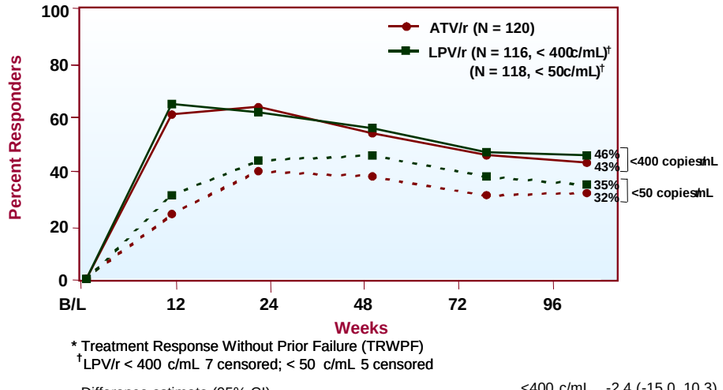
RESULTS (cont'd)

Figure 5. Virologic Response < 400 c/mL and < 50 c/mL at Week 96 (ITT-censored)

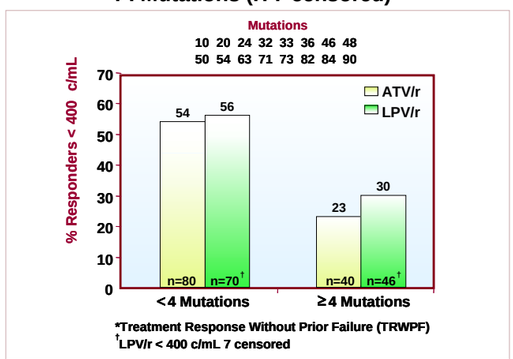


* Treatment Response Without Prior Failure (TRWPF)
†LPV/r < 400 c/mL 7 censored; < 50 c/mL 5 censored

Difference estimate (95% CI)

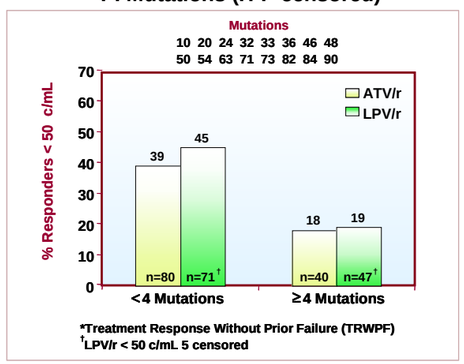
<400 c/mL -2.4 (-15.0, 10.3)
<50 c/mL -3.1 (-15.0, 8.9)

Figure 6a. Virologic Response < 400 c/mL at Week 96 by Number of Baseline PI Mutations (ITT- censored)



*Treatment Response Without Prior Failure (TRWPF)
†LPV/r < 400 c/mL 7 censored

Figure 6b. Virologic Response < 50 c/mL at Week 96 by Number of Baseline PI Mutations (ITT- censored)



*Treatment Response Without Prior Failure (TRWPF)
†LPV/r < 50 c/mL 5 censored

SUMMARY

- Through 96 weeks, comparable overall efficacy of ATV/r and LPV/r was observed, as assessed by the primary endpoint, TAD thus supporting the durability of the antiviral efficacy, previously demonstrated at Week 48:
  - The ATV/r and LPV/r regimens were comparable in terms of number and frequency of PI mutations at baseline
  - No significant difference was seen in the secondary measurements of efficacy between the ATV/r and the LPV/r regimens through 96 weeks assessed by percent of subjects < 50 copies/mL, percent of subjects < 400 copies/mL in an ITT analysis
  - 56% of ATV/r and 53% of LPV/r patients remained on study through Week 96
  - 72% of patients on both arms had HIV RNA < 50 c/mL (on-treatment analysis)
- In this treatment-experienced cohort, median exposure to antiretrovirals was 129-136 weeks on PIs, 251-269 weeks on NRTIs and 69-84 weeks on NNRTIs.
- The decline in plasma HIV RNA from baseline through 96 weeks was similar in subjects treated with ATV/r or LPV/r who had less than 4 protease inhibitor resistance mutations detected at baseline. Responses were also similar in subjects with 4 or more protease inhibitor resistance mutations detected at baseline. A potential limitation is that there were relatively fewer patients with ≥ 4 PI mutations.
- Mean time on study therapy was approximately 76 weeks for both the ATV/ and the LPV/r treatment regimens. Overall, discontinuation of study therapy during the period from Week 48 to Week 96 was comparable between treatment regimens.

