PHARMACOKINETICS OF ATAZANAVIR BOOSTED WITH COBICISTAT DURING PREGNANCY AND POSTPARTUM

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Background

- Atazanavir (ATV), a human immunodeficiency virus (HIV-1) protease inhibitor, is metabolized primarily by CYP3A and requires co-administration with a pharmacokinetic (PK) booster to allow once a day dosing.

- The PK of ATV when co-administered with ritonavir (RTV) have been described in pregnancy; however, ATV boosted with cobicistat (COBI) has not been studied in pregnant women.

- This study described ATV exposure when administered in fixed-dose combination with COBI during pregnancy and postpartum.

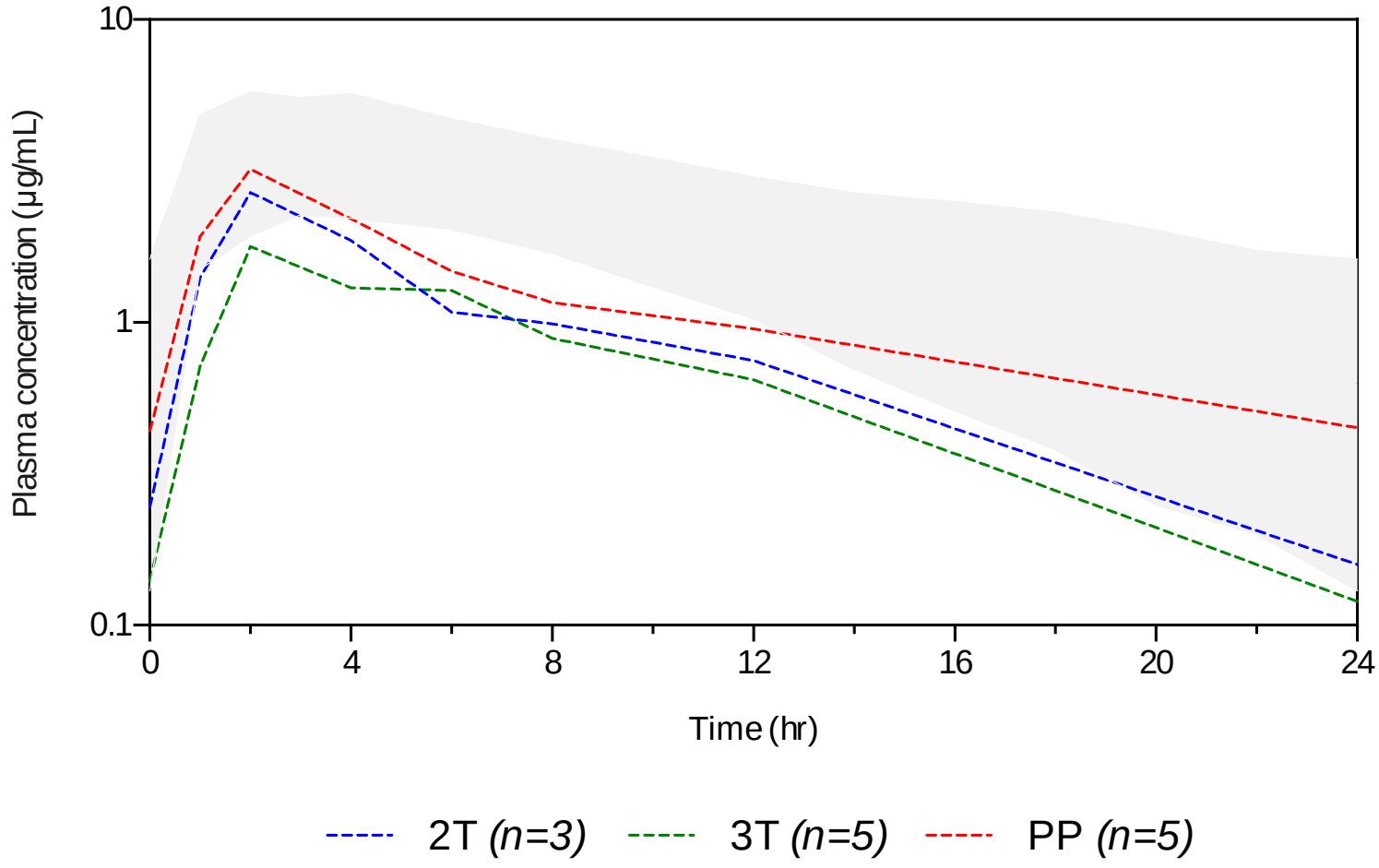
Methods

- IMPAACT protocol P1026s is an ongoing, nonrandomized, opportunistic, open-label, multi-center, prospective study of antiretroviral pharmacokinetics (PK) in HIV-infected pregnant women.
- Pregnant women living with HIV receiving ATV 300 mg with COBI 150 mg once daily as part of clinical care were eligible for enrollment.
- All medications were prescribed by the participants' clinical care providers, who managed toxicities and adverse events and evaluated virologic response.
- Intensive steady-state 24 hour PK profiles of ATV were performed during the 2nd trimester, 3rd trimester, and 6-12 weeks postpartum.
