Continuation of BID boosted PI vs switch to once-daily ATV/RTV for the management of lipodystrophy: 48-week primary analysis of the 96-week multicenter, open-label, randomized, prospective REAL Study

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BACKGROUND

- Atazanavir (ATV) is a potent, well-tolerated, once-daily, HIV-1 protease inhibitor (PI) that has been extensively studied in naïve and experienced patients with HIV. Previous studies in treatment-experienced patients have shown that the atazanavir/ritonavir (ATV/RTV) combination provided similar efficacy on viral suppression as the fixed-dose combination of lopinivir/ritonavir (LPV/RTV).[1,2] These studies have also revealed that the ATV/RTV combination is associated with reduced levels of dyslipidemia compared with LPV/RTV
- The **RE**search into **A**tazanavir in **L**ipodystrophy (REAL) trial is a randomized parallel group study designed to assess the impact of switching from any BID boosted PI-containing HAART regimen (PI/RTV) to a QD ATV/RTV-containing highly active antiretroviral therapy (HAART) regimen on body fat distribution in patients with HIV-1 infection and established (abdominal) lipohypertrophy
- Here we present the primary outcome measure of the study, plus interim secondary outcomes based on analysis of data at Week 48

METHODS

Study population

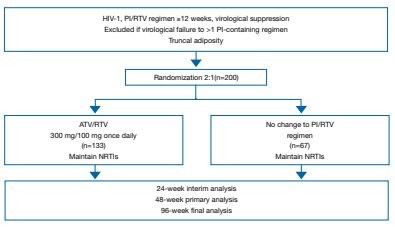
- HIV-1 infected individuals aged 18 years or older who had received a HAART regimen containing 2 NRTIs and a boosted PI for at least 12 weeks immediately prior to screening
- Patient selection criteria:
  - Controlled virologic response (HIV RNA level <400 copies/mL by Roche Amplicor Ultrasensitive assay) at screening
  - Virologic stability maintained for at least 6 months
  - No confirmed virologic failure to more than one prior PI-containing regimen
  - Not receiving a non-nucleoside reverse transcriptase inhibitor (NNRTI) at study entry
  - Fat redistribution confirmed on physical examination and defined by the presence of lipohypertrophy with or without lipoatrophy. Lipohypertrophy was defined as a waist/hip ratio >0.90 (either sex) and a waist circumference >88.2 cm (men) or >75.3 cm (women)

Treatment

- Patients randomized to the ATV/RTV arm received atazanavir 300 mg once daily and ritonavir 100 mg once daily for up to 96 weeks, and continued treatment with the same two NRTIs as at entry. Patients randomized to the PI/RTV arm continued their previous HAART regimen (boosted PI plus two NRTIs) unchanged (Figure 1)
- The NRTI components of treatment remained unchanged throughout the 96-week study period, unless necessitated due to poor tolerability or toxicity

Figure 1

Study Design



Study procedures

- Dual energy X-ray absorptiometry (DEXA) scans and computed tomography (CT) scans were performed in individual study centers at baseline and at Weeks 24, 48 and 96. Results were assessed at a centralized reading center
- All other study measures were assessed at baseline, Weeks 4 and 12, and every 12 weeks thereafter up to Week 96
- Blood samples were taken under fasting conditions for determination of biochemical parameters of fat distribution, metabolic status and HIV status. All determinations were made at a central laboratory

Assessments

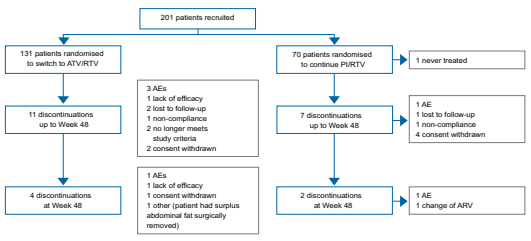
- Change from baseline in trunk-to-limb fat ratio measured by DEXA (primary endpoint)
- Change from baseline in trunk, limb and total body fat by DEXA
- Change from baseline in visceral, subcutaneous, and total adipose tissue (VAT, SAT, and TAT) and in VAT-to-SAT and VAT-to-TAT ratios measured by CT scan
- Changes from baseline in fasting lipid parameters, body weight, body mass index, waist/hip ratio and waist circumference
- Maintenance of virologic control
- Safety and tolerability of treatment

