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The Safety, Efficacy, and Steady State Pharmacokinetics of Atazanavir/Ritonavir (ATV/r) Once Daily During Pregnancy: Results of Study AI424182

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BACKGROUND

Introduction

- There are very limited options for the use of protease inhibitors as a component of HAART in HIV-infected pregnant women
- There remains an unmet medical need for a once-daily, safe, efficacious and well tolerated protease inhibitor (PI) for use during pregnancy
- Atazanavir (ATV) is a potent, well-tolerated, once-daily HIV-1 PI with established efficacy in both treatment-naïve and treatment-experienced adult, non-pregnant HIV-infected patients
- HIV protease inhibitor exposures are generally reduced during pregnancy, especially during the 3rd Trimester
- There are some data to suggest that atazanavir levels, while reduced during pregnancy, may nonetheless be adequate to recommend dosing at the usual non-pregnant dose of atazanavir 300mg boosted with low-dose ritonavir 100mg (ATV/r 300/100mg)[1]
- However, further data are needed before a recommendation can be made regarding adequate ATV/r dosing in pregnancy

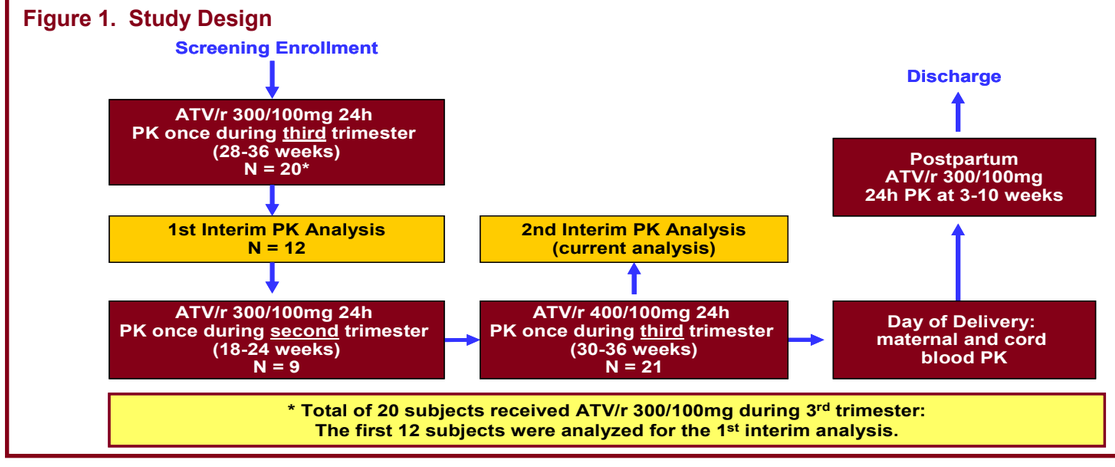
Objectives

- Primary objective: To determine what dosing regimen of ATV/r produces adequate drug exposure during pregnancy compared to historical data in HIV-infected subjects
- Secondary objectives
  - Measure maternal:infant ATV level ratio
  - Safety of ATV/r in pregnant women
  - Safety in infants born to women exposed to ATV/r during pregnancy
  - Antiviral efficacy
    - Suppression of HIV RNA in mothers
    - Prevention of mother-to-child transmission of HIV-1

Methods

- Multicenter, open-label, prospective, single-arm phase 1 study
  - Enrollment in South Africa, Puerto Rico, and the USA
- Study Population: HIV-1 infected pregnant women between 12- 32 weeks gestation; CD4 ≥ 200 cells/mm^3
- Treatment: ATV/r 300 or 400/100 mg once-daily and ZDV/3TC 300/150 mg twice-daily
- Planned First Interim PK analysis after 12 subjects received ATV/r 300/100mg during third trimester with pre-specified criteria for increasing dose to ATV/r 400/100mg
- Second Interim Analysis after primary endpoint data available (all third trimester PK data at both ATV/r 300/100 mg and 400/100mg)
- Second trimester PK data for ATV/r 300/100 mg was collected in a limited number of subjects
- Post-partum PK was assessed between 3-10 weeks after delivery
- Infants were assessed by HIV DNA testing on the date of delivery and at week 2, 6, 16 and 24

