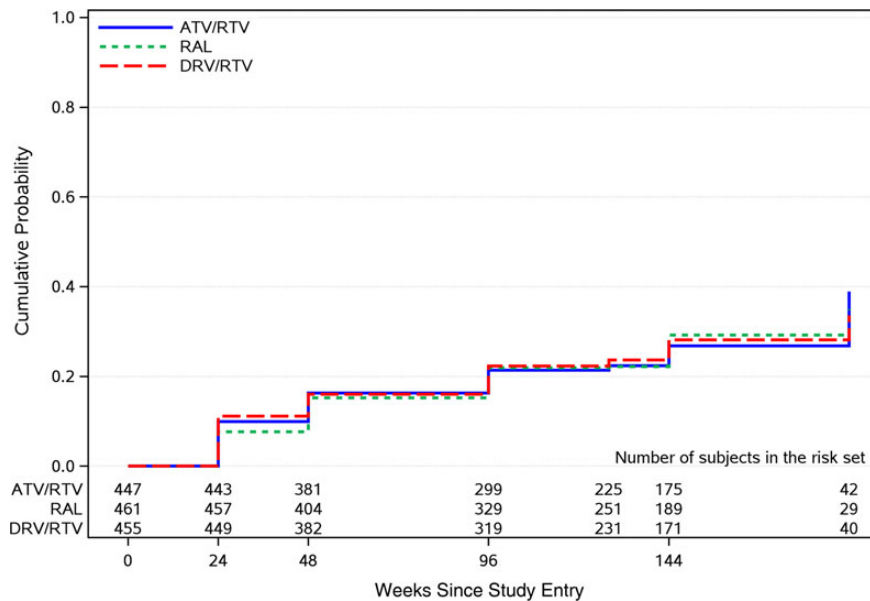


Figure 2. Cumulative probability of metabolic syndrome, by treatment group. A total of 1363 subjects were included in this analysis; 381 subjects who had metabolic syndrome at baseline and 53 subjects who were censored at baseline were excluded. Abbreviations: ATV/RTV, ritonavir-boosted atazanavir; DRV/RTV, ritonavir-boosted darunavir; RAL, raltegravir.

During the study, the cumulative probability of developing new metabolic syndrome was high (approximately 22% at 96 weeks). However, contrary to expectation due to the known effects of ritonavir-boosted PI regimens on lipids, no differences between the study arms were apparent. The greater increase in waist circumference observed with the raltegravir-based therapy

counterbalanced the contribution of higher TG levels in the PI arms, accounting for the comparable cumulative probability of metabolic syndrome in all three treatment arms. This notwithstanding, the high rate of metabolic syndrome at baseline and following ART in this population should raise some concern, as individuals with metabolic syndrome are susceptible to a

Table 3. Linear Regression Estimates Evaluating the Association Between Plasma Ritonavir Trough Concentrations and Changes in Lipid Parameters Over 48 and 96 Weeks

Parameter	LDL		TG		Non-HDL	
	Estimate (95% CI)	P Value	Estimate (95% CI)	P Value	Estimate (95% CI)	P Value
Associations with change to week 48, mg/dL						
Intercept	3.78 (−0.02 to 7.57)	. . .	15.85 (5.17–26.52)	. . .	8.21 (4.10–12.31)	. . .
RTV C ₂₄ (per 1 log [ng/mL]) ^a	0.51 (−1.58 to 2.61)	.63	1.71 (−4.25 to 7.68)	.57	0.99 (−1.30 to 3.28)	.40
Test for PI-specific association (2 df)	P = .09		P = .23		P = .10	
Associations with change to week 96, mg/dL						
Intercept	4.23 (0.30–8.16)	. . .	17.45 (6.18–28.73)	. . .	8.87 (4.54–13.20)	. . .
RTV C ₂₄ (per 1 log [ng/mL]) ^a	−0.15 (−2.28 to 1.99)	.89	−0.14 (−6.36 to 6.08)	.97	−0.25 (−2.63 to 2.14)	.84
Test for PI-specific association (2 df)	P = .53		P = .35		P = .22	

Estimates (mg/dL) are from simple linear regression analysis of RTV C₂₄ on change from baseline to the given week for each lipid parameter. RTV C₂₄ values (on the natural log scale) were centered on the group mean for modeling, so the intercept estimate represents the average lipid change from baseline for an average (geometric mean) RTV C₂₄ of approximately 55 ng/mL. The test for a PI-specific association is a 2-df F test for nonzero treatment group main (intercept) and interaction (RTV C₂₄ × treatment) coefficients.