RESULTS

- Patients were recruited from 38 centers in Europe (28), Mexico (3), Canada (1), and USA (6)
- A total of 201 patients were randomized (200 treated, 131 ATV/RTV, 69 PI/RTV). Patient disposition is summarized in Figure 2

Figure 2

Patient Disposition and Flow in the Study



- Demographic characteristics were balanced between treatment regimens (Table 1). Across regimens, most subjects were male (76%) and white (63%); the median age was 43 years
- Anti-HIV drug exposure before screening was comparable between treatment groups for PIs, NRTIs and NNRTIs. The proportion of subjects having stavudine in their regimen at randomization was 9% in the ATV/RTV arm and 13% in the PI/RTV arm. Prior exposure to stavudine was similar between treatment groups
- Baseline HIV characteristics were consistent with controlled virologic suppression as required by study entry criteria. The median CD4+ cell count was comparable between treatment regimens (470 vs 437 cells/mm³ for the ATV/RTV and PI/RTV groups, respectively)
- Baseline central adiposity and physical measurements (Table 1) were comparable between treatment regimens. Fasting lipids and glucose parameters were also comparable between the two regimens at baseline

Table 1

Demographics and Baseline Characteristics of Treated Patients

	Treatment Regimen		
	ATV/RTV n=131	PI/RTV n=69	Total n=200
Age: median (min, max)	43 (23, 79)	42 (25, 65)	43 (23, 79)
Gender: Male n (%)	96 (73%)	55 (80%)	151 (76%)
Race:			
White n (%)	83 (63%)	43 (62%)	126 (63%)
Mestizo n (%)	31 (24%)	15 (22%)	46 (23%)
Black/African American n (%)	15 (11%)	10 (14%)	25 (13%)
American Indian/Alaska Native n (%)	1 (<1%)	0	1 (<1%)
Latino n (%)	1 (<1%)	0	1 (<1%)
Hispanic n (%)	0	1 (1%)	1 (<1%)
Region:			
Europe n (%)	77 (59%)	39 (57%)	116 (58%)
North America n (%)	54 (41%)	30 (43%)	84 (42%)
AIDS: n (%)	14 (11%)	9 (13%)	23 (12%)
Baseline HIV RNA <400 copies/mL: n (%)	97%	100%	98%
Baseline CD4 (cells/mm³): median (min, max)	470 (90, 1,919)	437 (100, 1,078)	459 (90, 1,919)
Waist (cm): median	94	95	94
BMI (kg/m²): median	25.9	25.7	25.9
Waist/hip ratio: median (min, max)	0.99 (0.78, 1.23)	0.97 (0.90, 1.18)	0.98 (0.78, 1.23)
Weeks on prior PI therapy: mean (se)	206.0 (11.62)	202.6 (15.3)	204.8 (9.24)
Weeks on prior NRTI/NtRTI: mean (se)	285.2 (17.79)	251.8 (20.33)	273.7 (13.61)
Prior use of stavudine: n (%)	54 (41)	33 (48)	87(44)
NRTI regimen including stavudine at randomization: n (%)	12 (9)	9 (13)	22 (11)
Weeks on prior NNRTI: mean (se)	101.5 (13.7)	97.1 (15.8)	99.8 (10.3)

- Mean time on study therapy was 50 weeks for ATV/RTV and 49.1 weeks on PI/RTV
- In the PI/RTV arm, lopinavir was the most frequently given PI (72%); followed by saquinavir (10%); indinavir (8.7%); fosamprenavir (8.7%); and amprenavir (1.4%)

Fat distribution

- At Week 48 there was no statistically significant difference between regimens in the mean changes from baseline in trunk-to-limb fat ratio (primary endpoint, Table 2), which were +0.02 in the ATV/RTV group (n=112) and -0.02 in the PI/RTV group (n=54); difference in mean changes +0.03 (95% CI; -0.06, 0.12; *P*=0.48)

