Intraindividual comparison of efavirenz, atazanavir, or ritonavir plasma pharmacokinetics before and during 21-days of vaginally administered hormone contraception

AIDS Clinical Trials Group A5316

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K. Scarsi has no financial relationships with commercial entities to disclose.
Background

• Rates of unintended pregnancy remain high in women living with HIV
• There are known drug-drug interactions between ART (perpetrator) and hormonal contraceptives (victim)
• Hormones may also induce or inhibit drug-metabolizing enzymes, with potential to influence antiretroviral exposure
  – Statistically lower exposure described for EFV, RTV, and NFV when combined with various routes of contraceptive methods
  – Others find no difference in antiretroviral exposure
• Few intensive PK studies have evaluated antiretroviral exposure with and without exogenous administration of hormones on ART
Rationale and Objectives

**Combined contraceptive vaginal ring**

NuvaRing<sup>®</sup>:

ethinyl estradiol/etonogestrel 15/120 mcg/day

- Etonogestrel (ENG)
- Ethinyl estradiol (EE)

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**Primary Study Objective**

- Characterize plasma hormone exposure when combined with EFV- or ATV/r-based ART
  (Scarsi et al. CROI 2018)

  - ATV/r-based ART ↓ ethinyl estradiol (EE) concentrations 29-35%, yet ↑ etonogestrel (ENG) concentrations by 71-79%
  - EFV-based ART ↓ EE by 53-57% and ↓ ENG concentrations by 76-79%

**Secondary objective**

- Estimate the effect of ENG/EE on the pharmacokinetics of ATV, RTV, and EFV

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Methods

• For antiretroviral PK: within group pharmacokinetic evaluation of two groups of women living with HIV and currently receiving ART

Inclusion Criteria:
• ≥ 16 years of age and of reproductive potential
• Willing to use a second, non-hormonal form of effective contraception
• If not yet receiving ART: CD4+ cell count ≥350 cells/mm³ at screening
• ART groups: Stable regimen ≥ 30 days with HIV-1 RNA ≤400 copies/mL

Exclusion criteria:
• No concurrent hormonal therapies or drugs that interact with ART or hormone
• Approved by ethics committees at each site and registered as NCT01903031

Control Group:
Not yet receiving ART

EFV Group:
EFV 600mg daily + ≥ 2 NRTIs

ATV/r Group:
ATV/r 300/100mg + TDF 300mg daily + ≥1 NRTI
Entry:
ATV/r and EFV PK assessment:
0 (pre-dose), 1, 3, 4, 5, and 8 hours post-observed dose;
HIV-RNA

Day 21:
ATV/r and EFV PK repeated:
0 (pre-dose), 1, 3, 4, 5, and 8 hours post-observed dose;
HIV-RNA

- Adherence to ART was assessed by self report
  - PK visit rescheduled if participant reported a missed dose in the prior 3 days

Antiretroviral Pharmacokinetic (PK) and Statistical Analysis:
- $AUC_{0-24h}$ and $AUC_{0-8h}$ were calculated using the linear trapezoidal rule
  - $AUC_{0-24h}$: pre-dose concentration ($C_{0h}$) as the imputed concentration as $C_{24h}$
  - $AUC_{0-8h}$ was not calculated if the $C_{8h}$ was missing
- Intraindividual ART PK was compared between Day 21 and Day 0 by GMR (90% CI) and statistically compared with Wilcoxon signed-rank test
Results: participants included in ART PK analyses

