Pharmacokinetics and Drug Interaction Profile of Cobicistat boosted-Elvitegravir with Atazanavir, Rosuvastatin or Rifabutin

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Abstract #O_03
Introduction

- **Elvitegravir (EVG) Profile:**
  - ~ -2.0 log\(_{10}\) mean change in HIV-1 RNA over 10 days as monotherapy\(^1\)
  - High rates of efficacy, fewer CNS/psychiatric AEs as EVG/COBI/FTC/TDF (QUAD) vs. EFV/FTC/TDF (Atripla®) or Atazanavir/r + TVD in treatment-naïve patients\(^2,3\)
  - Metabolized primarily via CYP3A, secondarily via UGT1A1/3
  - Boosted substantially by COBI 150 mg similar to RTV 100 mg

- **EVG/r PK**
  - EVG 150 mg → 85 mg with ATV; Rifabutin 300 mg QD → 150 mg QOD\(^4\)
  - No data with newer (non-CYP3A) statins

- **COBI Profile**
  - Potent CYP3A inhibitor, weak 2D6 inhibitor, no effects on other CYPs or UGT
  - Similar inhibition as RTV of Pgp, BCRP (intestinal), OATP1B1/3 (liver)

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\(^1\) DeJesus E, et al. JAIDS 43(1):1-5, 2006; \(^2\) Sax et al. CROI, 2012; \(^3\) DeJesus et al. CROI, 2012; \(^4\) German et al. IWCPHT, 2008
Objective

- COBI-boosted EVG 85 mg plus ATV PK
- COBI-boosted EVG and statin (non-CYP3A) interaction
  - Rosuvastatin minimally metabolized (CYP2C9)
  - Substrate for BCRP, OATP1B1, OATP1B3
  - Dosing guidance for QUAD
- COBI-boosted EVG and dose-reduced rifabutin (150 mg QOD)
  - Dosing guidance for QUAD

Design

- Three cohorts with fixed-sequence crossover design
  - Rosuvastatin given as single dose
  - All other treatments given as multiple doses
Demographics and Safety

- Demographics across three cohorts
  - Equal distribution by gender
  - Roughly 80% white, 20% black
  - Median age 35 years and BMI 28 kg/m²

- Safety Results
  - No Grade 4 or serious adverse events (serious AEs)
  - Five discontinuations during EVG/co plus ATV
    - Three Grade 3 hyperbilirubinemia, one Grade 3 rash, one Grade 2 abdominal pain
      - AEs generally consistent with ATV product labeling
      - Hyperbilirubinemia returned to baseline levels upon treatment discontinuation
    - Other AEs: constipation and headache, mostly Grade 1
Elvitegravir and Rosuvastatin (ROS) PK

- No ROS dose adjustment with QUAD per US PI
- EVG, COBI PK unaffected

### Rosuvastatin PK

<table>
<thead>
<tr>
<th></th>
<th>EVG/co + ROS</th>
<th>ROS</th>
<th>GMR (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (%CV)</td>
<td>38 (40)</td>
<td>27 (41)</td>
<td>138 (114, 167)</td>
</tr>
<tr>
<td>(AUC_{\text{inf}}) (ng.hr/ml)</td>
<td>38 (40)</td>
<td>27 (41)</td>
<td>138 (114, 167)</td>
</tr>
<tr>
<td>(C_{\text{max}}) (ng/ml)</td>
<td>5.0 (41)</td>
<td>2.7 (55)</td>
<td>189 (148, 242)</td>
</tr>
<tr>
<td>(T_{1/2}) (hr)</td>
<td>18 (17, 21)</td>
<td>21 (14, 27)</td>
<td>-</td>
</tr>
<tr>
<td>Median (Q1, Q3)</td>
<td>Presented at the 13th Int. W</td>
<td></td>
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</tbody>
</table>
Elvitegravir and Atazanavir PK

ATV, EVG, COBI PK comparable with reference/historical data
Effect of EVG/co on Rifabutin/metabolite PK