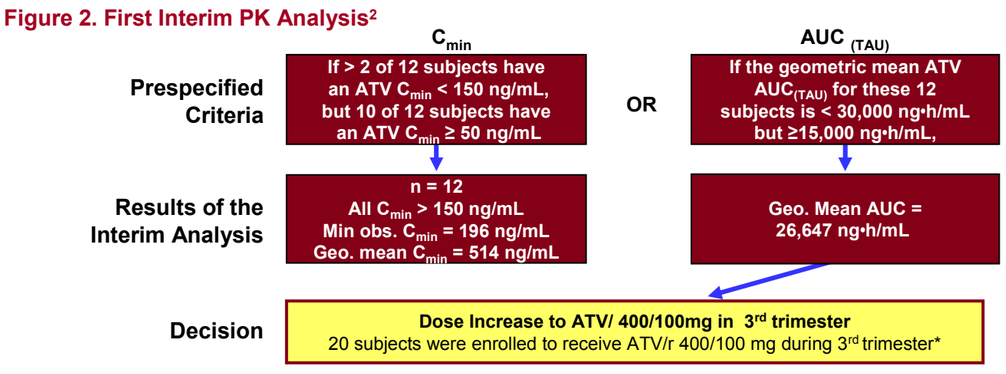
Figure 1. Study Design



RESULTS

- The prespecified criteria for C_{min} and $AUC_{(TAU)}$ to determine if an increased dose of ATV 400 mg QD/RTV 100 mg QD should occur in the 3rd trimester are shown in **Figure 2**

Figure 2. First Interim PK Analysis[2]



*After decision to increase 3rd trimester dose, subjects enrolled in the study who were in the 2nd trimester underwent blood sampling for PK analysis of ATV/r 300/100mg in the 2nd trimester

Table 1. Disposition & Clinical Efficacy

	ATV/r 300/100 n = 20 n (%)	ATV/r 400/100 n = 21 n (%)
Disposition		
Treated	20 (100)	21 (100)
Discontinued treatment before delivery	1 (5)	2 (10)
– Due to AEs	0	1 (5)*
– Other	1 (5)∞	0
– Subject request	0	1 (5)^
Clinical Efficacy		
Maternal HIV RNA < 50 copies/mL at the time of delivery	19 / 19 (100)∞	19 / 20 (95) ^†
Maternal HIV RNA < 400 copies/mL at the time of delivery	19 / 19 (100)	20 / 20 (100)
– Infant HIV DNA negative result	20 / 20 (100)	20 / 20 (100)

* Subject diagnosed with preeclampsia with a grade 3-4 transaminitis; all ARVs held and infant delivered by C-section 4 days later; HIV RNA < 50 copies/mL prior to ARV discontinuation and HIV RNA < 50 copies/mL on day of delivery.
∞ One subject was discontinued from study drug when premature labor developed; delivered 12 days later. HIV RNA < 50 copies/mL at delivery.
^ One subject withdrew from study (withdrew consent) after three weeks of therapy and therefore no HIV RNA is available from the time of delivery.
† One subject had 3 consecutive HIV RNA < 50 copies/mL prior to delivery, an HIV RNA of 59 copies/mL on the date of delivery, with subsequent re-suppression to < 50 copies/mL post-partum

Figure 3. Primary Endpoint: Boosted ATV/r 300/100 and 400/100 in Pregnancy Compared to 300/100 mg in Non-pregnant Adults (Historical Data)