- Assigned to arm based on ART
  - EFV group (n=28)
    - Missed day 21 visit (n=1);
    - Treatment discontinued per participant request (n=2);
    - Poor venous access (n=1)
    - Included in PK analyses (n=24)
  - ATV/r group (n=29)
    - Consent withdrawn (n=1);
    - Did not receive intervention (n=1);
    - Protocol violations (TDF omitted, n=2 and vaginal ring adherence n=1);
    - Poor venous access (n=1)
    - Included in PK analyses (n=23)
## Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>EFV Group (n=24)</th>
<th>ATV/r Group (n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>36 (24, 55)</td>
<td>37 (24, 48)</td>
</tr>
<tr>
<td>Race/Ethnicity; n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>15 (63)</td>
<td>9 (39)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>8 (33)</td>
<td>8 (35)</td>
</tr>
<tr>
<td>Asian, Pacific Islander</td>
<td>0 (0)</td>
<td>5 (22)</td>
</tr>
<tr>
<td>White</td>
<td>1 (4)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>26.9 (17.4, 64.5)</td>
<td>25.8 (19.2, 59.5)</td>
</tr>
<tr>
<td>CD4 (cells/mm$^3$)*</td>
<td>746 (343, 1941)</td>
<td>656 (301, 1515)</td>
</tr>
<tr>
<td>Viral load (copies/mL)*</td>
<td>&lt;40 (&lt;40, 2071)</td>
<td>&lt;40 (&lt;40, 327)</td>
</tr>
</tbody>
</table>

Data presented as median (range), unless indicated.

*Variable n per group
<table>
<thead>
<tr>
<th>EFV Median (range)</th>
<th>Geometric Mean Ratio (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day 0</strong> (ART alone)</td>
<td><strong>Day 21</strong> (ART + NuvaRing)</td>
</tr>
<tr>
<td><strong>Cmax (mcg/mL)</strong></td>
<td>4.54 (1.35, 18.67)</td>
</tr>
<tr>
<td><strong>Cmin (mcg/mL)</strong></td>
<td>2.12 (0.90, 13.62)</td>
</tr>
<tr>
<td><strong>AUC(_{0-24h}) (h*mcg/mL)</strong></td>
<td>68.95 (27.11, 367.99)</td>
</tr>
<tr>
<td><strong>AUC(_{0-8h}) (h*mcg/mL)</strong></td>
<td>26.97 (8.64, 131.62)</td>
</tr>
</tbody>
</table>

BLQ: Below the lower limit of quantitation, 20 ng/mL (n=1)  
^\(\text{AUC}\(_{0-8h}\) n=23\)  
*Wilcoxon Signed-Rank test <0.05
Efavirenz concentration-time-curve, median (IQR)

Proportion of participants with:
- $\text{AUC}_{0-24h}$ decrease = 15 of 24 (62.5%)
- EFV concentration $<1 \text{mg/L} = 4$ of 24 (16.7%)
Atazanavir pharmacokinetic parameters (n=23)

<table>
<thead>
<tr>
<th></th>
<th>ATV Median (range)</th>
<th>Geometric Mean Ratio (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 0 (ART alone)</td>
<td>Day 21 (ART + NuvaRing)</td>
</tr>
<tr>
<td><strong>Cmax (ng/mL)</strong></td>
<td>4291 (770, 9440)</td>
<td>3583 (84, 6578)</td>
</tr>
<tr>
<td><strong>Cmin (ng/mL)</strong></td>
<td>797 (BLQ, 2731)</td>
<td>599 (BLQ, 3599)</td>
</tr>
<tr>
<td><strong>AUC_{0-24h} (h*mcg/mL)</strong></td>
<td>44.31 (8.80, 91.77)</td>
<td>36.76 (10.85, 108.45)</td>
</tr>
<tr>
<td><strong>AUC_{0-8h} (h*mcg/mL)</strong></td>
<td>20.56 (4.41, 42.68)</td>
<td>18.32 (0.42, 43.88)</td>
</tr>
</tbody>
</table>

BLQ: Below the lower limit of quantitation, 20 ng/mL (n=3)

^AUC_{0-8h} n=21
Atazanavir concentration-time curve, median (IQR)

Proportion of participants with:
- $\text{AUC}_{0-24\text{h}}$ decrease = 14 of 23 (60.9%)
- ATV concentration $<150$ ng/mL: 4 of 23 (17.4%)
Ritonavir pharmacokinetic parameters (n=23)

