Poster
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Darunavir or Atazanavir vs Raltegravir Lipid Changes are unlinked to Ritonavir Exposure: ACTG 5257

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ABSTRACT

- **Background**: Lipid profiles following antiretroviral therapy (ART) vary by regimen type and by ritonavir (RTV) exposure. Changes in fasting lipid profile (FLP) were assessed after ART initiation in all treatment arms in the A5257 study and correlated with plasma RTV trough concentrations (C_{24}) in the two RTV boosted protease inhibitors (PI) arms.
- **Methods**: ART-naïve individuals ≥ age 18 years with HIV-1 RNA level > 1000 copies/mL were eligible. Subjects were randomized 1:1:1 to ATV (atazanavir 300 mg daily (QD) + RTV 100 mg QD), RAL (raltegravir 400mg twice daily) or DRV (darunavir 800mg QD + RTV 100 mg QD); all subjects received emtricitabine/tenofovir (FTC/TDF) 200/300 mg QD. Subjects were followed until the last enrolled reached 96 weeks. FLP was measured at weeks 0, 24, 48, 96, and 144, and steady state RTV C24 (24 ± 2 hours post dose) was measured once for a subset of subjects on RTV tablet. Mean changes in FLP over time from baseline were plotted with 95% confidence intervals (CI), differences between ART regimens were estimated with 97.5% CI and compared using pairwise Student's T-tests. Associations between RTV C_{24} and changes in FLP at 48 weeks were evaluated via Spearman correlations.
- **Results:** A total of 1809 subjects were enrolled; 34% non-Hispanic white, 42% non-Hispanic black, 22% Hispanic (regardless of race). 24% were women. Subjects with confirmed baseline fasting samples were included in the analyses (n=1797). Baseline overall median total cholesterol (TC) 154 mg/dL, HDL-cholesterol (HDL-C) 38 mg/dL, triglycerides (TG) 103 mg/dL, and calculated LDL-cholesterol (LDL-C) 92 mg/dL. TC, TG and LDL-C levels increased with ATV and DRV but not with RAL from baseline to week 144 (Fig 1). While these 3 lipid parameters were not different between ATV and DRV, each PI arm had greater increases in these parameters compared with the RAL arm (all p≤ 0.001). HDL-C increased modestly with no differences between arms (all p>0.05) [Fig 1 c]. As-treated and sensitivity analyses excluding subjects on lipid-lowering agents did not change results. RTV C_{24} was quantified in a subset (109 on ATV and 121 on DRV) with median values of 69 ng/mL and 74 ng/mL in the ATV and DRV arms, respectively (p>0.9). No significant correlation existed between RTV C_{24} and changes in any of the lipid parameters (p>0.1) (Table 3).
- **Conclusion:** The RAL arm produced the most favorable lipid profile. RTV C_{24} was not different between the 2 PI arms and had no relationship with the modest but similar increases in lipids observed with either the ATV or the DRV arm. The long-term clinical significance of the lipid changes noted in the PI arms relative to the RAL arm are unknown.

BACKGROUND

- A5257 trial evaluated the virologic efficacy and tolerability of RAL and 2 RTV boosted PIs (ATV and DRV) co-administered with FTC/TDF in treatment naïve HIV-infected individuals.
- HIV-1 PIs are associated with dyslipidemia and other metabolic disorders, however the contribution of RTV boosting is unclear as higher RTV exposure has been previously correlated with greater elevation in lipids
- RTV is a substrate of cytochrome (CYP) 3A and to a lesser extent CYP2D6. The activities of the CYP isoenzymes are variably influenced by the PIs. The *K_i-value*, a measure of the affinity constant of inhibitor-enzyme complex, has been shown to vary among the PIs for the CYP3A isoenzyme.
- Thus, the plasma concentrations of RTV vary depending on the co-administered PI and as such the differential effect of co-administered PI on RTV plasma levels could impact the overall safety profile and the metabolic effect of a boosted PI-regimen.
  - In the TMC114-C159 trial for example, ATV was shown to increase the plasma exposure of RTV; DRV on the other hand had the opposite effect. Nevertheless, this healthy volunteer study, with follow-up of only 28 days, failed to demonstrate clinically relevant metabolic consequences of this differential plasma RTV exposure.

OBJECTIVES

- The primary metabolic objectives of the A5257 study were to examine in ART naïve HIV-infected subjects
  - A. Changes overtime (baseline to week 144) in fasting lipid levels in all 3 arms of the study.
  - B. Quantify the impact of RTV exposure on changes in fasting lipid profile in the 2 PI arms.