Abbreviations: C₂₄, plasma trough concentration; CI, confidence interval; df, degrees of freedom; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PI, protease inhibitor; RTV, ritonavir; TG, triglycerides.

^a Estimate represents the estimated difference in the lipid change from baseline to given week for each 1-log (natural) difference in RTV C₂₄; note that 1 log is approximately the difference between the first and third quartiles of observed RTV C₂₄ in the A5257 study.

variety of conditions including cardiovascular diseases, type 2 diabetes, certain malignancies, polycystic ovarian syndrome, and reactive airway disease [26–28].

The lipid changes experienced with ritonavir-boosted PI therapy are speculated to be driven to a larger extent by the ritonavir component of the regimens. In the TMC114-C159 trial [29], ritonavir-boosted atazanavir increased the plasma exposure of ritonavir, whereas ritonavir-boosted darunavir had an opposite effect. That healthy volunteer study with only 28 days' duration could not evaluate the metabolic consequences of this differential ritonavir systemic exposure. The present study provided an opportunity to rigorously evaluate this question. Steady-state ritonavir trough concentrations in our study population were comparable to previous reports for the tablet formulation [30], and were not different between the ritonavir-boosted atazanavir and darunavir regimens. Associations between ritonavir exposure and lipid changes over 48 and 96 weeks were also not apparent (both overall and within specific PI regimens). Several reasons may account for the differences between our findings and the TMC114-C159 trial, including the larger size of our study population, which may have limited the confounding effect of intrasubject variability in drug concentrations; the use of HIV-infected rather than healthy volunteers; and the longer study follow-up time points at which lipid sampling was performed in the current study. It should also be noted that it is possible that ritonavir exposure may affect other metabolic outcomes other than plasma lipids, although the scant published literature to date does not support an association between ritonavir concentration and changes in anthropometric measurements [31].

The diversity of the study population with relatively high proportions of women and participants of ethnic minority backgrounds, which closely mirrors the demography of the HIV/AIDS epidemic in many parts of the United States, makes these findings of the current analyses generalizable to clinical practice. Furthermore, the pharmacokinetic/pharmacodynamic analysis included a robust sample of >200 ritonavir C₂₄ samples collected within a specific time interval. This robust sample size is large enough to militate against the confounding effect of intrasubject variability in plasma antiretroviral concentrations that have limited the interpretation of previous smaller studies. In addition, this study captured data from baseline to week 144, allowing a longer assessment of changes in metabolic measures relative to other studies. Self-reported adherence to ART and nonobservance of ritonavir administration prior to pharmacokinetic sampling limits nearly all studies of this type. Fasting plasma lipid fractions were limited only to TC, TG, non-HDL-C, LDL-C, and HDL-C. Typically, dual-energy X-ray absorptiometry (DEXA) data are used to assess changes in body fat composition with therapy. However, DEXA scans were not obtained in the general study participants, but were obtained on a subset of participants and will be reported separately.

In this large, randomized prospective trial, raltegravir produced the most favorable lipid profile compared with 2 ritonavir-boosted PIs. Metabolic syndrome rates at baseline were high, and the cumulative probability of developing new metabolic syndrome post-ART was similar across all arms. Ritonavir C₂₄ was not different between the 2 ritonavir-boosted PIs arms, and had no relationship with the modest but similar increases in plasma lipids observed with either the ritonavir-boosted atazanavir-based or ritonavir-boosted darunavir-based regimen. The long-term clinical significance of the lipid changes noted with the two ritonavir-boosted PI regimens relative to the raltegravir-based regimen deserves further evaluation, particularly when initiating ART in patients with high cardiovascular risk profiles.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (<http://cid.oxfordjournals.org>). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Disclaimer. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Allergy and Infectious Diseases (NIAID) or the National Institutes of Health.

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APPENDIX

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