Pharmacokinetics Of Increased Dose Atazanavir With And Without Tenofovir During Pregnancy

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Background

• Pharmacokinetics (PK) of many drugs, especially protease inhibitors, affected by pregnancy
• In previous study, plasma atazanavir (ATV) exposure decreased by:
  – ~30% during 3\textsuperscript{rd} trimester
  – an additional ~30% when coadministered with tenofovir (TDF)
• Goal of this study was to study ATV PK during pregnancy with an increased dose in the 3\textsuperscript{rd} trimester
P1026s Protocol

• IMPAACT network protocol
• Prospective, non-blinded study of PK of antiretrovirals in HIV-infected pregnant women receiving drugs of interest as part of clinical care
• Included 2 cohorts receiving ATV/RTV either with or without TDF according to the following schedule:
  – 300/100 mg once daily during the 2nd trimester (2\textsuperscript{nd} trim)
  – 400/100 mg during the 3rd trimester (3\textsuperscript{rd} trim)
  – 300/100 mg from delivery through 2 weeks postpartum (PP)
Methods

• Intensive steady-state 24-hour PK profiles were performed during 2nd trim, 3rd trim and PP
• Maternal and umbilical cord blood samples obtained at delivery
• ATV concentrations measured by HPLC with a detection limit of 0.047 mcg/mL
• PK targets:
  – AUC > 29.4 mcg*hr/mL, estimated 10th percentile in non-pregnant adults on standard dose (50% AUC=57 mcg*hr/mL)
  – C24h > 0.15 mcg/mL, suggested minimum target trough concentration
• Infant bilirubin concentrations were measured at 24-48 hours and 4-6 days after birth
Results

• ATV PK data available for 59 women
  – 28 without TDF, 31 with TDF
  – Ethnicity: 16 Black, 23 Hispanic, 3 White, 16 Asian, 1 Unknown
  – At delivery:
    • Median maternal age = 29.7 (19.8-44.7) years
    • Median maternal weight = 71.8 (53.0-134.4) kg
    • Median gestational age = 38.0 (32.4-41.0) weeks
    • Median birth weight = 3088 (1470-3750) grams
### PK Results

<table>
<thead>
<tr>
<th></th>
<th>ATV, no TDF</th>
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<th>ATV + TDF</th>
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<tbody>
<tr>
<td></td>
<td>2nd Trim</td>
<td>3rd Trim</td>
<td>PP</td>
<td>2nd Trim</td>
</tr>
<tr>
<td></td>
<td>(n=6)</td>
<td>(n=28)</td>
<td>(n=22)</td>
<td>(n=17)</td>
</tr>
<tr>
<td>AUC (mcg*hr/mL)</td>
<td>24.6 (9.2-93.8)</td>
<td>46.6 (11.0-88.3)</td>
<td>55.1 (9.9-99.5)</td>
<td>26.2* (6.8-60.9)</td>
</tr>
<tr>
<td>Met AUC target/total</td>
<td>3/6</td>
<td>22/28</td>
<td>17/22</td>
<td>7/17</td>
</tr>
<tr>
<td>Cmax (mcg/mL)</td>
<td>2.96 (0.99-6.66)</td>
<td>4.73 (0.88-7.50)</td>
<td>4.52 (0.93-9.45)</td>
<td>2.73* (0.61-5.70)</td>
</tr>
<tr>
<td>C24h (mcg/mL)</td>
<td>0.31 (0.09-2.82)</td>
<td>0.74 (0.14-2.09)</td>
<td>0.88 (bdl-2.73)</td>
<td>0.44* (0.12-1.06)</td>
</tr>
<tr>
<td>Met C24h target/total</td>
<td>5/6</td>
<td>27/28</td>
<td>17/22</td>
<td>16/17</td>
</tr>
</tbody>
</table>

PK parameters presented as medians (range)

bdl=below assay limit of detection

*P<0.05 compared to PP

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**ATV, no TDF**

- Median Atazanavir (mcg/mL) for nonpregnant 2nd Trim: n=6
- Median Atazanavir (mcg/mL) for nonpregnant 3rd Trim: n=28
- Median Atazanavir (mcg/mL) for nonpregnant PP: n=22

**ATV plus TDF**

- Median Atazanavir (mcg/mL) for nonpregnant 2nd Trim: n=17
- Median Atazanavir (mcg/mL) for nonpregnant 3rd Trim: n=31
- Median Atazanavir (mcg/mL) for nonpregnant PP: n=29
Clinical Outcomes

• ATV well tolerated by mothers
• 37 maternal grade 3 or 4 AE’s:
  – 23 elevated bilirubin
  – 2 increased amylase
  – 1 each for increased SGOT, increased SGPT, fever, hypotension, lower back pain, proteinuria, chronic hypertension, headache, diarrhea, vomiting, abdominal pain
• All newborn bilirubin concentrations were normal
• Infant infection status:
  17 uninfected, 32 pending/indeterminate
Maternal Delivery and Cord Blood ATV Concentrations

- Maternal delivery and cord blood samples available from 50 mother-infant pairs
- Median time between maternal dosing and delivery was 12.0 (0.6-47.7) hours
- Maternal ATV concentration above assay limit of detection at delivery in 48 mothers, with median ATV concentration of 1.38 (0.18-5.63) mcg/mL
- Median cord blood ATV concentration (n=48) was 0.15 (bdl – 1.33) mcg/mL
- Median ratio of cord blood/maternal delivery ATV concentration was 0.14 (0.02-4.08)
Conclusion

• ATV exposure is low with standard dosing during 2\textsuperscript{nd} trim but improved during 3\textsuperscript{rd} trim with the dose increase to 400/100mg

• ATV exposure PP on the standard dose equaled or exceeded that in the 3\textsuperscript{rd} trim on the increased dose

• ATV/r 400/100 mg provides adequate ATV exposure during the 3\textsuperscript{rd} trim and should be investigated during the 2\textsuperscript{nd} trim as well