Table 2

Body Fat Changes from Baseline at Week 48 a) Assessed by DEXA; b) Assessed by CT

	ATV/RTV		PI/RTV		Difference Estimate (95% CIs) ATV/RTV - PI/RTV	*P* value
	n	Mean Change	n	Mean Change		
a) Fat distribution (DEXA)						
Trunk fat	112	2.6%	57	1.8%	4.4% (-1.4%, 10.6%)	0.14
Limb fat	112	0.9%	54	-3.6%	4.6% (-1.7%, 11.4%)	0.15
Total body fat	112	2.1%	54	-2.2%	5.0% (0.3%, 9.7%)	0.0385
Trunk/limb fat ratio	**112**	**0.02**	**54**	**-0.02**	**0.03 (-0.06, 0.12)**	**0.48**
b) Adipose tissue (CT)						
Visceral (VAT)	108	4.6%	59	-0.5%	5.2% (-3.9%, 15.1%)	0.27
Subcutaneous (SAT)	108	-2.1%	59	-5.9%	4.0% (-1.6%, 10.0%)	0.16
Total (TAT)	108	0%	59	-3.5%	3.6% (-1.8%, 9.4%)	0.19
VAT/TAT ratio	**108**	**0.01**	**59**	**0.01**	**0.00 (-0.02, 0.02)**	**0.98**
VAT/SAT ratio	**108**	**0.04**	**59**	**0.06**	**-0.01 (-0.11, 0.09)**	**0.81**

- There was a statistically significant difference between regimens in mean percent change from baseline in total body fat (ATV/RTV +2.1% vs PI/RTV -2.2%; *P*=0.0385) (Table 2a). In the PI/RTV arm, the observed mean decrease of 2.2% in total body fat was associated with a mean 1.8% increase in trunk fat and a mean 3.6% decrease in limb fat, which suggests that the decrease in total body fat seems to be driven mainly by loss of limb fat
- Data from CT scans showed no statistically significant difference between regimens in mean change from baseline in visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), total adipose tissue (TAT), or VAT/TAT and VAT/SAT ratios (Table 2b). In the PI/RTV arm, a mean decrease of 3.5% in TAT was observed, which was associated with a mean 0.5% decrease in VAT and a mean 5.9% decrease in SAT. This finding is consistent with the observations from the DEXA analysis suggesting that fat loss occurs mainly from the limbs
- There was a statistically significant difference between regimens in mean change from baseline in weight and body mass index in favor of the PI/RTV arm but the mean changes within each arm were not clinically relevant. No significant changes in waist circumference or waist/hip ratios were found

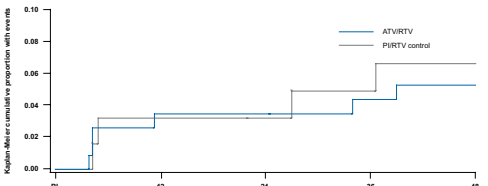
RESULTS (continued)

Viral suppression

- Switching patients from PI/RTV to ATV/RTV was not associated with any change in virologic suppression. Viral rebound rates were similar between groups. HIV RNA ≥50 copies/mL were 5% vs 6% for ATV/RTV and PI/RTV, respectively, and HIV RNA ≥400 copies/mL were 4% vs 1.4% for ATV/RTV and PI/RTV, respectively
- Figure 3 shows that Kaplan-Meier estimates of time to virologic rebound (HIV RNA ≥50 copies/mL) were also similar

Figure 3

Kaplan-Meier Estimates of Time to Virologic Rebound (LOQ ≥50 copies/mL)