- ATV plasma concentrations were measured by a validated high-performance liquid chromatography (HPLC) assay with UV detection. The lower limit of quantification of the assay was 0.047 µg/mL.
- PK parameters were calculated with non-compartmental analysis using Phoenix, version 8.1 (Certara Corp., Princeton, NJ).
- For protocol management purposes, the minimum exposure target for ATV was the 10th percentile area under the concentration-time profile over the dosing interval at steady state (AUC_{tau}) in non-pregnant HIV infected patients receiving once daily ATV/RTV (28.4 µg*hr/mL).

Results: Clinical Characteristics

Maternal Demographics	Median (Range) or N (%) (*n*=6 enrolled)
Age at Delivery (years)	37.7 (28.1, 43.0)
Weight at Delivery (kg)	99.3 (60.9, 134.6)
Race/Ethnicity Black Non-Hispanic; Hispanic (regardless of race); White Non-Hispanic	4 (67%); 1 (17%); 1 (17%)
Country: United States	6 (100%)
2nd Trimester	
Gestational Age (wk)	23.3 (21.0, 26.6)
HIV-1 RNA ≤ 50 copies/mL	3/3 (100%)
3rd Trimester	
Gestational Age (wk)	33.1 (32.1, 34.1)
HIV-1 RNA ≤ 50 copies/mL	5/5 (100%)
Postpartum	
Weeks After Delivery	8.3 (7.3, 8.9)
HIV-1 RNA ≤ 50 copies/mL	5/5 (100%)
Pregnancy Outcomes	
Gestational Age (weeks)	36.4 (33.7, 40.0)
Birth Weight (grams)	2,997.5 (2,030.0, 3,280.0)

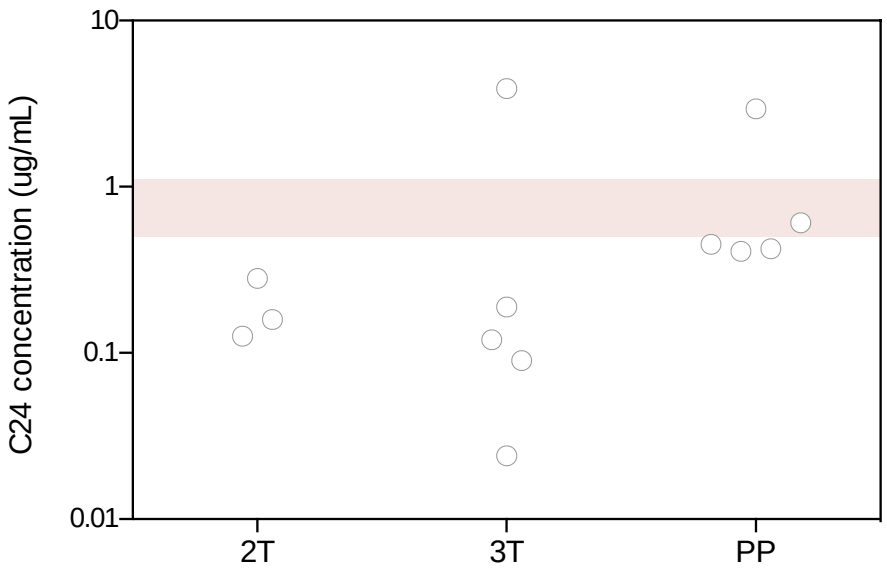
ATV median plasma concentration versus time profiles in the second trimester (2T), third trimester (3T), and postpartum (PP)