METHODS

- **Study Design**: A5257 was a phase III, prospective, randomized, open-label trial comparing 3 non-nucleoside reverse transcriptase inhibitor (NNRTI)-sparing ART regimens. Subjects were randomized 1:1:1 to ATV 300 mg QD + RTV 100 mg QD, RAL 400mg twice daily or DRV 800mg QD + RTV 100 mg QD; all subjects received FTC/TDF 200/300 mg QD.
- **Sample Size:** A5257 enrolled 1809 subjects for the co-primary efficacy and tolerability endpoints. The main metabolic objective was to detect an association between RTV C_{24} at steady state and 48 week changes in fasting TG. The target n = 258 subjects randomized to each of the boosted PI arms was determined to provide 90% power to detect a 1.4 SD difference in change in fasting TG for a 30% lower RTV C_{24}.
- **Blood Sampling**: All A5257 subjects were followed until the last enrolled subject reached 96 weeks. Per protocol, fasting metabolic outcomes of interest were assessed at weeks 0, 24, 48, 96, and 144, and steady state RTV C_{24} (24 ± 2 hours post dose) was measured once for a subset of subjects on RTV tablet.
- **Selected Inclusion Criteria**: ART-naïve individuals ≥ age 18 years; HIV-1 RNA level > 1000 copies/mL; no CD4 cell count restriction, absence of major nucleoside (tide) reverse transcriptase (NRTI) or PI resistance mutations. The first 258 subjects with steady state RTV C_{24} measured 4-8 weeks after initiation of RTV in tablet form were included in the PK-PD analysis.
- **Statistical Considerations**: Mean changes in fasting lipid profile over time from baseline were plotted with 95% confidence intervals (CI), differences between ART regimens were estimated with 97.5% CI and compared using pairwise Student's T-tests. Associations between RTV C_{24} and changes in fasting lipid profile at 48 weeks were evaluated via Spearman correlations.

RESULTS

- Of the 1809 subjects enrolled in A5257, 1797 with confirmed baseline fasting samples were included in the metabolic analyses. Baseline demographic characteristics and metabolic profile were similar across arms and are summarized in Table 1.
- At baseline, 57% of subjects had the National Cholesterol Education Program (NCEP) target TC < 160 mg/dL and 43% had HDL-C ≥ 40 mg/dL, 75% had TG < 150 mg/dL, and 90% had calculated LDL < 130 mg/dL (Table 1).
- At study entry, 106 subjects (6%) were taking lipid lowering agents, but this proportion rose over time at similar rates for all 3 arms; from 5% to 11% in the ATV/RTV arm, 6% to 9% in the RAL arm, and 6% to 14% in the DRV/RTV arm (baseline to week 96).
- Fasting TC, TG, and LDL-C levels increased with ATV and DRV but not with RAL from baseline to week 144 (Table 2 and Figure 1). While these 3 fasting lipid parameters were not different between ATV and DRV, each PI arm had greater increases in these parameters compared with the RAL arm (all p≤ 0.001). HDL-C increased modestly in all arms (an average increase of 6 mg/dL over 96 weeks) with no differences between arms (all p>0.06) [Figure 1 B]. As-treated and sensitivity analyses excluding subjects on lipid-lowering agents did not change results (data not shown).
- RTV C_{24} was quantified in a subset (109 on ATV and 121 on DRV) with median values of 69 ng/mL and 74 ng/mL in the ATV and DRV arms, respectively (p>0.9). No significant correlation existed between RTV C_{24} and changes in any of the lipid parameters (p>0.1) at week 48 (Figure 2 and Table 3).

Table 1. Baseline Demographic Characteristics and Metabolic Parameters Among Fasted Subjects

Characteristics		Total (n=1797)	ATV/RTV (n=602)	RAL (n=600)	DRV/RTV (n=595)
Sex	Female	**432 (24%)**	143 (24%)	146 (24%)	143 (24%)
Age	Mean (SD)	**37 (11)**	38 (11)	37 (11)	38 (11)
Race/Ethnicity	White	**612 (34%)**	212 (35%)	212 (35%)	188 (32%)
	Black	**753 (42%)**	250 (42%)	253 (42%)	250 (42%)
	Hispanic	**385 (21%)**	124 (21%)	115 (19%)	146 (25%)
	Others	**47 (3%)**	16 (3%)	20 (3%)	11 (2%)
Fasting TC (mg/dL)	median (Q1, Q3)	**154 (133, 178)**	154 (134, 176)	155 (134, 181)	154 (133, 179)
	< 160 mg/dL	**57%**	57%	57%	57%
Fasting HDL-C (mg/dL)	median (Q1, Q3)	**38 (31, 46)**	37 (30, 45)	38 (31, 46)	38 (31, 47)
	≥ 40 mg/dL	**43%**	41%	46%	43%
Fasting TG (mg/dL)	median (Q1, Q3)	**103 (73, 148)**	105 (74, 150)	103 (73, 146)	99 (73, 148)
	< 150 mg/dL	**75%**	75%	76%	75%
Fasting calc LDL-C (mg/dL)**	median (Q1, Q3)	**92 (74, 112)**	93 (75, 111)	93 (74, 115)	89 (73, 111)
	< 130 mg/dL	**90%**	90%	87%	90%
On lipid lowering treatment	n (%)	**106 (6%)**	33 (5%)	35 (6%)	38 (6%)