Number at risk

ATV/RTV	117	109	108	106	104
PI/RTV	64	59	58	55	53

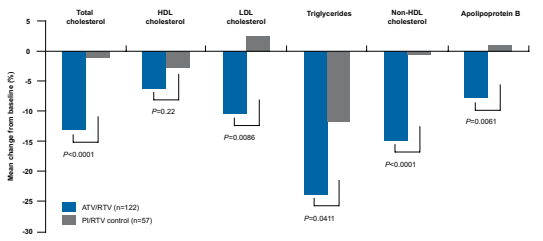
- The mean change from baseline in CD4+ cell counts at Week 48 was 14.5 cells/mm³ for the ATV/RTV regimen and 44 cells/mm³ for the PI/RTV regimen; difference estimate: -29.5, 95% CI (-75.1, 16.1); *P*=0.20

Lipid changes

- In the ATV/RTV regimen, there was a clinically significant decrease from baseline in all atherogenic lipids at Week 48 (Figure 4). There was a statistically significant difference (*P*<0.01) between regimens in mean percent change in favor of the ATV/RTV regimen in total cholesterol, LDL cholesterol, non-HDL cholesterol and apolipoprotein B

Figure 4

Percent Change from Baseline[a] in Fasting Lipid Parameters[b] at Week 48 LOCF



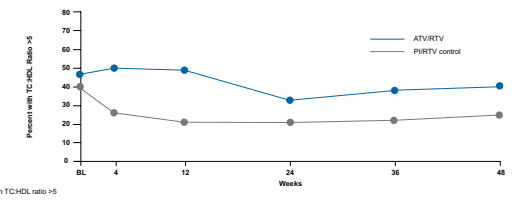
Lipid	Difference Estimate (%) ATV/RTV-PI/RTV	Confidence Intervals (%)	
Total cholesterol	-12.1	-16.3	-7.6
HDL cholesterol	-3.7	-9.4	2.4
LDL cholesterol	-12.6	-20.9	-3.4
Triglycerides	-13.7	-25.1	-0.6
Non-HDL cholesterol	-14.3	-19.4	-8.7
Apolipoprotein B	-8.6	-14.2	-2.6

[a]LOCF: mean baseline lipids (in mg/dL) for the ATV/RTV and PI/RTV regimens respectively were: total cholesterol 220, 212; HDL cholesterol 48, 47; LDL cholesterol 119, 108; triglycerides 285, 325; non-HDL cholesterol 172, 165; apolipoprotein B 97, 94.
[b]Values were excluded after changing lipid lowering therapy, if during treatment.
[c]For LDL cholesterol, n=56.
P-values were evaluated at the 0.01 significance level

- From Week 4 onwards, the proportion of subjects with total cholesterol/HDL-cholesterol ratio >5 was lower in the ATV/RTV arm compared with to the PI/RTV arm and this difference was maintained up to Week 48 (Figure 5)

Figure 5

Percent Patients with Fasting Total Cholesterol/ HDL Cholesterol Ratio >5 from Baseline (BL) to Week 48



(%) with TC:HDL ratio >5

ATV/RTV	49/123 (40)	32/121 (26)	23/108 (21)	23/110 (21)	22/101 (22)	24/95 (25)
PI/RTV	29/62 (47)	29/58 (50)	29/59 (49)	17/51 (33)	20/52 (38)	20/50 (40)

Safety

- Both treatment regimens were well tolerated. There were no deaths. Only 9% of patients discontinued prior to Week 48 and the discontinuation rate was similar between treatment regimens (8% ATV/RTV vs 10% PI/RTV)
- A summary of serious adverse events (SAEs) and frequently reported adverse events (AEs) is shown in Table 3. The frequencies of SAEs reported in the ATV/RTV and the PI/RTV regimens were comparable. AEs leading to discontinuation occurred only for 3% of patients in both regimens. AEs which led to discontinuation from ATV/RTV treatment were hyperbilirubinemia (n=3; 2%); jaundice (n=1; <1%) and Stevens-Johnson syndrome (n=1; <1%). Causes of discontinuation from the PI/RTV regimen were hypertriglyceridemia (n=1; 1%) and squamous cell carcinoma (n=1; 1%)
- Grade 3–4 total bilirubin abnormalities was reported in 53% of ATV/RTV patients but none of these patients experienced concomitant grade 3–4 transaminase elevations