CONCLUSIONS

- Once-daily ATV/r demonstrated efficacy similar to LPV/r twice-daily through 96 weeks in treatment-experienced patients.
- Sub-set assessments of virologic response showed comparable efficacy between the two regimens for the sub-groups of subjects with < 4 and ≥ 4 PI mutations.
- The magnitude of response for both regimens was inversely related to the number of baseline PI mutations, with greater mean reduction in HIV RNA in patients with < 4 PI mutations compared with those with 4 PI mutations.

05-049

The Influence of Baseline Protease Inhibitor (PI) Mutations on the Efficacy of Ritonavir-Boosted Atazanavir (ATV/r), Atazanavir Plus Saquinavir, and Lopinavir/Ritonavir (LPV/r) In Patients Who Have Experienced Virologic Failure on Multiple HAART Regimens

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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 naïve patients versus a standard of care regimen containing EFV and treatment experienced patients versus a standard of care regimens containing LPV/r.
- ATV/r has demonstrated comparable efficacy in treatment experienced patients to the standard of care regimen containing LPV/r.
- BMS AI424-045 was undertaken to evaluate the efficacy and safety of ATV/r and a dual PI combination of ATV and SQV, in comparison with LPV/r, each co-administered with tenofovir (TDF) and 1 NRTI in treatment-experienced patients who had failed two or more prior HAART regimens that included one or more NRTI, NNRTI and PI. Overall efficacy and safety results at weeks 24, 48 and 96 have been previously presented.
- Resistance to ATV is associated with the unique I50L substitution, which is found in clinical isolates from some subjects (primarily previously treatment-naive) experiencing virologic failure during ATV-containing therapy.
- HIV isolates typically show increasingly broad resistance to marketed PIs with an increase in the number of PI-associated mutations. The present analysis was performed to assess the influence of baseline PI mutations on the virologic response to ATV- and LPV/r- containing regimens through 96 weeks.

OBJECTIVES

Primary

- Antiviral efficacy assessed by the time-averaged difference (TAD) from baseline in viral load (log_{10}) between each of 2 ATV-containing regimens and a LPV/r-containing regimen at Week 96.

Secondary

- To assess the proportion of subjects with HIV RNA levels less than the limit of quantification ([LOQ] equals 400 c/Ml and LOQ equals 50 c/mL) through Week 96
- To assess the magnitude of changes in CD4 cell counts through Week 96
- Additional secondary objectives include the assessment of serum lipids, safety and tolerability

Sub-set Analysis by Baseline PI Mutations

- Describe the antiviral efficacy, assessed by change in HIV RNA, treatment response rates below LOQ 400 c/mL and 50 c/mL using ITT analyses based upon number of baseline PI mutations (≥ or <4)

METHODS

- Multinational, open-label, 3-arm, randomized Phase III study in treatment-experienced patients with virologic failure on ≥ 2 HAART regimens that included, in total, at least 1 PI, NRTI, and NNRTI

Primary Efficacy Analysis

- Similarity (noninferiority) of efficacy between the ATV/r regimen and the LPV/r regimen was based on an upper 97.5% confidence interval (CI) for the TAD estimate of <0.5 log_{10} copies/mL
- Interim analysis at 24 weeks found the ATV/SQV arm to be inferior to both ATV/r and LPV/r arms. Patients were given the option of changing therapy and therefore analysis of this arm was not continued past 48 weeks.
- The study was subsequently extended and is currently continuing past Week 96.

