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

<table>
<thead>
<tr>
<th>Maternal Demographics</th>
<th>Median (Range) or N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal Demographics</td>
<td>(n=6 enrolled)</td>
</tr>
<tr>
<td>Age at Delivery (years)</td>
<td>37.7 (28.1, 43.0)</td>
</tr>
<tr>
<td>Weight at Delivery (kg)</td>
<td>99.3 (60.9, 134.6)</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td></td>
</tr>
<tr>
<td>Black Non-Hispanic; Hispanic (regardless of race);</td>
<td>4 (67%); 1 (17%); 1 (17%)</td>
</tr>
<tr>
<td>White Non-Hispanic</td>
<td></td>
</tr>
<tr>
<td>Country: United States</td>
<td>6 (100%)</td>
</tr>
</tbody>
</table>

### 2nd Trimester
- **Gestational Age (wk)**: 23.3 (21.0, 26.6)
- **HIV-1 RNA \( \leq 50 \) copies/mL**: 3/3 (100%)

### 3rd Trimester
- **Gestational Age (wk)**: 33.1 (32.1, 34.1)
- **HIV-1 RNA \( \leq 50 \) copies/mL**: 5/5 (100%)

### Postpartum
- **Weeks After Delivery**: 8.3 (7.3, 8.9)
- **HIV-1 RNA \( \leq 50 \) 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 10th to 90th percentile AUC_{\text{tau}} in non-pregnant HIV infected patients receiving once daily ATV/RTV
• 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.

ATV Pharmacokinetic Parameters in the 2\textsuperscript{nd} Trimester, 3\textsuperscript{rd} Trimester, and Postpartum

<table>
<thead>
<tr>
<th>Parameter</th>
<th>2\textsuperscript{nd} Trimester (n = 3)</th>
<th>3\textsuperscript{rd} Trimester (n = 5)</th>
<th>Postpartum (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC\textsubscript{0-24} (\mu g*hr/mL)</td>
<td>21.2 (20.6 – 22.5)</td>
<td>17.0 (8.9 – 27.5)</td>
<td>27.4 (24.0 – 36.4)</td>
</tr>
<tr>
<td>C\textsubscript{max} (\mu g/mL)</td>
<td>2.7 (2.0 – 3.2)</td>
<td>1.78 (0.80 – 2.78)</td>
<td>3.21 (1.93 – 3.90)</td>
</tr>
<tr>
<td>C\textsubscript{24} (\mu g/mL)</td>
<td>0.16 (0.14 – 0.22)</td>
<td>0.12 (0.09 – 0.19)</td>
<td>0.45 (0.42 – 0.61)</td>
</tr>
<tr>
<td>CL/F (L/hr)</td>
<td>12.61 (13.38 – 14.61)</td>
<td>17.65 (10.91 – 33.71)</td>
<td>10.95 (8.24 – 12.50)</td>
</tr>
<tr>
<td>t\textsubscript{1/2} (hr)</td>
<td>6.45 (5.56 – 6.71)</td>
<td>6.68 (4.72 – 8.60)</td>
<td>14.78 (10.20 – 20.97)</td>
</tr>
</tbody>
</table>

The frequency of participants meeting the target AUC\textsubscript{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.
Acknowledgements

• We wish to thank the women and infants who participated in the protocol and the staff of the participating IMPAACT sites, as well as the entire P1026 protocol team

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