Similar Efficacy and Tolerability of Atazanavir (ATV) Compared to ATV/Ritonavir (RTV), each in Combination with Abacavir/Lamivudine (ABC/3TC), after Initial Suppression with ABC/3TC + ATV/RTV in HIV-1 Infected Patients: Final (144 Weeks) Results of the Open-label, Multicenter, Non-inferiority ARIES Study

Poster MOPE215

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Introduction

- Treatment simplification strategies involving induction with a ritonavir-boosted protease inhibitor regimen followed by simplification (discontinuing ritonavir) are appealing because they may result in sustained virologic suppression while minimizing potential long-term ritonavir-associated adverse effects. While ATV drug levels can be reduced when co-administered with some ART, ABC/3TC use does not affect drug levels of ATV administered without ritonavir. The ARIES trial previously demonstrated the non-inferiority of ATV to ATV/r, both with ABC/3TC over 84 weeks after induction with ATV/r + ABC/3TC.[1,2]
- The ARIES study extension phase (from 84 to 144 weeks) results, which assessed long-term efficacy and safety, are reported.

Methods

- ART-naïve subjects received ABC/3TC + ATV/r followed by randomization (1:1) at Week 36 to maintain or discontinue RTV to 84 weeks (**Figure 1**); eligible subjects could continue to 144 weeks. Randomization criteria were as follows: confirmed HIV-RNA <50 c/mL prior to Week 36; HIV-RNA <50 c/mL immediately preceding Week 36, and no protocol defined virologic failure.
- The objectives of this study extension were to collect extended treatment data in subjects who had completed 84 weeks of study, and evaluate the proportion of subjects with HIV RNA <50 and 400 c/mL (TLOVR) at Weeks 120 and 144, the change from baseline in HIV RNA and CD4+ cell count, resistance in subjects with virologic failure and safety endpoints. Results of the final analysis at 144 weeks are presented.
- Protocol defined virologic failure (VF) after Week 36 was defined as a confirmed HIV-1 RNA (RNA) ≥400 copies/mL.

Results

Figure 1. ARIES Study Design

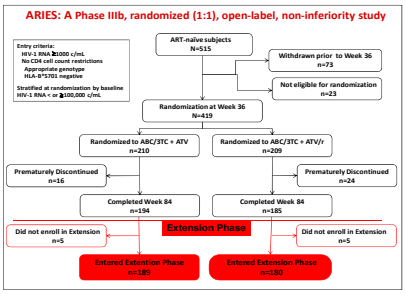


Table 1. ITT-Extension Phase Subject Demographics

	ATV	ATV/r	Total
Mean age, years	38	40	39
Male	160 (85%)	155 (86%)	315 (85%)
Racial Distribution			
White	122 (65%)	114 (63%)	236 (64%)
Black	58 (31%)	57 (32%)	115 (31%)
Other	9 (5%)	9 (5%)	18 (5%)
CDC Class C	32 (17%)	15 (8%)	47 (13%)
Hepatitis C positive	9 (5%)	11 (6%)	20 (5%)
Median HIV RNA, log_{10} c/mL	5.06	5.08	5.06
<100,000 c/mL	85 (45%)	79 (44%)	164 (44%)
≥100,000 c/mL	104 (55%)	101 (56%)	205 (56%)
Median CD4+ count, cells/mm³	190	203	198
≥200	91 (48%)	92 (51%)	183 (50%)
50 - <200	66 (35%)	70 (39%)	136 (37%)
<50	32 (17%)	18 (10%)	50 (14%)

Table 2. Subject Disposition During the Extension Phase of ARIES

	ATV n=189	ATV/r n=180	Total N=369
Completion Status			
Completed 144 weeks	160 (85%)	154 (86%)	314 (85%)
Prematurely withdrawn	29 (15%)	26 (14%)	55 (15%)
Investigator Defined Primary Reason for withdrawal			
n	29	26	55
Adverse event	1	3	4
Insufficient viral load response	1	1	2
Protocol violation	1	0	1
Protocol defined VF*	3	2	5
Lost to follow-up	9	9	18
Subject decision	4	3	7
Non-compliance	1	1	2
Other**	9	7	16

* Subjects with protocol defined VF with HIV-RNA>2000c/mL at cVF were required to WD; those with HIV-RNA<2000 c/mL at cVF could remain on study; the investigator could also conclude factors other than meeting cVF were primary.
**reasons included: sponsor termination of site (3 on each arm); pregnancy (3 on ATV arm); subject moved (1 per arm); physician decision (1 ATV/r arm); sponsor request (1 per arm); unknown(1 ATV arm); subject could not return from Cuba(1 ATV/r arm).