<table>
<thead>
<tr>
<th></th>
<th>RTV Median (range)</th>
<th>Geometric Mean Ratio (90% CI)</th>
<th>Day 21:Day 0</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 0 (ART alone)</td>
<td>Day 21 (ART + NuvaRing)</td>
<td></td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>1437 (426, 3078)</td>
<td>1063 (BLQ, 2297)</td>
<td>0.59*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.38, 0.91)</td>
</tr>
<tr>
<td>Cmin (ng/mL)</td>
<td>70.0 (BLQ, 1042)</td>
<td>51.9 (BLQ, 917)</td>
<td>0.67</td>
</tr>
<tr>
<td></td>
<td>(BLQ, 1042)</td>
<td></td>
<td>(0.38, 1.19)</td>
</tr>
<tr>
<td>$\text{AUC}_{0-24h}$ (h*mcg/mL)</td>
<td>10.74 (3.92, 32.63)</td>
<td>7.21 (0.24, 31.73)</td>
<td>0.63*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.45, 0.89)</td>
</tr>
<tr>
<td>$\text{AUC}_{0-8h}$ (h*mcg/mL)</td>
<td>6.75 (2.29, 15.88)</td>
<td>5.35 (0.08, 13.65)</td>
<td>0.66*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.46, 0.96)</td>
</tr>
</tbody>
</table>

BLQ: Below the lower limit of quantitation, 20 ng/mL (n=6)

*Wilcoxon Signed-Rank test <0.05

^$\text{AUC}_{0-8h}$ n=21
Proportion of participants with:

- $\text{AUC}_{0-24h}$ decreased = 16 of 23 (69.6%)
HIV-RNA at entry (Day 0) and after 21 days of vaginally administered contraception

<table>
<thead>
<tr>
<th>Treatment arm</th>
<th>Day 0</th>
<th>Day 21</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HIV-RNA (copies/mL); median (range)</td>
<td>HIV-RNA (copies/mL); median (range)</td>
</tr>
<tr>
<td>EFV-based ART</td>
<td>&lt;40 (&lt;40, 2071)</td>
<td>&lt;40 (&lt;40, 3451)</td>
</tr>
<tr>
<td>HIV-RNA &lt;400 copies/mL; n (%)</td>
<td>22 (96%)</td>
<td>23 (96%)</td>
</tr>
<tr>
<td>HIV-RNA &lt;40 copies/mL; n (%)</td>
<td>21 (91%)</td>
<td>20 (83%)</td>
</tr>
<tr>
<td>ATV/r-based ART</td>
<td>&lt;40 (&lt;40, 327)</td>
<td>&lt;40 (&lt;40, 98)</td>
</tr>
<tr>
<td>HIV-RNA &lt;400 copies/mL; n (%)</td>
<td>23 (100%)</td>
<td>23 (100%)</td>
</tr>
<tr>
<td>HIV-RNA &lt;40 copies/mL; n (%)</td>
<td>21 (91%)</td>
<td>20 (87%)</td>
</tr>
</tbody>
</table>
Conclusions and Discussion

• We observed moderately lower EFV (13-36%) and RTV (34-41%) concentrations after 21 days of continuous vaginal ring (ethinyl estradiol/etonogestrel) contraceptive use.

• Despite lower RTV exposure, ATV exposure was not statistically different.

• Median Cmin values remained within the expected range for each antiretroviral at Day 21.
  - Four participants in each ART group had at least one EFV or ATV concentration below a conservative concentration threshold.

    • 1 of 8 participants plasma HIV-RNA increased from <40 copies/mL at entry to 54 copies/mL on Day 21.
    • 7 of 8 remained virologically suppressed.

• Despite lower ARV concentrations, a significant DDI was still observed with the combined hormonal contraceptive (Scarsi et al. CROI 2017).
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