Shaded area displays the the 10th to 90th percentile AUC_{tau} in non-pregnant HIV infected patients receiving once daily ATV/RTV

ATV steady state trough concentrations

- The median (IQR) 24-hour trough concentration at steady state was 0.16 µg/mL (0.14 – 0.22) in 2T, 0.12 µg/mL (0.09 – 0.19) in 3T, and 0.45 µg/mL (0.42 – 0.61) in PP.
- ATV trough concentrations in 2T, 3T, and PP were 80%, 85%, and 44% lower, respectively, than previously reported values in non-pregnant, HIV-1 infected adult patients receiving once-daily dosing of 300/150 mg ATV/COBI.[1]
- One patient had a trough concentration below the lower limit of quantitation of the assay (0.047 µg/mL) which occurred in 3T.



Shaded area displays the 95% confidence interval for the mean ATV steady state trough concentration in non-pregnant, HIV-1 infected adult patients receiving once-daily dosing of 300/150 mg ATV/COBI.[1]

One BLOQ concentration is displayed as ½ the lower limit of quantitation.

1. Evotaz (atazanavir and cobicistat) [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2015.

ATV Pharmacokinetic Parameters in the 2nd Trimester, 3rd Trimester, and Postpartum

Parameter	2nd Trimester (n = 3)	3rd Trimester (n = 5)	Postpartum (n = 5)
$AUC_{0\text{-}24}$ (µg*hr/mL)	21.2 (20.6 – 22.5)	17.0 (8.9 – 27.5)	27.4 (24.0 – 36.4)
C_{max} (µg/mL)	2.7 (2.0 – 3.2)	1.78 (0.80 – 2.78)	3.21 (1.93 – 3.90)
C_{24} (µg/mL)	0.16 (0.14 – 0.22)	0.12 (0.09 – 0.19)	0.45 (0.42 – 0.61)
CL/F (L/hr)	12.61 (13.38 – 14.61)	17.65 (10.91 – 33.71)	10.95 (8.24 – 12.50)
$t_{1/2}$ (hr)	6.45 (5.56 – 6.71)	6.68 (4.72 – 8.60)	14.78 (10.20 – 20.97)

The frequency of participants meeting the target AUC_{tau} was 0/3 in 2T, 1/5 in 3T, and 2/5 in PP.

Maternal and Infant Safety

- 3 mothers with AE's ≥ grade 2:
  - 1 with low hemoglobin
  - 1 with high blood pressure and gestational diabetes (evaluated as possibly related to treatment)
  - 1 with hyperbilirubinemia (evaluated as treatment related)

- 2 infants with AE's ≥ grade 2:
  - 1 with prematurity, respiratory distress syndrome and hypoglycemia
  - 1 with prematurity, respiratory distress syndrome, seizures and a choroid plexus cyst

Conclusions

- In pregnant women living with HIV receiving ATV in fixed-dose combination with COBI as part of clinical care, ATV exposure appeared to be lower in pregnancy compared to postpartum, and compared to non-pregnant adults.

- Cobicistat plasma concentrations from this study are currently being analyzed.

- Additional PK, safety, and outcome data in a larger cohort of pregnant women are needed before ATV/COBI can be considered for use during pregnancy.

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