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AI424067: Improvement in Lipid Profiles After 12 Weeks of Switching to Atazanavir (ATV) From Boosted or Unboosted Protease Inhibitors (PIs) in Patients With No Previous PI Virologic Failure and Hyperlipidemia at Baseline

Poster # 858

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BACKGROUND

- Atazanavir is a potent, well-tolerated, once daily PI that has been extensively studied, including Phase III clinical trials of naive patients versus a standard of care regimen containing EFV and treatment experienced patients versus a standard of care regimen containing LPV/r.
- Elevated plasma lipid levels are associated with increased cardiovascular risk. The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) guidelines recommend pharmacologic intervention when fasting LDL-C values are >130 mg/dL to mitigate the risk of cardiovascular complications.
- Studies have demonstrated that ATV, RTV-boosted or not, in contrast to other currently approved PIs, does not lead to increases in total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and/or triglycerides (TG).
- DHHS Guidelines for the treatment of adults with HIV infection include switching to ATV as an option for the management of the increased cardiovascular risk likely associated with all other PIs.
- Prior exploratory studies (AI424044, AI424043) suggested that a switch to ATV led to improved lipid levels as early as 12 weeks of follow-up, and that the improvement was maintained through at least 48 weeks.
- This study was designed to examine the effect on lipid parameters of a switch to ATV 400 mg QD from another PI (boosted or not) in a virologically suppressed, treatment-experienced patient population.
- Plasma concentration of Apolipoprotein B and Lipoprotein a are strongest predictors of cardiovascular risk events. This is the first systematic evaluation of the changes associated when switching to ATV.

OBJECTIVES

Primary

- Compare the week 12 percent (%) change from baseline in fasting LDL-C between patients on an ATV-containing ARV-regimen and those remaining on a comparator PI-regimen

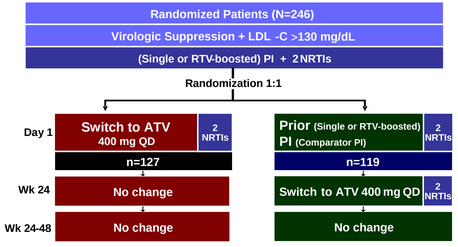
Secondary

To evaluate:

- Changes from baseline at week 12 in fasting TC, HDL cholesterol (HDL-C), fasting TG, non-HDL cholesterol, Apolipoprotein B (ApoB), Lipoprotein a (Lpa)
- Time to virologic rebound
- Changes from baseline in CD4 cell counts through week 12
- Changes from baseline in serum fasting glucose and insulin levels at week 12
- Safety and tolerability of ATV

METHODS

Figure 1. Study Design (Primary Analysis at Week 12)



- Use of tenofovir not allowed due to the pharmacokinetic (PK) interaction with ATV
- Use of lipid lowering therapy within 4 weeks of study or during the study prohibited
- Change of nucleosides prohibited

Study Patients

- HIV-1-infected men and women ≥ 16 years of age
- On stable PI-containing ARV regimen (with or without RTV-boosting) for a period ≥ 3 months
- HIV RNA <50 copies/ml at screening
- No known history of virological rebound while on PI therapy
- Fasting LDL-C > 130 mg/dl at screening

Evaluations

- Safety
  - Through week 12:
    - Mean % changes from baseline in fasting LDL-C, TC, HDL-C, non-HDL-C, ApoB, Lp(a) and TG
    - Directly measured LDL-C
    - Median and mean changes from baseline in fasting glucose and insulin
  - All observations available through week 24
    - Frequency and severity of all clinical and laboratory adverse events, and discontinuations for adverse events.
- Efficacy (through week 12)
  - Time to virological rebound (2 consecutive HIV RNA levels ≥ 400 copies/ml)
  - Hazard ratio for subjects with HIV RNA <50 copies/ml at baseline
  - Magnitude and durability of increases from baseline of CD4 cell counts in terms of time-averaged difference (TAD)
- Statistical Analyses
  - 90% power to detect a difference of ≥ 14% between the immediate and delayed switch groups in Week 12 mean % change from baseline in fasting LDL-C
  - Primary analyses included the assessment of the mean percent change from baseline in fasting LDL-C at Week 12. The ATV (immediate switch) regimen declared to be superior to the comparator PI (delayed switch) if UL 95% CI for difference < 0