Figure 2. HIV RNA <50 copies/mL (ITT-Extension,TLOVR)

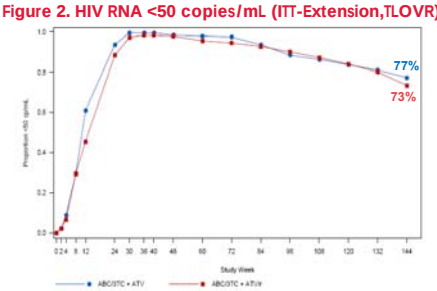


Figure 3. HIV RNA <50 copies/mL at Week 144 (ITT Extension)

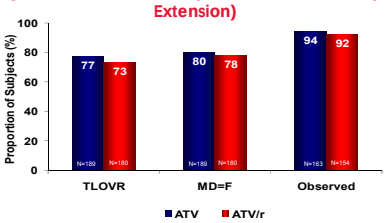
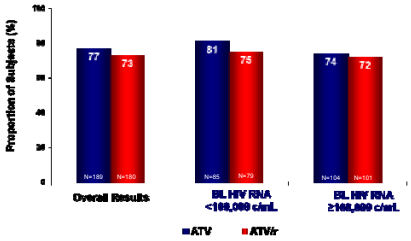
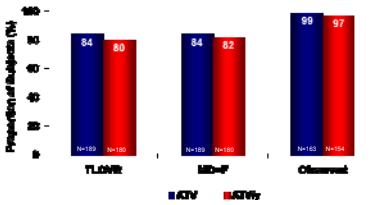


Figure 4. HIV RNA <50 copies/mL by Baseline Viral Load at Week 144, (ITT-Extension, TLOVR)



- Most subjects (369/419; 88%) included in the Week 84 analysis participated in the extension phase (ITT-Extension population) through 144 weeks.
- Extension subjects demographics are shown in **Table 1** and were demographically similar to the randomized population[1] and between arms: mean age 39 yrs; 85% male; 64% white; median baseline RNA and CD4+ count were 5.06 log_{10} c/mL, 198 cells/mm³, respectively.
- 314 subjects completed 144 weeks on study (**Table 2**); 85% on the ATV arm and 86% on the ATV/r arm.
- HIV RNA <50 copies/mL (ITT-Extension,TLOVR; **Figures 2 & 3**) was 77% for subjects randomized to the ATV arm; 73% for subjects in the ATV/r arm; with stratification by baseline HIV-RNA (**Figure 4**) efficacy was also similiar.
- HIV RNA <400 copies/mL (ITT-Extension, TLOVR; **Figure 5**) was 84% for subjects randomized to the ATV arm; 80% for subjects in the ATV/r arm.

Figure 5. HIV RNA <400 copies/mL at Week 144 (ITT-Extension)



- Few subjects (11; 3%)met protocol defined VF (**Table 3**) in the extension phase; virus from only one VF subject selected major PI or RT mutations.
- Subjects on both arms experienced a positive CD4 increase (**Figure 6**).
- Post randomization, higher treatment-related AEs were observed (**Table 4**) in the ATV/r arm (23%) compared to the ATV arm (13%). Hyperbilirubinemia was the only treatment-related AE with ≥3% incidence from Week 36-144 (ATV/r arm 14% vs. ATV arm 6%).

Table 3. HIV Mutation Profiles for ITT-Extension Subjects with Protocol Defined Virologic Failure From Week 84 through Week 144

	ATV N=189	ATV/r N=180	Total N=369
Confirmed Virologic Failures	**5 (2.6%)**	**6 (3.3%)**	**11 (3.0)**
Treatment Emergent IAS-USA Resistance Mutations	2	1	3
RT Region			
M184MV	0	1	1
T215F	0	1	1
Major PI Mutations			
N88S	0	1	1

Figure 6. Median CD4+ Cell Count Changes from Baseline for Both Arms by the ITT-Extension, Observed Analysis Through 144 Weeks

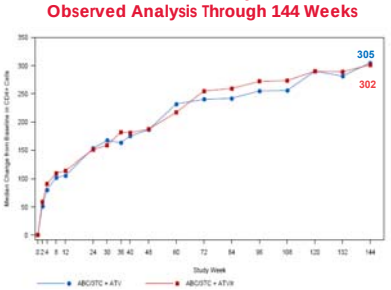
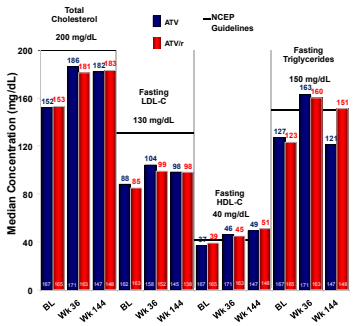