Table 3

Summary of Serious Adverse Events (SAEs) and Adverse Events (AEs) of Interest

Adverse Event	ATV/RTV n=131	PI/RTV n=69
Deaths	0	0
SAEs	11 (8)	4 (6)
SAEs related to study therapy	4 (3)	0
AEs leading to discontinuation	4 (3)	2 (3)
Any AE, all grades	111 (85)	48 (70)
Most common AEs (≥5%) and AEs of interest		
Hyperbilirubinemia	39 (30)	1 (1)
Jaundice	33 (25)	0
Bronchitis	9 (7)	3 (4)
Blood bilirubin increased	10 (8)	2(3)
Headache	8 (6)	2 (3)
Gastrointestinal disorders	22 (17)	10 (14)
Diarrhea	4 (3)	4 (6)
Hypertriglyceridemia	11 (8)	13 (19)
Cough	9 (7)	4 (6)
Skin and subcutaneous tissue disorders	1 (<1)	3 (4)
Lipodystrophy acquired	1 (<1)	2 (3)
Lipoatrophy	0	1 (1)

- Overall AEs were comparable on both regimens. The most common AEs in the ATV/RTV regimen were hyperbilirubinemia (30%) and jaundice (25%). Grade 3–4 hyperbilirubinemia was reported in 26% of ATV/RTV subjects, with no concomitant increase in grade 3–4 transaminases. However, grade 3–4 jaundice was only reported in 2% of ATV/RTV subjects
- Gastrointestinal disorders were reported in 17% of ATV/RTV patients and 14% of PI/RTV patients; the rate of diarrhea was 3% in the ATV/RTV arm and 6% in the PI/RTV group. Antidiarrheal agents were taken concomitantly with study drug by 4% of the subjects in the ATV/RTV arm and 7% of subjects in the PI/RTV arm

DISCUSSION

- Persistently elevated plasma cholesterol lipids are an established risk factor for cardiovascular disease. However, there is currently a poor understanding of the duration of exposure of patients with HIV to a pro-atherogenic lipid balance needed to translate from an increased risk factor into identifiable disease. A recent study has shown that the increased risk of myocardial infarction associated with abacavir or didanosine treatment in patients with HIV was reversible within 6 months of cessation of treatment[3] and the authors concluded that the increased risk could not be explained in terms of established cardiovascular risk factors
- The relationship between plasma lipid profile and body fat redistribution is also unclear. After 48 weeks of the present study, the beneficial changes in lipid profile in patients receiving ATV/RTV did not result in statistically significant differences in distribution of body fat. However, patients in the PI/RTV group showed a slight (non-significant) loss of total fat and the fat loss appears to be mainly from limb fat/ subcutaneous tissue
- Consequently, the dynamics of body fat redistribution in patients receiving different HAART regimens remain to be fully explored. It is possible that an assessment period of 48 weeks currently reached in the REAL study is insufficient time to detect anatomical changes that reflect the changes to a more favorable blood lipid profile. Follow-up though Week 96 is planned

CONCLUSIONS

- In this 48-week analysis, a switch from BID PI/RTV to QD ATV/RTV in patients experiencing lipohypertrophy maintained virologic suppression. No statistically significant difference between regimens was observed for rates of virologic rebound ≥50 copies/mL or ≥400 copies/mL, time to virological rebound, or changes in CD4+ cell count, up to Week 48
- Both regimens were well tolerated with an AE profile consistent with the known profile of each regimen
- In the ATV/RTV regimen, there was a clinically significant decrease from baseline in all atherogenic lipids at Week 48. There was a statistically significant difference (*P*<0.01) between regimens in mean percent change in favor of the ATV/RTV regimen in total cholesterol, LDL cholesterol, non-HDL cholesterol and apolipoprotein B
- In HIV patients with lipohypertrophy (with or without lipoatrophy) at baseline, switching to ATV-based HAART from regimens based on a different PI did not lead to significant changes in fat distribution after 48 weeks of therapy

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