Results

- Prior ARV Therapy, Study Drug Exposure, Disposition and Demography results
  - Mean time on PI, NNRTI and NRTI prior to baseline: 184, 74, and 220 weeks, respectively
  - 39% of patients were on a RTV-boosted PI-containing regimen
  - Mean time on study regimen:
    - ATV: 22 weeks
    - PI-comparator: 19 weeks
- Subject disposition (see Table 1)

RESULTS

Table 1. Subject Disposition and Demographics at Baseline

	Treatment Regimen		
	ATV	Comparator PI	Total
Randomized Subjects	**127**	**119**	**246**
Treated - N (%)	**126 (99)**	**118 (99)**	**244 (99)**
Discontinued Prior to Week 12, n (%)	5 (4)	7 (6)	12 (5)
Adverse Events	3 (2)	1 (<1)	4 (2)
Other[a]	2 (2)	6 (5)	8 (3)
Discontinued After Week 12, n (%)	4 (3)	8 (7)	12 (5)
Adverse Events	1 (<1)	0 (0)	1 (<1)
Lack of Efficacy	1 (<1)	1 (<1)	2 (<1)
Other[b]	2 (2)	7 (6)	9 (4)
Completed Study of Time of Analysis	20 (16)	15 (13)	35 (14)
Continuing on Treatment - N (%)	97 (76)	88 (74)	185 (75)
Age: Median (Min, Max)	42 (26, 78)	44 (22, 74)	43 (22, 78)
Gender : Male	80%	80%	80%
Race : White	77%	71%	74%
Hispanic/Latino	11%	14%	12%
Black/Mixed	10%	15%	13%
AIDS	34%	31%	33%
Baseline HIV RNA: Median (log_{10} c/mL) (Min, Max)	1.69 (1.69, 2.97)	1.69 (1.69, 3.84)	1.69 (1.69, 3.84)
Baseline CD4: Median (cells/mm^3) (Min, Max)	463 (110, 1987)	470 (128, 2020)	465 (110, 2020)
Weeks on Prior PI Therapy (mean (SE))	183 (9.3)	184.4 (9.7)	183.7 (6.7)
Weeks on Prior NRTI Therapy (mean (SE))	222.9 (12.1)	217.8 (12.1)	220.4 (8.6)
Weeks on Prior NNRTI Therapy (mean (SE))	79.5 (15.5)	68.8 (17.4)	74.3 (11.5)
Most Recent PI Therapy[c]:			
Any PI, n (%)	126 (100)	118 (100)	244 (100)
IDV, n (%)	47 (37)	42 (36)	89 (36)
LPV, n (%)	23 (18)	26 (22)	49 (20)
NFV, n (%)	41 (33)	39 (33)	80 (33)
RTV, n (%)	50 (40)	45 (38)	95 (39)
SQV, n (%)	14 (11)	8 (7)	22 (9)

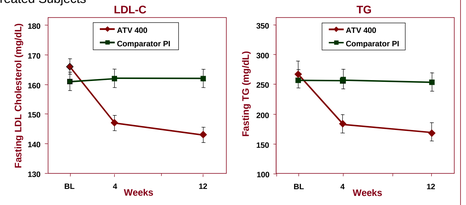
[a]Includes the following categories: lost to follow-up, noncompliance, subject no longer meets study criteria, subject withdrew consent and other.
[b]Includes boosted PIs
NOTE: Baseline demographics and subject characteristics are based on randomized subjects.

