Mucosal Tissue Pharmacokinetics of Maraviroc and Raltegravir in Women: Implications for Chemoprophylaxis

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## Once Daily PrEP May Not Be Feasible in Women

<table>
<thead>
<tr>
<th>Study Title</th>
<th>Study Population</th>
<th>Treatment(s)</th>
<th>Effect Size HR (95% CI)</th>
<th>PK Evidence of Recent Use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Protection</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partners PrEP</td>
<td>Serodiscordant Couples</td>
<td>Daily Oral TDF</td>
<td>0.33 (0.19, 0.56)</td>
<td>&gt;80%</td>
</tr>
<tr>
<td>Partners PrEP</td>
<td>Serodiscordant Couples</td>
<td>Daily Oral TDF/FTC</td>
<td>0.25 (0.13, 0.45)</td>
<td>&gt;80%</td>
</tr>
<tr>
<td>iPrEx</td>
<td>MSM</td>
<td>Daily Oral TDF</td>
<td>0.56 (0.37, 0.85)</td>
<td>28%</td>
</tr>
<tr>
<td>TDF2</td>
<td>Heterosexuals</td>
<td>Daily Oral TDF/FTC</td>
<td>0.38 (0.17, 0.84)</td>
<td>78%</td>
</tr>
<tr>
<td>Bangkok TDF</td>
<td>IV Drug Users</td>
<td>Daily Oral TDF/FTC</td>
<td>0.51 (0.29, 0.91)</td>
<td>65%</td>
</tr>
<tr>
<td>CAPRISA004</td>
<td>Women</td>
<td>BAT24 TFV Gel</td>
<td>0.63 (0.42, 0.94)</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Futility</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEM-PrEP</td>
<td>Women</td>
<td>Daily Oral TDF/FTC</td>
<td>Futile</td>
<td>&lt;25%</td>
</tr>
<tr>
<td>VOICE</td>
<td>Women</td>
<td>Daily Oral TDF</td>
<td>Futile</td>
<td>&lt;30%</td>
</tr>
<tr>
<td>VOICE</td>
<td>Women</td>
<td>Daily Oral TDF/FTC</td>
<td>Futile</td>
<td>&lt;30%</td>
</tr>
<tr>
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<td>Women</td>
<td>Daily TFV Gel</td>
<td>Futile</td>
<td>&lt;30%</td>
</tr>
</tbody>
</table>

FTC Emtricitabine, MSM men who have sex with men, TDF Tenofovir disoproxil fumarate, TFV Tenofovir

PrEP Adherence Requirement May Differ by Exposure Site

Phase I, single center, open-label, dose ranging single-dose Maraviroc and Raltegravir PK study

- Study Aims
  1. Determine if mucosal tissue concentrations are dose proportional
  2. Develop a predictive PK model of tissue distribution

- UNC IRB # 10-1393

- ClinicalTrials.gov: NCT01330199
Study Design

Inclusion Criteria
- Healthy, premenopausal women
- 18-49 years
- Intact gastrointestinal and genital tracts
- Regular menstrual cycles
- History of normal Pap smear

Exclusion Criteria
- Medication allergies
- Clinically significant medical conditions
- Abnormal laboratory tests
- Symptomatic bacterial vaginosis or any STI
- Pregnant or lactating
- Positive urine drug screen

Dose w/in 45 days

Screening visit

Intensively sampled blood plasma

Dose

0 0.5 1 2 3 4 6 9 12 18 24 36 48

PK visit (hours)

7-10 days after last biopsy

Follow up visit

Sparsely sampled cervical, vaginal, and rectal tissue
Treatment Arms

Total Subjects
N=49

Maraviroc
N=25

50%
150mg
N=8

100%
300mg
N=9

200%
600mg
N=8

Withdrew
N=1

Raltegravir
N=24

50%
200mg
N=8

100%
400mg
N=8

200%
800mg
N=8

Not Analyzed
N=1

Maraviroc N=25

150mg N=8

300mg N=9

600mg N=8

Withdrew N=1

Raltegravir N=24

200mg N=8

400mg N=8

800mg N=8

Not Analyzed N=1
Methods

- Sample Analysis – LC-MS/MS
  - Plasma calibration range: 5-5000ng/ml
  - Tissue homogenate calibration range: 0.02-20ng/ml

- Data Analysis - WinNonlin®
  - Individual plasma NCA
  - Composite tissue NCA

- Statistical Analysis
  - Dose proportionality
    - Power model equation:\( AUC = e^{\beta_1 \cdot \text{Dose}^{\beta_2}} \)
    - Assumed if the 90% CI of slope (\( \beta_1 \)) falls within: 0.64, 1.36
  - SigmaPlot ® Mann-Whitney Rank Sum and Wilcoxon Signed Rank test, where appropriate
  - SigmaPlot ® Linear regression