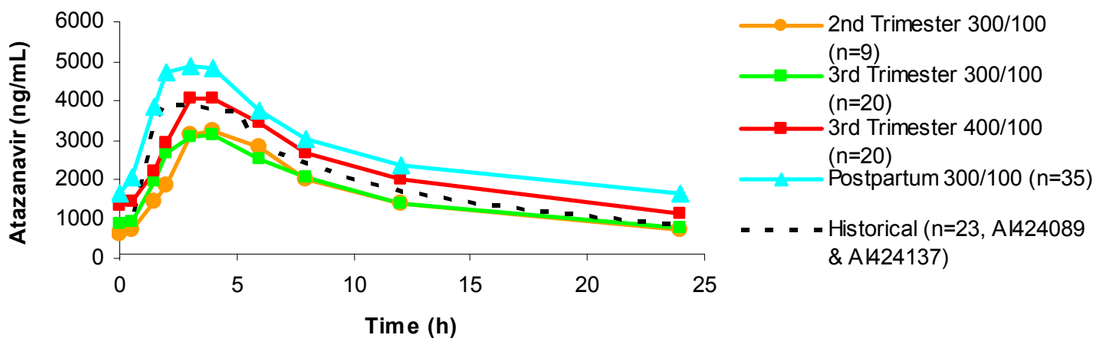


Table 2. Comparison of ATV Exposures in Pregnancy to Historical Data

	2nd Trimester 300/100mg n=9	3rd Trimester 300/100mg n=20	3rd Trimester 400/100mg n=20	Post-Partum 300/100mg n=35	Historical^ 300/100mg n=23
C_{max} (ng/mL) GM	3729	3281	4211	5739	4285
GMR (90% CI)	0.83 (0.65, 1.06)	0.73 (0.56, 0.96)	0.94 (0.76, 1.17)	1.28 (1.11, 1.48)	–
AUC_{tau}(ng•h/mL) GM	34399	34130	46571	62090	43388
GMR (90% CI)	0.79 (0.61, 1.03)	0.79 (0.62, 0.99)	1.07 (0.84, 1.37)	1.43 (1.22,1.68)	–
$C_{24(min)}$ (ng/mL) GM	664	666*	917	1456	662
GMR (90% CI)	1.00 (0.65, 1.54)	1.01 (0.73, 1.39)	1.39 (0.96, 2.00)	2.20 (1.70, 2.87)	–

*The lowest observed C_{min} was 196 ng/mL
^ Source: AI424-089, AI424-137

Table 3. Pharmacokinetics of ATV Peripartum

	ATV/RTV 300/100 mg Geo Mean (%CV)	ATV/RTV 400/100 mg Geo Mean (%CV)
Maternal concentration at delivery (ng/mL)	(n=19) 1199 (63)	(n=17) 1224 (54)
Cord Blood Conc. (ng/mL)	(n=14) 224 (67)	(n=14) 189 (67)
Fetal / maternal ratio	(n=14) 0.19 (41)	(n=14) 0.12 (51)

Table 4. Adverse Events Summary: Maternal

		ATV/r 300/100 n = 20 n (%)	ATV/r 400/100 n = 21 n (%)
Serious Adverse Events (SAEs)		7 (35)*	7 (33)^
All grade 2-4 treatment-related AEs		4 (20)	5 (24)
Grade 2-4 treatment-related AEs of Clinical Interest	Hyperbilirubinemia†	0	1 (5)
	Anemia	1 (5)	3 (14)
	Vomiting	1 (5)	0
	Diarrhea	1 (5)	0
	Impaired glucose tolerance	0	1 (5)
	Rash	1 (5)	0

Related SAEs: *anemia (n = 1); ^ anemia (n = 2) & hyperbilirubinemia (n = 1)
†Based on AE reports, not laboratory values

Table 5. Selected Maternal Grade 3-4 Laboratory Abnormalities

	ATV/r 300/100 n = 20 n (%)	ATV/r 400/100 n = 21 n (%)
Total bilirubin elevation (> 2.5 × ULN)	6 (30)	13 (62)
ALT elevation (> 5 × ULN)	0	1 (5)
AST elevation (> 5 × ULN)	0	1 (5)
Total cholesterol (≥ 240 mg/dL)*	1/14 (7)	3/15 (20)
Hematocrit (< 24%)	2 (10)	1 (5)
Hypocarbia (≤ 14 meq/L)	1 (5)	8 (38)

*Fasting Lipids were measured at Screening and Postpartum Week 4 only

Table 6. Infant Grade 3-4 Laboratory Abnormalities*

	Mothers 3rd Trimester Regimen	
	ATV/r 300/100 n = 20 n (%)	ATV/r 400/100 n = 19 n (%)
Total bilirubin	3 (15)	4 (21)
Hypoglycemia	0	1/18 (6)
Hemoglobin	0	1/4 (25)
Hyperkalemia	4 (20)	5/17 (29)

