Making Sense of Oral and Topical PrEP trials: Little Studies to Inform Big Studies

Craig W. Hendrix, MD
Johns Hopkins University School of Medicine
Informing in what ways?

- Concentration-response
  - Target concentration?
  - Target location?

- Explain variable response among populations?

- Adherence assessment
  - Post hoc Interpretation of RCT outcomes?
  - Real-time study intervention?
Little studies inform…

- concentration-response relationship (target)
- site of action
- colon tissue “advantage” falls with dose frequency
- topical dosing advantage dose per dose
- RCT adherence rates “on average”
- individual adherence assessments fare less well
- design of RCT best when done prior to RCT
<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>Relative Risk Reduction (95% CI)</th>
<th>All Subjects</th>
<th>Drug Detectible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partners</td>
<td>TDF po qd</td>
<td>0.67 (0.44 – 0.81)</td>
<td>0.86 (0.57–0.95); BLQ 0.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TDF/FTC po qd</td>
<td>0.75 (0.55 – 0.87)</td>
<td>0.90 (0.56–0.98); BLQ 0.3</td>
<td></td>
</tr>
<tr>
<td>CDC TDF2</td>
<td>TDF/FTC po qd</td>
<td>0.62 (0.22 – 0.83)</td>
<td>50% SC, 80+% NSC; BLQ 0.3</td>
<td></td>
</tr>
<tr>
<td>iPrEX</td>
<td>TDF/FTC po qd</td>
<td>0.42 (0.15 – 0.63)</td>
<td>0.92 (0.40 – 0.99) ; BLQ 10</td>
<td></td>
</tr>
<tr>
<td>FEM-PrEP</td>
<td>TDF/FTC po qd</td>
<td>0.06 (-0.41 – 0.52)</td>
<td>No diff. 25% v 35%;BLQ 10</td>
<td></td>
</tr>
<tr>
<td>VOICE</td>
<td>TDF po qd</td>
<td>-0.49 (-1.30 – 0.035)</td>
<td>No difference; BLQ .0.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TDF/FTC po qd</td>
<td>-0.04 (-0.50 – 0.30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAPRISA 004</td>
<td>TFV gel BAT24</td>
<td>0.39 (0.04 – 0.60)</td>
<td>&gt;1,000 CVF increased RRR</td>
<td></td>
</tr>
<tr>
<td>VOICE</td>
<td>TFV gel qd(^e)</td>
<td>0.15 (-0.20 – 0.40)</td>
<td>No difference; BLQ 0.3</td>
<td></td>
</tr>
</tbody>
</table>
Why no consistent pattern in the data?
Tissue Cell Frame of Reference (F.O.R.)

Pharmacokinetics (PK)  Pharmacodynamics (PD)

Topical  Oral, Rectal, Vaginal  Oral
Lumen  Oral  Tissue  Blood
5  3  1
CD4+ Cells  CD4+ Cells  CD4+ Cells
TFV→TFVpp  TFV→TFVpp  TFV→TFVpp
6  4  2

[Tissue CD4+ TFV-Diphosphate]

Relative Risk Reduction

At the site of action oral and topical dosing achieves the same effective concentration (best PK/PD model fit).

iPrEx Concentration-response

$EC_{90} = 16 \text{ fmol/M (95\%CI 3-28) viable cells (mean 24-48 fresh lysed cells).}$

Can single dose achieve EC$_{90}$?

Most subjects below iPrEx EC$_{90}$ with single dose (16 viable = 24-48 fresh lysed)

Are rectal > vaginal tissue concentrations?

- Single dose TDF, 6 women (paired across all matrices)
- Weekly tissue sampling x 2 weeks
- RV:VT TFV-DP homogenate c/w Patterson (STM 2011)
- RT:VT ratio varies with drug moiety & sample type
- Initial 24h colon:vaginal gradients not sustained
  - colon homogenate and CD4 cell half-life < vaginal tissue
- Rectal “advantage” clearest with > weekly dosing

<table>
<thead>
<tr>
<th>Day</th>
<th>RT:VT TFV Plasma Median (IQR)</th>
<th>RT:VT TFV-DP Homogenate Median (IQR)</th>
<th>RT:VT TFV-DP CD4 Cells Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>33.8 (6.8, 37.8)</td>
<td>123.7 (8.4, 155.4)</td>
<td>19.20 (9.60, 28.8)</td>
</tr>
<tr>
<td>8</td>
<td>4.5 (0.9, 31.3)</td>
<td>1.7 (0.3, 2.8)</td>
<td>0.20 (0.17, 0.23)</td>
</tr>
<tr>
<td>15</td>
<td>0.3 (0.3, 0.3)</td>
<td>2.5 (2.5, 2.6)</td>
<td>0.15 (0.15, 0.15)</td>
</tr>
</tbody>
</table>

Louissaint, et al. ARHR 2013
Does dosing route affect concentrations?

- 144 women daily oral, vaginal, & combination dosing, 6 weeks each

- Vaginal tissue TFV-DP **Vaginal** 130x > Oral (topical tissue advantage)

- Serum TFV Oral 56x > Vaginal (serum doesn’t reflect tissue)

- Large pre-dose concentration variation warned of poor VOICE adherence

Hendrix, et al. PLOS One 2013
How does PK inform VOICE Adherence?

<table>
<thead>
<tr>
<th>Adherence Measure</th>
<th>TDF</th>
<th>FTC/TDF</th>
<th>TFV Gel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product return</td>
<td>87%</td>
<td>92%</td>
<td>86%</td>
</tr>
<tr>
<td>ACASI Self report</td>
<td>90%</td>
<td>91%</td>
<td>90%</td>
</tr>
<tr>
<td>TFV ever detected (0.31 ng/mL)</td>
<td>42%</td>
<td>50%</td>
<td>45%</td>
</tr>
</tbody>
</table>
VOICE: Unadjusted TFV Concentrations

- TDF Oral
- TDF/FTC Oral
- TFV 1% Gel

Expected 24 hour post-dose plasma TFV concentration with single dose
Requires adjustment to compare distributions of oral and vaginal dosing
VOICE: Adjusted TFV Concentrations

Oral TDF

Vaginal 1% TFV Gel

Density

log(1+TFV concentration)
Unadjusted plasma

Density

log(1+TFV concentration*56)
Tissue adjusted plasma

Oral v. vaginal dosing adjustment suggests similar oral and topical adherence.
Can tissue provide useful frame of reference?

![Graph showing relative risk reduction for HIV infection against unadjusted plasma tenofovir levels.](image-url)
[Tissue] nicely informs concʼn-response
PK-based adherence intervention

- “Study X”: 3 product, 8 week per product, cross-over study
- 4 & 8 week plasma “real time” for drug concentration
- How do I select Yes/No PK result to inform adherence counseling?

- “Non-Adherence” (below limit quantitation - pink) varies with route
- Equivalent adherence - oral 10 ng/mL c/w topical 0.3 ng/mL
- PBMC, hair, DBS – insensitive +/- or Tss too long with 8 week/product
PK or PD based adherence threshold?

<table>
<thead>
<tr>
<th>Week</th>
<th>PK Threshold</th>
<th>PD Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt; Lower LOQ (0.25 ng/mL)</td>
<td>&gt; 1,000 ng/mL</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adherence assessments using CVF PK (0.25) or PD (1,000) thresholds
Little studies inform…

- …concentration-response relationship (target)
- …site of action
- …colon tissue “advantage” falls with dose frequency
- …topical dosing advantage dose per dose
- …RCT adherence rates “on average”
- …individual adherence assessments fare less well
- …design of RCT best when done prior to RCT
Questions