Table 2. Difference Estimates of Lipids Change from Baseline Through Week 12 – Treated Subjects[a]

	Lipids Mean Percent Change From Baseline	
	95% CI and P-Value	
	Treatment Regimen	
Lipid	ATV-Comparator PI	P-Value
Fasting LDL Cholesterol[b] (mg/dL)	**-15.0% (-19.1%, -10.8%)**	**<0.0001**
Fasting Total Cholesterol (mg/dL)	-17.4% (-20.3%, -14.4%)	<0.0001
Fasting HDL Cholesterol (mg/dL)	5.1% (-0.1%, 10.6%)	0.057
Fasting Non-HDL Cholesterol (mg/dL)	-22.1% (-25.5%, -18.5%)	<0.0001
Fasting ApoB (mg/dL)	-19.5% (-22.9%, -15.9%)	<0.0001
Fasting LP(a) (mg/dL)	-21.1% (-31.6%, -8.9%)	0.0014
Fasting Triglycerides (mg/dL)	-34.6% (-41.8%, -26.5%)	<0.0001

[a]Observed Values
[b]Primary endpoint

Figure 2. Mean Fasting LDL Cholesterol and TG From Baseline Through Week 12 – Treated Subjects



Subjects with measurements			
ATV 400	124	116	119
Comparator PI	115	108	106

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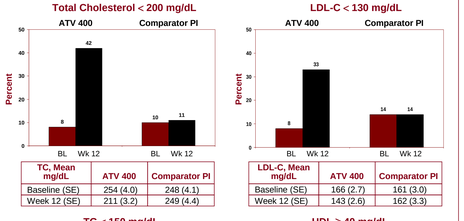
ATV 400	124	117	119
Comparator PI	115	108	106

Difference Estimates of Lipid Changes from Baseline through Week 12			
Fasting LDL-C	Week 12 Observed Values ATV 400-Comparator:	-15.0%(-19.1%, -10.8%)	P<0.0001
Fasting TG	Week 12 Observed Values ATV 400-Comparator:	-34.6%(-41.8%, -26.5%)	P<0.0001

Lipid Parameters by NCEP-ATP III Criteria

- Based on the NCEP-ATP III criteria, the lipid profile of the subjects at week 12 in the ATV arm was more favorable than that of the patients in the comparator PI arm (see Figures 3a and 3b)
  - More patients in the ATV arm had a fasting LDL cholesterol level of < 130 mg/dL (33% vs 14%)
  - More patients in the ATV arm had TC levels < 200mg/dL (42% vs 11%) and triglycerides levels of < 150 mg/dL (52% vs 22%)
  - More patients in the ATV arm had HDL cholesterol levels of ≥ 40 mg/dL (68% vs 54%)
  - Patients in the ATV arm experienced improvement in NCEP categories from 8% at baseline to 42% at week 12 for TC < 200 mg/dL, for LDL-C < 130 mg/dL from 8% to 33 %, for TG < 150 mg/dL from 20% to 52% and for HDL-C ≥ 40 mg/dL from 59% at baseline to 68% at week 12
  - More patients experienced an improvement in the ATV arm in LDL/HDL-C ratio of less than 3 (43% vs 17%)

Figure 3a. Lipid Levels Categorized by NCEP ATP III Guidelines – Treated Subjects



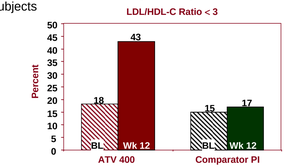
TC, Mean mg/dL	ATV 400	Comparator PI
Baseline (SE)	254 (4.0)	248 (4.1)
Week 12 (SE)	211 (3.2)	249 (4.4)

LDL-C, Mean mg/dL	ATV 400	Comparator PI
Baseline (SE)	166 (2.7)	161 (3.0)
Week 12 (SE)	143 (2.6)	162 (3.3)

