Pharmacokinetics of Two Common Antiretroviral Regimens in Older HIV-Infected Patients: A Pilot Study

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Abstract O_12

2nd International Workshop on HIV and Aging
Background

• By 2015, 50% of the U.S. HIV-infected population will be ≥ 50 years old\(^1\)

• Treatment outcomes:\(^2\)
  – Excellent virologic response
  – Blunted immune response

• Role of altered PK?
  – Known changes in physiology
  – Has not been systematically explored

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Study Objective

• Describe PK of 2 common regimens in non-frail HIV+ patients ≥55 years
  – Tenofovir/emtricitabine/efavirenz (TFV/FTC/EFV)
  – Tenofovir/emtricitabine/atazanavir/ritonavir (TFV/FTC/ATV/r)

• Support future long-term population PK/PD studies

PK: Pharmacokinetics; PD: Pharmacodynamics
Inclusion/Exclusion Criteria

**Inclusion**

- ≥55 years of age
- On study regimen for ≥2 weeks
- Adherent to medications
  - ≥90% of doses in 30 days

**Exclusion**

- Frailty phenotype
- Concomitant medication expected to cause a significant change in Cmax and/or AUC
- Clinically significant lab abnormalities
  - DAIDS Grade 2 or higher

Cmax: maximal concentration; AUC: area under the concentration-time curve


Presented at the 2nd Int. workshop on HIV & Aging, 27 – 28 Oct 2011, Baltimore, USA
Study Design

- Screening Visit: informed consent, adherence assessment, safety labs, frailty phenotyping

- PK Visit:

- Follow-up visit: CBC, adverse events

CBC: Complete blood count
Data Analysis

- Drug concentrations
  - HPLC/UV \(^1, 2\)
- Noncompartmental Analysis
  - Phoenix Win Nonlin
- PK Modeling
  - MC-PEM in S-ADAPT with S-ADAPT TRAN\(^3\)
- Nonparametric Statistics
  - SAS JMP 7; alpha = 0.05

1. Rezk NL et al. *Journal of Chromatography B* 2005
2. Rezk NL et al. *Journal of Chromatography B* 2004
## Results: Demographics (mean ± SD)

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>TFV/FTC/EFV Subjects (n = 6)</th>
<th>TFV/FTC/ATV/r Subjects (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yrs)</strong></td>
<td>60.7 ± 5.4</td>
<td>58.7 ± 1.4</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>3 (50%)</td>
<td>3 (50%)</td>
</tr>
<tr>
<td>African American</td>
<td>3 (50%)</td>
<td>3 (50%)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>4 (66.7%)</td>
<td>2 (33.3%)</td>
</tr>
<tr>
<td>Male</td>
<td>2 (33.3%)</td>
<td>4 (66.7%)</td>
</tr>
<tr>
<td><strong>Duration with HIV (yrs)</strong></td>
<td>14.3 ± 10.3</td>
<td>8.4 ± 3.9</td>
</tr>
<tr>
<td><strong>Duration on current regimen (yrs)</strong></td>
<td>3.5 ± 3.65</td>
<td>3.4 ± 1.7</td>
</tr>
<tr>
<td><strong>CD4+ T-cell count (cells/mm³)</strong></td>
<td>683 ± 226</td>
<td>952 ± 455</td>
</tr>
<tr>
<td><strong>HIV RNA &lt;50 copies/mL</strong></td>
<td>5/6</td>
<td>6/6</td>
</tr>
<tr>
<td><strong>Creatinine clearance (ml/min)</strong></td>
<td>69.4 ± 25.0</td>
<td>70.9 ± 7.46</td>
</tr>
</tbody>
</table>

p = NS
TFV PK

Tenofovir Concentration vs. Time:
TFV/FTC/EFV

Kiser JJ et al, JAIDS 2008

Tenofovir Concentration vs. Time:
TFV/FTC/ATV/r

Presented at the 2nd Int. workshop on HIV & Aging, 27 – 28 Oct 2011, Baltimore, USA
Rousseau FS et al, JAC 2001
## TFV/FTC PK Parameters

**median (IQR)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Regimen</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (ug/L)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt;: Published Comparator (ug/L)</th>
<th>AUC&lt;sub&gt;0-24hr&lt;/sub&gt; (hr*ug/L)</th>
<th>AUC&lt;sub&gt;0-24hr&lt;/sub&gt;: Published Comparator (hr*ug/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TFV&lt;sup&gt;1&lt;/sup&gt;</strong></td>
<td>EFV</td>
<td>295 (223, 421)</td>
<td>340</td>
<td>3430 (3050, 4050)</td>
<td>3710</td>
</tr>
<tr>
<td></td>
<td>ATV/r</td>
<td>319 (275, 417)</td>
<td></td>
<td>3330 (2920, 4230)</td>
<td></td>
</tr>
<tr>
<td><strong>FTC&lt;sup&gt;2&lt;/sup&gt;</strong></td>
<td>EFV</td>
<td>1780 (1410, 2050)</td>
<td>1410</td>
<td>14 100 (10 300, 19 100)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ATV/r</td>
<td>1840 (1470, 2130)</td>
<td></td>
<td>10 500 (8540, 12 400)</td>
<td>8010</td>
</tr>
</tbody>
</table>