** Calculated as fasting calc LDL-C (mg/dL) = fasing TC - fasing HDL-C - (fasting TG/5).
Only for subjects with fasting TG ≤ 400 mg/dL; subjects with fasting TG > 400 mg/dL were excluded.

Table 2. Treatment Differences in the Mean Changes from Baseline in Metabolic Parameters

Study Week	Metabolic Parameters	ATV/RTV vs. RAL Mean Difference (97.5% CI)	ATV/RTV vs. RAL P-value**	DRV/RTV vs. RAL Mean Difference (97.5% CI)	DRV/RTV vs. RAL P-value**	ATV/RTV vs. DRV/RTV Mean Difference (97.5% CI)	ATV/RTV vs. DRV/RTV P-value**
24	Fasting TC (mg/dL)	11 (7, 15)	<0.001	13 (9, 17)	<0.001	-2 (-6, 2)	0.21
	Fasting HDL-C (mg/dL)	0 (-1, 2)	0.55	0 (-2, 1)	0.61	1 (-1 2)	0.25
	Fasting TG (mg/dL)	32 (22, 42)	<0.001	27 (16, 38)	<0.001	5 (-7, 16)	0.36
	Fasting LDL-C (mg/dL)	5 (2, 8)	0.001	8 (5, 11)	<0.001	-3 (-7, 0)	0.05
48	Fasting TC (mg/dL)	12 (8, 17)	<0.001	14 (10, 19)	<0.001	-2 (-6, 3)	0.42
	Fasting HDL-C (mg/dL)	1 (0, 3)	0.07	0 (-1, 2)	0.72	1 (-1, 3)	0.13
	Fasting TG (mg/dL)	27 (17, 37)	<0.001	25 (13, 36)	<0.001	2 (-10, 13)	0.70
	Fasting LDL-C (mg/dL)	7 (3, 11)	<0.001	9 (6, 13)	<0.001	-2 (-6, 1)	0.16
96	Fasting TC (mg/dL)	12 (8, 17)	<0.001	11 (6,15)	<0.001	2 (-3, 7)	0.39
	Fasting HDL-C (mg/dL)	1 (-1, 3)	0.29	-1 (-2, 1)	0.46	1 (0, 3)	0.06
	Fasting TG (mg/dL)	28 (17, 40)	<0.001	24 (11, 38)	<0.001	4 (-9, 17)	0.53
	Fasting LDL-C (mg/dL)	7 (3, 11)	<0.001	7 (3,11)	<0.001	0 (-4, 4)	0.88

**P-values was reported from Student's test

Figure 1. Mean of changes from Baseline in Fasting Lipid Profile (mg/dL) Over Time with 95% CI