TG, Mean mg/dL	ATV 400	Comparator PI
Baseline (SE)	267 (16.0)	257 (14.0)
Week 12 (SE)	168 (7.9)	254 (12.8)

HDL, Mean mg/dL	ATV 400	Comparator PI
Baseline (SE)	44 (1.0)	41 (1.1)
Week 12 (SE)	46 (1.0)	42 (1.1)

Figure 3b. LDL/HDL-C Ratios Categorized by NCEP ATP III Guidelines – Treated Subjects



Efficacy

- No differences in efficacy between arms were observed through week 12. Full assessment of antiviral efficacy end-points will be completed at 48 weeks of follow up.
- Of the 209 patients on treatment with HIV RNA < 50 c/mL at baseline, 2 patients in the ATV-arm (2%) and 1 in the Comparator PI arm (1%) had viral rebound > 400 copies/ml through week 12
- The proportion of patients discontinuing due to lack of efficacy was the same for each treatment group (<1%)
- Mean increases from baseline in CD4 cell counts were comparable between treatment arms, although smaller increases were observed in ATV arm

Safety

- Discontinuations
  - Discontinuations due to AEs were low and comparable for both groups [ATV=3(2%), comparator PI=1(<1%)]
  - Clinical manifestations of ATV-related hyperbilirubinemia were infrequent with only 1 discontinuation (<1%) in the ATV arm occurring due to ocular icterus
- No deaths occurred in either group
- On-study emergent Grade 2-4 AEs and Grade 3-4 laboratory abnormalities were comparable between groups
- Low incidence of jaundice (5%) and ocular icterus (2%) of any grade was reported in ATV arm, with only 1 subject having Grade 3-4 jaundice or ocular icterus
- A significant difference was observed in Grade 3-4 hyperbilirubinemia between the ATV and comparator PI arms (22% and <1% respectively, P<0.0001); these elevations were not associated with increases in AST or ALT levels

Table 3. Deaths, Adverse Events, and Laboratory Abnormalities Through Week 24

	ATV N=126	Comparator PI N=118
Deaths[a,b]	0	0
Adverse Events Leading to Discontinuation	3 (2%)	1 (<1%)
Serious Adverse Events[b,c]	2 (2%)	4 (3%)
Grade 3-4 Laboratory Abnormalities[d]		
Neutrophil reduction	2/124 (2%)	0/111 (0%)
ALT elevation	1/124 (<1%)	3/112 (3%)
AST elevation	1/124 (<1%)	1/112 (<1%)
Total bilirubin elevation	27/124 (22%)	1/112 (<1%)

[a] Percentage is based on the number of enrolled subjects. [b] No deaths were reported after that time point.
[c] Five additional serious adverse events were reported up to 22-Jul-2004 in subjects who had passed the Week 24 follow-up (all patients in the study were on ATV after Week 24). These events were pneumococcal infection/hemolytic anemia/hyperbilirubinemia, dyspnea/overdose/hyperbilirubinemia, aseptic necrosis, road traffic accident. [d] Number/number evaluable.

CONCLUSIONS

- Significant reductions in LDL-C were observed at 12 weeks following switch from another PI to ATV compared to those remaining on the comparator PI.
- Clinically relevant beneficial changes consistent with the NCEP-ATP III guidelines were observed in all lipid parameters by the 12th week after the switch to ATV from comparator PI.
- Viral load suppression was similarly maintained through week 12 in those patients switching to ATV compared to those remaining on the comparator PI. Efficacy measures of virologic suppression will be monitored through Week 48.
- Clinical manifestations of ATV-related hyperbilirubinemia were infrequent with only 1 discontinuation due to ocular icterus.
- These results demonstrate the safety, tolerability and lipid benefits of switching within the PI class to an ATV-containing regimen while maintaining virological suppression at week 12.
- This study will continue through Week 48 to further evaluate the effect of a switch to ATV from boosted or unboosted PI-based HAART in virologically suppressed, treatment-experienced patients with elevated LDL-C.