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2. Rousseau FS et al, JAC 2001

Presented at the 2<sup>nd</sup> Int. workshop on HIV & Aging, 27 – 28 Oct 2011, Baltimore, USA
### PK Parameter Ratios

**median (IQR)**

<table>
<thead>
<tr>
<th>Drug Regimen</th>
<th>TFV</th>
<th>FTC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AUC (_{0-24 hr})</strong></td>
<td>↓ 0.92 (0.84, 0.99) ↓ 0.90 (0.82, 0.96) ↑ 1.75 (1.39, 2.23) ↑ 1.31 (1.21, 1.42)</td>
<td></td>
</tr>
<tr>
<td><strong>C(_{max})</strong></td>
<td>↓ 0.87 (0.72, 1.15) ↓ 0.94 (0.85, 1.05) ↑ 1.26 (1.08, 1.35) ↑ 1.31 (1.17, 1.40)</td>
<td></td>
</tr>
</tbody>
</table>
Sustiva Full US Prescribing Information, *Bristol-Myers Squibb; Taburet AM et al*, AAC 2004
EFV, ATV PK Parameters
median (IQR)

<table>
<thead>
<tr>
<th>Drug</th>
<th>$C_{\text{max}}$ (ug/L)</th>
<th>$C_{\text{max}}$: Published Comparator (ug/L)</th>
<th>$\text{AUC}_{0-24\text{hr}}$ (hr*ug/L)</th>
<th>$\text{AUC}_{0-24\text{hr}}$: Published Comparator (hr*ug/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFV$^1$</td>
<td>3403 (2840, 6120)</td>
<td>4070</td>
<td>60 800 (46 000, 96 000)</td>
<td>58 000</td>
</tr>
<tr>
<td>ATV$^2$</td>
<td>3750 (2120, 4610)</td>
<td>3440</td>
<td>34 700 (25 500, 38 500)</td>
<td>39 300</td>
</tr>
</tbody>
</table>

PK Parameter Ratios
median (IQR)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>EFV</th>
<th>ATV</th>
</tr>
</thead>
<tbody>
<tr>
<td>$AUC_{0-24hr}$</td>
<td>$\leftrightarrow$</td>
<td>↓ 0.88 (0.79, 0.91)</td>
</tr>
<tr>
<td></td>
<td>1.05 (0.83, 1.23)</td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$</td>
<td>↓ 0.84 (0.73, 1.24)</td>
<td>↑ 1.09 (0.81, 1.15)</td>
</tr>
</tbody>
</table>

$p = \text{NS}$
PK Modeling

![PK Model Diagram]

<table>
<thead>
<tr>
<th>Drug</th>
<th>TFV₁</th>
<th>FTC²</th>
<th>EFV³</th>
<th>ATV⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean CL ± SD</td>
<td>1401 ± 327 (mL/min)</td>
<td>276 ± 57 (mL/min)</td>
<td>2.1 ± 0.8 (mL/min/kg)</td>
<td>184 ± 116 (mL/min)</td>
</tr>
<tr>
<td></td>
<td>807.7 ± 279.2 (mL/min)</td>
<td>168 ± 10 (mL/min)</td>
<td>3 (mL/min/kg)</td>
<td>128 (mL/min)</td>
</tr>
</tbody>
</table>

1. Viread U.S. Prescribing Information
2. Emtriva U.S. Prescribing Information
4. Dickinson L et al, JAC 2009

Presented at the 2nd Int. workshop on HIV & Aging, 27 – 28 Oct 2011, Baltimore, USA
Conclusions

<table>
<thead>
<tr>
<th></th>
<th>TFV</th>
<th>FTC</th>
<th>EFV</th>
<th>ATV</th>
</tr>
</thead>
<tbody>
<tr>
<td>$AUC_{0-24hr}$</td>
<td>↓</td>
<td>↑</td>
<td>↔</td>
<td>↓</td>
</tr>
<tr>
<td>$C_{max}$</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
</tr>
</tbody>
</table>

- TFV and FTC CL > CrCL
  - Filtration and secretion intact
- CrCL does not explain PK results
  - Decreased TFV, increased FTC
- EFV\(^1\) and ATV results unexpected

Moving Forward…

• Intracellular tenofovir diphosphate/emtricitabine triphosphate PK
• Protein-free EFV and ATV
• Sparse-sampling population PK/PD analysis
  – Frail and non-frail subjects of all ages
• Ultimate goal:
  – Determine if age-specific ARV dosing recommendations are warranted
Acknowledgements

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  – Society of Infectious Diseases Pharmacists (JBD)
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  – NIAID/NIH
    • K23AI093156 (JBD), K23AI077355 (KBP)
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