Secondary Efficacy Analysis

- ITT (NC=F) response rates include all randomized patients and count as responders patients with a minimum of two sequential HIV RNA measurements < 400 c/mL (or < 50 c/mL) maintained through week 96
- ITT (censored): patients who completed the study at week 48 while in response were removed from the analysis at the point of study completion

Sub-set Analysis of Efficacy by Baseline PI Mutations

- Resistance mutations were selected using the Stanford Panel
- Efficacy was assessed using TAD for HIV RNA levels, ITT response rates were conducted as described above

Figure 1. Study Design

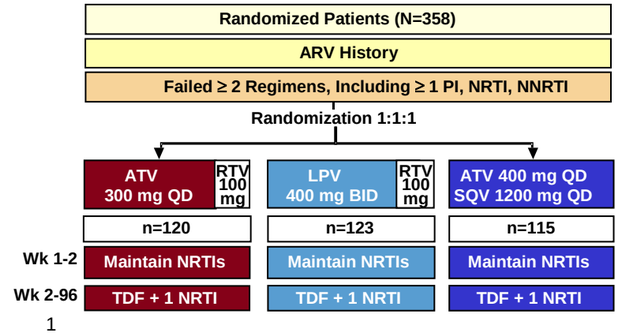


Table 1. Randomized Patient Baseline Characteristics

	ATV/r n=120	LPV/r n=123	ATV 400/SQV n=115
Age, median, yr	39	39	41
Female (%)	20	22	23
Race (%)			
White	63	58	61
Hispanic/Latino	23	22	23
Black	15	17	14
AIDS (%)	28	29	28
Hepatitis B or C (%)*	16	18	18
HIV RNA, median, log_{10} c/mL	4.44	4.47	4.42
HIV RNA, =100,000 c/mL (%)	23	23	27
CD4, median, cells/mm^3	317	283	286
CD4, <200 cells/mm^3 (%)	31	29	31

*Percentages based on treated subjects.

Table 2. Randomized Patient Disposition and Treatment Outcomes

	ATV/r n=120	LPV/r n=123	Difference Estimate (95% CI)
Treated, n (%)	119 (99)	118 (96)	
Total discontinuations prior to Week 48, n (%)	26 (22)	13 (11)	
Total discontinuations on or after Week 48 and prior to Week 96, n (%)	26 (22)	30 (24)	
Adverse event	4 (3)	5 (4)	
Treatment failure/lack of efficacy	16 (13)	18 (15)	
Other[a]	6 (5)	7 (6)	
On treatment at Week 96, n (%)	67 (56)	65 (53)	
Completed treatment, n (%)	0	10 (8)	
Censored, n			
< 400 c/mL	0	7	
< 50 c/mL	0	5	
ITT* (NC=F), % Responders			
< 400 c/mL	43	43	0.2 (-12.2, 12.7)
< 50 c/mL	32	33	-1.7 (-13.4, 10.1)
ITT* (Censored), % Responders			
< 400 c/mL	43	46	-2.4 (-15.0, 10.3)
< 50 c/mL	32	35	-3.1 (-15.0, 8.9)
As Treated, % Responders			
< 400 c/mL	84	82	2.0 (-10.9, 15.0)
< 50 c/mL	72	72	-0.7 (-16.0, 14.7)

[a] Includes disease progression or relapse, lost to follow-up, noncompliance and death.
* Using TRWPF definition (Treatment Response Without Prior Failure) as described in methods.

Table 3. Randomized Patient Treatment History and Resistance Characteristics

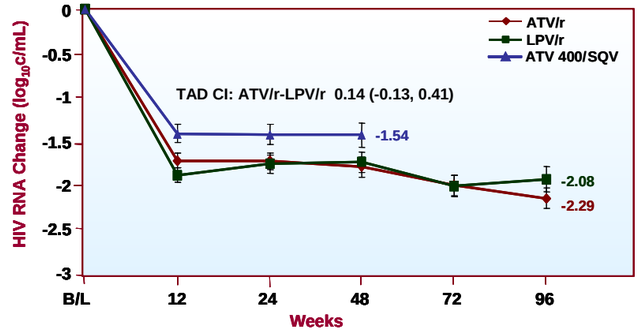
	ATV/r n=120	LPV/r n=123	ATV 400/SQV n=115
Number of Prior ARVs at baseline, median (maximum)			
PI	2 (5)	2 (5)	2 (5)
NRTI	4 (6)	4 (6)	4 (6)
NNRTI	1 (2)	1 (3)	1 (2)
Prior ARV use, median, yr			
PI	2.5	2.6	2.5
NRTI	5.2	5.1	4.8
NNRTI	1.5	1.3	1.6
Preceding Therapy at baseline, n (%)			
PI	44 (37)	44 (36)	34 (30)
NNRTI	72 (60)	69 (56)	73 (63)
Phenotypic Susceptibility at Screening*, n (%)			
ATV	88 (73)	-	84 (73)
LPV	-	88 (72)	-
Presence of mutations at baseline[†], n (%)			
PI			
Any	102 (85)	111 (90)	104 (90)
< 4	62 (52)	64 (52)	66 (57)
≥ 4	40 (33)	47 (38)	38 (33)
NRTI			
≥ 4	50 (42)	56 (46)	52 (45)