<table>
<thead>
<tr>
<th></th>
<th>Rifabutin Exposures</th>
<th>25-O-desacetyl rifabutin Exposures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (%CV)</td>
<td>Rifabutin + EVG/co</td>
<td>Rifabutin</td>
</tr>
<tr>
<td>AUC (ng.hr/ml)</td>
<td>8370 (13)</td>
<td>9320 (29)</td>
</tr>
<tr>
<td>C_max (ng/ml)</td>
<td>566 (17)</td>
<td>529 (27)</td>
</tr>
<tr>
<td>C_tau (ng/ml)</td>
<td>74 (30)</td>
<td>80.1 (39)</td>
</tr>
</tbody>
</table>

• Similar Rifabutin exposures, 21% higher antimycobacterial activity with EVG/co vs alone

Presented at the 13th Int. Workshop on Clin. Pharmacology of HIV Pharmacology – 2012, Barcelona Spain
Effect of Rifabutin on EVG PK

<table>
<thead>
<tr>
<th></th>
<th>EVG/co + RIF</th>
<th>EVG/co</th>
<th>GMR (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC&lt;sub&gt;τ&lt;/sub&gt;</td>
<td>18400 (26)</td>
<td>23000</td>
<td>79.4 (74.1, 85.1)</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>2050 (25)</td>
<td>2250</td>
<td>91.1 (83.6, 99.4)</td>
</tr>
<tr>
<td>C&lt;sub&gt;τ&lt;/sub&gt;</td>
<td>164 (61)</td>
<td>452</td>
<td>32.9 (26.9, 40.1)</td>
</tr>
</tbody>
</table>

- EVG C<sub>τ</sub> lower with rifabutin
  - Range (45-318 ng/ml) in Ph 3 bottom quartile
  - Conservatively, QUAD codosing not recommended

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Effect of Rifabutin on COBI PK

- COBI exposures lower with rifabutin

### COBI Exposures

<table>
<thead>
<tr>
<th></th>
<th>EVG/co + RIF</th>
<th>EVG/co</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC_{tau}</td>
<td>11400 (29)</td>
<td>11200 (19)</td>
</tr>
<tr>
<td>C_{max}</td>
<td>1880 (29)</td>
<td>1640 (19)</td>
</tr>
<tr>
<td>C_{tau}</td>
<td>6.5 (72)</td>
<td>22.8 (61)</td>
</tr>
</tbody>
</table>

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Historical data: Effect of Rifampin on ATV, RTV

**ATV**
- ATV/r 300/100
- ATV 400
- ATV/r 400/200 + RIF
- ATV/r 300/200 + RIF
- ATV/r 300/100 + RIF

**RTV**
- ATV/r 300/100
- ATV/r 400/200 + RIF
- ATV/r 300/200 + RIF
- ATV/r 300/100 + RIF

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>ATV 400</th>
<th>ATV/r 300/100</th>
<th>ATV/r 300/100+RIF</th>
<th>ATV/r 300/200+RIF</th>
<th>ATV/r 400/200+RIF</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATV Cmin (ng/ml)</td>
<td>187</td>
<td>707</td>
<td>18</td>
<td>43</td>
<td>53</td>
</tr>
<tr>
<td>RTV AUC (ng.h/ml)</td>
<td>10200</td>
<td>1520</td>
<td>11,900</td>
<td>11,300</td>
<td></td>
</tr>
</tbody>
</table>

Figures shown with permission from Drs. Burger and Bertz
Conclusions

• COBI-boosted EVG and Rosuvastatin: no clinically relevant interactions
  – No relevant effects based on inhibition of BCRP, OATP1B1 and OATP1B3 by EVG/COBI
  – No dose adjustment of rosuvastatin necessary with QUAD

• No clinically relevant interactions with COBI-boosted EVG 85 mg + ATV
  – Consistent with historical data on EVG/r

• EVG and COBI exposures lower with rifabutin
  – Coadministration with QUAD not recommended presently
  – Additional evaluation with antimycobacterial agents planned