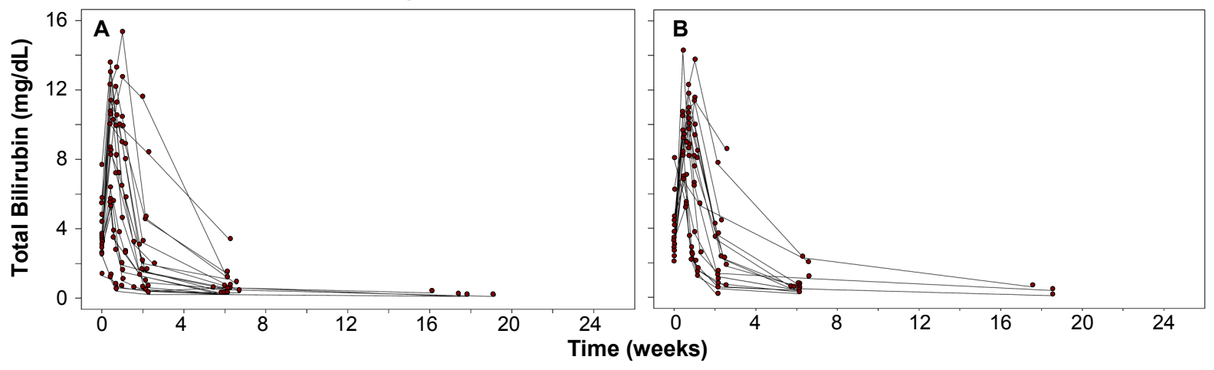
* Values for grade 3-4 abnormalities not provided as thresholds vary depending on age of newborn

Table 7. Serious Adverse Events: Infant

	Mothers 3rd trimester regimen	
	ATV/r 300/100 n = 20 n (%)	ATV/r 400/100 n = 19* n (%)
Any Serious Adverse Events (SAEs)	10 (50)	3 (16)
AZT Overdose	1 (5)	0
Anemia	1 (5)	0
Restrictive cardiomyopathy	1 (5)	0
Hypoglycemia	0	1 (5)
Prematurity	1 (5)	1 (5)
Respiratory Distress /neonatal RDS	2 (10)	0
Hyperkalemia	1 (5)	0
Infections & Infestations	4 (20)	1 (5)
Hyperbilirubinemia	0	1 (5)
Jaundice^	1 (5)	0
Cerebral Ischemia	1 (5)	0
Vomiting	1 (5)	0

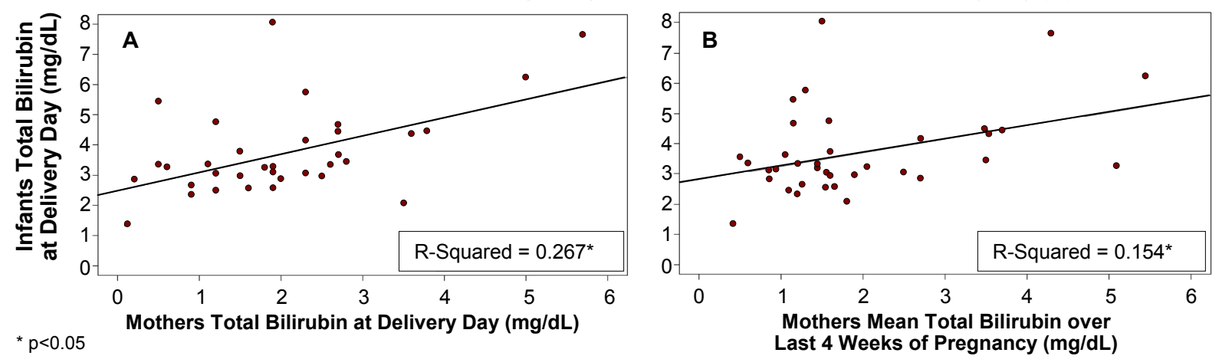
* One infant born after database lock for second interim analysis; HIV DNA negative at delivery and at week 2 and reported here in Table 1; no safety data available in database yet on this infant
^ Infant born at 35 weeks following premature rupture of membranes. Maternal bilirubin 2.3 g/dL on day of delivery. Birth weight 1.8 kg. Infant bilirubin 13 g/dL on Day 3; received 3 days of phototherapy. Discharged well