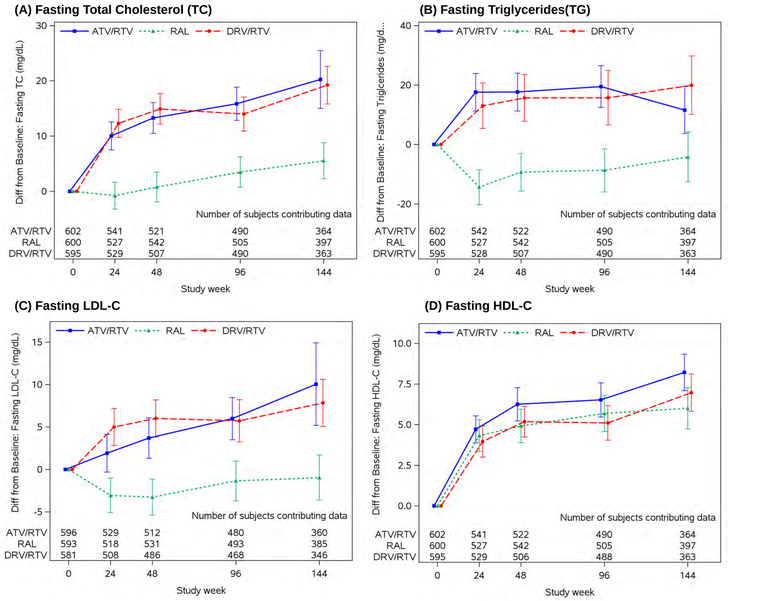
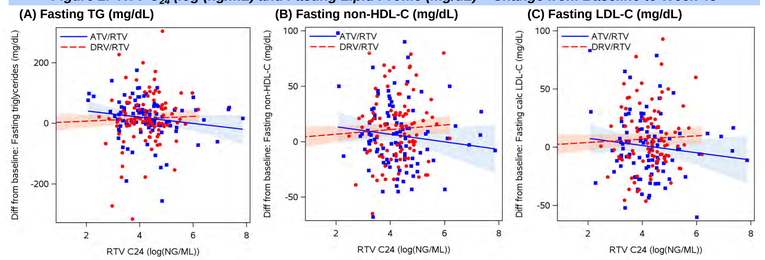


Figure 2. RTV C_{24} (log (ng/mL) and Fasting Lipid Profile (mg/dL) – Change from Baseline to Week 48



- Shaded area indicates 95% confidence interval of the regression line
- Individuals with 0 AUC were imputed to 0.001 for log scale

Table 3. RTV C_{24} (log (ng/mL)) and Fasting Lipids: Change from Baseline to Week 48

	Fasting TG (mg/dL) SRCC*	Fasting TG (mg/dL) Estimate (95% CI)**	Fasting TG (mg/dL) P-value**	Fasting non-HDL-C (mg/dL) SRCC*	Fasting non-HDL-C (mg/dL) Estimate (95% CI)**	Fasting non-HDL-C (mg/dL) P-value**	Fasting LDL-C (mg/dL) SRCC*	Fasting LDL-C (mg/dL) Estimate (95% CI)**	Fasting LDL-C (mg/dL) P-value**
Overall	**-0.02**	**0.60 (-1.50, 2.70)**	**0.57**	**-0.001**	**0.35 (-0.46, 1.15)**	**0.40**	**0.001**	**0.18 (-0.56, 0.92)**	**0.63**
ATV/RTV	-0.21	-3.61 (-8.13, 0.90)	0.12	-0.12	-1.19 (-3.25, 0.86)	0.25	-0.07	-1.09 (-2.97, 0.80)	0.26
DRV/RTV	0.13	1.38 (-1.22, 3.97)	0.30	0.12	0.72 (-0.15, 1.60)	0.10	0.07	-0.50 (-0.31, 1.30)	0.22

* SRCC: Spearman Rank Correlation Coefficient
** Estimate (95% CI) (per 70% AUC of RAL) and p-value of regression line

SUMMARY

- With the exception of HDL-C levels, at study entry the majority of this ART naïve HIV-infected study population had a relatively favorable fasting lipid profile as gauged by the NCEP lipids thresholds.
- Following ART initiation, fasting TG, non-HDL-C, and calculated LDL-C increased in the 2 RTV boosted PI arms, and decreased or remained stable in the RAL arm.
  - All pairwise comparisons between the ATV/RTV or DRV/RTV arm and the RAL arm showed greater increases with ATV/RTV or DRV/RTV treatment compared to RAL; no differences between ATV/RTV and DRV/RTV treatment were apparent.
  - As-treated and sensitivity analyses excluding subjects on lipid-lowering agents did not change results.
- Fasting TC increased in all treatment groups although this increase was smaller with RAL than with ATV/RTV or DRV/RTV.
- Fasting HDL-C increased across all treatment groups over time (an average increase of 6 mg/dL over 96 weeks) with no apparent differences between the groups.
- RTV plasma exposure were similar between the 2 boosted PI arms with no evidence of a difference between treatment arms in RTV C_{24}.
- There were no apparent association between RTV exposure as measured by plasma RTV C_{24} and changes in TG, non-HDL-C, and calculated LDL-C through week 48 and week 96 were apparent.

CONCLUSIONS

In the A5257 trial, RAL produced the most favorable lipid profile. RTV C_{24} was not different between the 2 RTV boosted PIs and had no relationship with the modest but similar increases in lipids observed with either ATV or DRV. The long-term clinical significance of the lipid changes noted with the two RTV boosted PIs relative to RAL are unknown.

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