## Sample Demographics

<table>
<thead>
<tr>
<th>Variable</th>
<th>MRV (n=24)</th>
<th>RAL (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Female</strong></td>
<td>24 (100)</td>
<td>24 (100)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>16 (67)</td>
<td>18 (75)</td>
</tr>
<tr>
<td>African American</td>
<td>7 (29)</td>
<td>4 (17)</td>
</tr>
<tr>
<td>Asian American</td>
<td>1 (4)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>American Indian</td>
<td>0 (0)</td>
<td>1 (4)</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>27 (22-31)</td>
<td>22 (21-27)</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>67 (60-76)</td>
<td>63 (58-72)</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>24.1 (21.5-26.3)</td>
<td>22.5 (20.8-26.5)</td>
</tr>
</tbody>
</table>
## Safety

<table>
<thead>
<tr>
<th>Adverse Event (≤ Grade 1)</th>
<th>Maraviroc [n (%)]</th>
<th>Raltegravir [n (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>8 (32)</td>
<td>10 (42)</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (4)</td>
<td>5 (21)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (8)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Bowel disturbances</td>
<td>1 (4)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Elevated transaminases</td>
<td>0</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Pelvic cramps</td>
<td>0</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Vaginal dryness</td>
<td>0</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

### Graph

- **Y-axis:** % Subjects Reporting Adverse Events
- **X-axis:** Dose Levels (50%, 100%, 200%)
- **Legend:**
  - Maraviroc
  - Raltegravir

The graph shows the percentage of subjects reporting adverse events at different dose levels for Maraviroc and Raltegravir.
Maraviroc Plasma Exposure and Dose Proportionality
Median ± IQR (N=24)

\[ \beta_1 \ (90\% \ CI) = 1.14 \ (0.88, 1.4) \]

Prespecified range = (0.64, 1.36)
Raltegravir Plasma Exposure and Dose Proportionality
Median ± IQR (N=23)

Log Dose
2.2 2.3 2.4 2.5 2.6 2.7 2.8 2.9 3.0
Log AUC₀-48
3.4 3.6 3.8 4.0 4.2 4.4 4.6

Regression Line
r²=0.64, p<0.001

β₁ (90% CI) = 0.79 (0.56, 1.02)
Prespecified range = (0.64, 1.36)
Similar Exposure between the Vaginal and Cervical Tissue

Maraviroc

Cervical Tissue
Vaginal Tissue

p=0.074

Raltegravir

Cervical Tissue
Vaginal Tissue

p=1.00
Maraviroc Pharmacokinetics in Tissue (Median ± Range)

Cervical/Vaginal Tissue

- Tmax = 6 (6,6) hr
- BLQ/BLD=0/48

Rectal Tissue

- Tmax = 6 (6,24) hr
- BLQ/BLD=0/24
Raltegravir Pharmacokinetics in Tissue
(Median ± Range)

**Cervical/Vaginal Tissue**

- **Tmax** = 6 (6,6) hr
- BLQ = 2/46, BLD = 1/46

**Rectal Tissue**

- **Tmax** = 24 (6,48) hr

BLQ/BLD = 0/23
Linearity and Dose Proportionality in Tissue

Maraviroc

CT/VT $\beta_1$ (90% CI) = 1.19 (0.9, 1.47)
RT $\beta_1$ (90% CI) = 1.56 (0.67, 2.46)

Raltegravir

CT/VT $\beta_1$ (90% CI) = 0.78 (0.34, 1.24)
RT $\beta_1$ (90% CI) = 2.35 (0.81, 3.89)

Prespecified range = (0.64, 1.36)
Exposure is Higher in the Rectal Tissue than Cervical/Vaginal Tissue [Median (±Range)]

- **Maraviroc**:
  - Median: 10 (8, 16)
  - Exposure is ~10-Fold higher in Rectal Tissue.

- **Raltegravir**:
  - Median: 4 (4, 6)
  - Exposure is ~25-Fold higher in Rectal Tissue.

* p<0.05
Plasma Concentrations Correlate with Cervical/Vaginal but not Rectal Tissue

Cervical/Vaginal Tissue

Rectal Tissue

Plasma Concentration (ng/ml)

Tissue Concentration (ng/g)

Maraviroc
Raltegravir

$r^2=0.72, p<0.001$

$r^2=0.76, p<0.001$

$r^2=0.04, p=0.786$

$r^2=0.001, p>0.4$
Conclusions

- **Rapid distribution**
  - CT/VT: Tmax ~6hr
  - RT: Tmax ~ 6hr for maraviroc and ~24hr for raltegravir
- **No difference between CT and VT concentrations**
- **Maraviroc tissue exposure vs dose**
  - ↑ 4 fold [CT/VT] and 8-fold [RT] across dosing range
  - Linear trend; Not dose proportional
- **Raltegravir tissue exposure vs dose**
  - ↑ 2 fold [CT/VT] and 28-fold [RT] across dosing range
  - Linear trend in CT/VT but not RT; Not dose proportional
- **10-25-fold higher concentration in RT than in the CT/VT**
- **Plasma concentrations correlate with CT/VT but not RT**
- **Future directions**: Predictive PK/PD modeling of concentrations achieved by various dosing schemes
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