Figure 4. Total Bilirubin over Time: Live-born Infants Whose Mothers Were Given ATV/r 300/100 (A) or ARV/r 400/100 (B) during the 3rd Trimester



Note: Thresholds for Grade 1-4 bilirubin are higher in the first 14 days of life due to the common occurrence of neonatal physiologic jaundice (~30-40% of all newborns). No Grade 1-4 bilirubin elevation occurred within the first 14 days in the study. All Grade 3-4 bilirubins occurred after Day 14 and as can be seen from Figures A & B, levels were decreasing in all cases from the elevated levels observed during the first 14 days.

Figure 5. Scatterplots of Mothers vs Infants Total Bilirubin at Delivery Day (A) and Mothers Mean Total Bilirubin over the Last 4 Weeks of Pregnancy vs Infants Total Bilirubin at Delivery Day (B)



* p<0.05

DISCUSSION

- Compared to ATV/r 300/100 mg in HIV-infected non-pregnant adults:
  - ATV/r 300/100 mg has a lower third trimester AUC, but similar C_{min}
  - ATV/r 400/100 mg has a similar third trimester AUC but higher C_{min}
- All C_{mins} observed were > 10X EC_{90} for ATV (EC_{90} = 14 ng/mL for wild-type virus). The lowest observed C_{min} was 196 ng/mL
- Levels of ATV are elevated in the post-partum period. This observation has been made for other PIs in the post-partum period. Levels of ATV appear to normalize by week 16 post partum[2]
- Both ATV/r 300/100 and ATV/r 400/100 were well tolerated with no unexpected, related AEs. However, ATV/r 400/100 dosing was associated with twice as much Grade 3-4 hyperbilirubinemia as ATV/r 300/100
- Most infants had some elevation of bilirubin. The level and pattern of bilirubin elevation in infants was generally consistent with physiologic jaundice, with the highest elevations around Day 3 with subsequent reductions to normal levels over the next several weeks. Bilirubin levels in infants on the day of birth are only partly explained by maternal levels at the time of delivery. One infant with risk factors for neonatal jaundice (premature birth and low birth weight) had phototherapy
- The ratio of maternal to cord blood ATV indicates that, as with other PIs, ATV does not freely cross the placenta, however, the levels achieved in the cord blood may provide some anti-viral protection to the fetus
- Full suppression of HIV viral replication (HIV RNA < 50 copies/mL) was achieved in all mothers, and no mother-to-child HIV transmission occurred

CONCLUSIONS

- ATV/r 300/100mg once daily dosing has a 27% lower AUC in the 3rd trimester of pregnancy compared to the AUC in non-pregnant adults, however, C_{mins} are similar. Increasing the dose to ATV/r 400/100mg achieves a similar AUC to non-pregnant adults and higher C_{mins}, but with more frequent grade 3-4 hyperbilirubinemia
- ATV/r 300/100mg once daily dosing appears to provide adequate ATV exposure throughout pregnancy and was well tolerated in these HIV-infected pregnant women. Adequate C_{mins} with reduced maternal hyperbilirubinemia compared to ATV/r 400/100mg, and no need for dose modification in the 3rd trimester or post-partum, suggests that ATV 300/r in combination with a SOC backbone could be a potential treatment option for HIV-infected pregnant women in need of HAART
- The clinical outcomes from this phase I study suggest that ATV 300/100mg once daily was efficacious in the suppression of HIV RNA in these patients, and prevented the transmission of mother-to-child HIV-1 infection when used in combination with AZT/3TC twice daily
- Treatment with ATV/r in the mothers appeared to be well tolerated by the newborn infants in this study. Bilirubin elevation was common among infants and is likely mostly physiologic in nature with only partial correlation with maternal levels at the time of delivery

ACKNOWLEDGEMENTS

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- This BMS-supported study is also known as Study AI424182 and is registered with ClinicalTrials.gov, number NCT00326716

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