CAN TENOFOVIR DIPHOSPHATE AND EMTRICITABINE TRIPHOSPHATE CONCENTRATIONS IN TOTAL BLOOD CELLS BE USED TO MEASURE ADHERENCE?

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Recent HIV Prevention Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Effect size (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>HPTN 052</td>
<td>96% (73; 99)</td>
</tr>
<tr>
<td>Partners in PrEP</td>
<td>73% (49; 85)</td>
</tr>
<tr>
<td>TDF2</td>
<td>63% (22; 83)</td>
</tr>
<tr>
<td>iPrEX</td>
<td>44% (15; 63)</td>
</tr>
<tr>
<td>CAPRISA 004</td>
<td>39% (6; 60)</td>
</tr>
<tr>
<td>FEM-PrEP</td>
<td>0% (-69; 41)</td>
</tr>
<tr>
<td>VOICE (tenofovir gel daily)</td>
<td>0% (-49; 34)</td>
</tr>
<tr>
<td>VOICE (tenofovir oral daily)</td>
<td>0%</td>
</tr>
</tbody>
</table>

Updated from Karim, *Lancet* 2011
Tenofovir (TFV) Concentrations in FEM-PrEP

Heterosexual women at 4 study sites in Africa were instructed to take tenofovir/emtricitabine by mouth daily and to return for monthly follow-up visits.

![Graph showing tenofovir concentrations in FEM-PrEP](image)

Van Damme, CROI 2012
TFV and FTC Plasma Concentrations Do Not Accurately Estimate Adherence

Dumond et al. AIDS 2007
FEM-PrEP “Upper Layer Packed Cells” (ULPC) Collection for HIV DNA

EDTA tubes collected at each monthly visit
✓ Both plasma and ULPC stored

ULPC ~10^6-7 PBMCs and ~10^9-10 RBCs

Presented at the 13th Int. Workshop on Clin. Pharmacology of HIV Pharmacology – 2012, Barcelona Spain
TFV-DP in Red Blood Cells

TFV DP Correlation

m=0.56
p=0.007

Fold Difference
1.7 (p=0.04)

Median half-life (IQR)
16.8 (15.2-19.9) days

Rower et al, Intl Workshop on Clinical Pharmacology of HIV Therapy 2011; Catillo-Mancilla CROI 2012

Presented at the 13th Int. Workshop on Clin. Pharmacology of HIV Pharmacology – 2012, Barcelona Spain
Objectives

• Evaluate the utility of ULPC collected in FEM-PrEP as a measure of longer-term adherence
  – Compare TFV-DP and FTC-TP concentrations in ULPC samples to PBMC samples in HIV+ subjects
  – Evaluate stability of TFV-DP and FTC-TP in ULPC samples as processed by FEM-PrEP investigators
## Study Methods & Analysis

<table>
<thead>
<tr>
<th>Subjects</th>
<th>10 HIV+ patients adherent to an ARV regimen containing Truvada (tenofovir/emtricitabine) with undetectable HIV RNA viral load</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>Paired ULPC and PBMC samples collected over 6 hours around a dose (either 0-6h or 12-18h)</td>
</tr>
<tr>
<td><strong>Laboratory Analysis</strong></td>
<td>TFV-DP and FTC-TP concentrations analyzed by LC-MS/MS with assay ranges for ULPC of 12.5-12,500 ng/ml (TFV-DP) and 12.5-2,500 ng/ml (FTC-TP) normalized by cell counts and MW to fmol/10^6 cells</td>
</tr>
<tr>
<td><strong>Data Analysis</strong></td>
<td>Descriptive statistics and partial areas under the curve (AUC) computed using WinNonlin v6.2. Spearman Rank Correlations (rho) between PBMC and ULPC determined using SAS 9.2</td>
</tr>
</tbody>
</table>
Results
Pharmacokinetics in ULPC vs PBMC

TFV-DP Concentrations 4.5X higher in ULPC
FTC-TP Concentrations 99.5% lower in ULPC

TFV-DP

FTC-TP

GMR (90% CI) = 4.63 (4.10–5.23)

GMR (90% CI) = 0.0048 (0.0037–0.0063)
Results

TFV-DP and FTC-TP Concentrations Correlate in ULPC Samples

\[ \rho = 0.74 \]
\[ p < 0.0001 \]
Results
TFV-DP and FTC-TP Concentrations Correlate Between ULPC and PBMC

TFV-DP
- TFV-DP in PBMCs (fmol/10^6 cells)
- TFV-DP in ULPC (fmol/10^6 cells)
- rho = 0.64
- p < 0.0001

FTC-TP
- FTC-TP in PBMCs (fmol/10^6 cells)
- FTC-TP in ULPC (fmol/10^6 cells)
- rho = 0.56
- p < 0.0001
Results

ULPC Discriminates Between Single and Multiple Dosing

Data presented as median (range)
Results

TFV-DP and FTC-TP Is Stable in ULPC With FEM PrEP Processing

Median (range) Increase 6% (-20 to 53%)  Median (range) Increase 54% (-29 to 115%)
Conclusions

• TFV-DP and FTC-TP detectable in all multi-dose samples
  – TFV-DP is 4.5X higher in ULPC samples than PBMCs
  – FTC-TP is 99.5% lower in ULPC samples than PBMCs

• ULPC concentrations significantly correlated with PBMC concentrations

• Preliminary single-dose data suggest good discrimination between intermittent vs. consistent dosing

• Limited intracellular drug degradation with 14 hour refrigeration of ULPC
Implications

- Red cells easier to obtain and process at study sites than PBMCs
- 100-fold difference in TFV-DP concentration between single and multiple dosing suggests potential discrimination in adherence patterns
- ~2500 FEM-PrEP ULPC samples currently being analyzed for adherence measures
  - case-cohort comparison with monthly plasma sampling
Acknowledgements

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