Table 4 . Treatment-Related AEs by Week

	ATV N=189	ATV/r N=180
BL to Week 36		
G2-4 AEs	50 (26%)	54 (30%)
Hyperbilirubinemia[a]	26 (13%)	24 (13%)
Diarrhea	8 (4%)	5 (3%)
Nausea	6 (3%)	3 (2%)
Week 36 to 144		
G2-4 AEs	25 (13%)	42 (23%)
Hyperbilirubinemia[a,b]	12 (6%)	25 (14%)

[a] Overall frequency ≥3%;
[b]p=0.0232; Fisher's exact test
Note: 2 fatalities were reported over the entire study period , both in the ATV/r arm (Castleman's disease/hepatic/renal failure and lung adenoma); not considered treatment-related by the investigator.

Figure 7. Median Fasting Lipid Profile by Week for ATV vs. ATV/r Study Arms*



*The number at the top of each bar indicates the actual median lipid concentration; the number within each bar reflects the number of subjects analyzed for that lipid at that time point.

Table 6. Comparison of Fasting Lipid Data by Week for ATV vs. ATV/r Study Arms

	Baseline Median Concentration *ATV, ATV/r*	Median Change from BL to Week 36 *ATV, ATV/r*	Median Change from Week 36 to Week 144 *ATV, ATV/r*	Median Change from BL to Week 144 *ATV, ATV/r*
Cholesterol Subject "n" *p*-value	152, 153 (167, 165) 0.763	31, 30 (152, 152) 0.414	**-10, 3** (136, 132) **.005**	**18, 37.5** (132, 138) **.0031**
Triglyceride Subject "n" *p*-value	127, 123 (167, 165) 0.755	27, 34 (152, 152) 0.701	**-42, -11** (136, 132) **<.0001**	**-8.5, 28.5** (132, 138) **.0001**
HDL Subject "n" *p*-value	37, 39 (167, 165) 0.864	10, 8 (152, 152) 0.727	**3, 3** (136, 132) **0.849**	**12, 12** (132, 138) **0.952**
LDL Subject "n" *p*-value	88, 85 (162, 163) 0.966	13, 10 (139, 140) 0.249	**-4, 0** (122, 116) **0.120**	**4, 15** (127, 128) **.05**
Chol/HDL Ratio Subject "n" *p*-value	4.15, 4.10 (167, 165) 0.921	-0.14, -0.14 (152, 152) 0.353	**-0.43, -0.19** (136, 132) **.008**	**-0.55, -0.23** (132, 138) **.0168**

- The change from baseline to Week 144 and the change from Week 36 to Week 144 are statistically significant (by Rank-sum test) for total cholesterol, triglycerides and the cholesterol/HDL ratio when comparing the ATV vs. ATV/r treatment groups.

Conclusions

- **Similar and sustained efficacy was demonstrated over 144 weeks in both the simplification (ABC/3TC + ATV) and continuation (ABC/3TC + ATV/r) arms in the ARIES study. For subjects who participated in the extension phase, HIV-RNA of <50 c/mL (TLOVR) was observed in 77% of subjects in the ATV arm vs. 73% in the ATV/r arm through Week 144.**
- **Both arms had substantial CD4 increases through Week 144 (305 CD4+ cells/cm³ for ATV-treated subjects; 302 CD4+cells/cm³ for ATV/r-treated subjects).**
- **Few subjects (11, ~3%) met protocol-defined virologic failure from Week 84 through Week 144.**
- **Both treatment regimens were generally well tolerated over 144 weeks, however the safety profile from randomization at Week 36 through Week 144 favors the ABC/3TC + ATV simplification arm, with higher treatment-related AEs in ATV/r arm (23%) compared to the ATV arm (13%).**
- **Hyperbilirubinemia was the only treatment-related AE with ≥3% incidence from Week 36-144 (ATV/r arm 14% vs. ATV arm 6%).**
- **Subjects in the simplification arm post-Week 36 randomization demonstrated a significantly more favorable fasting lipid (cholesterol, triglyceride and cholesterol/HDL ratio) & total bilirubin profile compared to those in the continuation arm.**

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References

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