*Defined as ≤ 2.5 x FC of control strain.
[†]Median number of baseline PI and NRTI mutations: 2 and 3, respectively, for all groups.

Table 4. Protease Mutations Detected in Study Subjects at Entry*

Mutation	ATV/r	LPV/r
L101/V/F	45	48
K20R/M/I	24	20
L24I	4	2
V32A/I	2	9
L33I/F/V	8	11
M36I/L/V	41	43
M46I/L	20	27
G48V	1	1
I50L	0	0
I50V	0	4
I54V/L	17	15
L63P	79	74
A71V/T/I	39	41
G73C/S/T/A	8	10
V82A/F/S/T	25	29
I84V	9	7
L90M	34	35

Figure 2. Mean Change in HIV RNA Levels Through Week 96

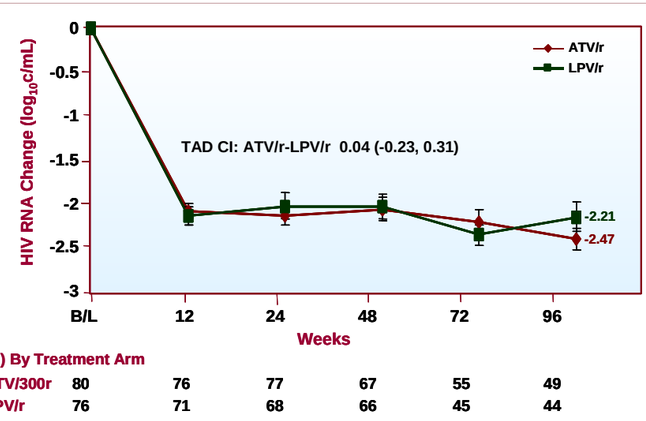


(N) By Treatment Arm

ATV/300r	120	111	112	91	79	64
LPV/r	123	115	110	102	69	65
ATV 400/	115	99	93	78		

TAD CI: ATV/r 0.14(-0.13, 0.41)

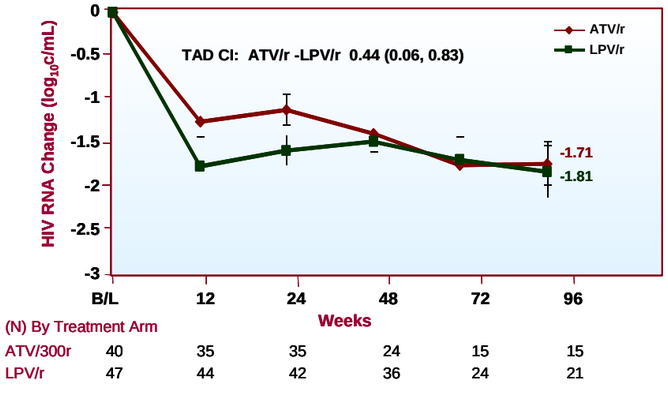
Figure 3. Plasma HIV RNA decline from baseline through 96 weeks: Subjects with less than 4 PI mutations detected at baseline



(N) By Treatment Arm

ATV/300r	80	76	77	67	55	49
LPV/r	76	71	68	66	45	44

Figure 4. Plasma HIV RNA decline from baseline through 96 weeks: Subjects with 4 or more PI mutations detected at baseline



(N) By Treatment Arm

ATV/300r	40	35	35	24	15	15
LPV/r	47	44	42	36	24	21