The Conundrum of Topical or Systemic PreP in Women:
Drug at the Right Place & Right Time

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## ASPIRE and The Ring Study Results – A Snapshot

<table>
<thead>
<tr>
<th>Study</th>
<th>The Ring Study (IPM 027) International Partnership for Microbicides</th>
<th>ASPIRE (MTN 020) Microbicide Trials Network</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study design and enrollment</td>
<td></td>
</tr>
<tr>
<td>Objectives</td>
<td>Long term safety and effectiveness</td>
<td>Safety and effectiveness</td>
</tr>
<tr>
<td>Study design</td>
<td>Double blind randomized placebo controlled with 2:1 randomization (active: placebo)</td>
<td>Double blind randomized placebo controlled with 1:1 randomization (active: placebo)</td>
</tr>
<tr>
<td>Enrollment</td>
<td>Total: 1959 women, ages 18-45 Active arm: ~1300</td>
<td>Total: 2629 women, ages 18-45 Active arm: ~1325</td>
</tr>
<tr>
<td>Regulatory requirement</td>
<td>3000 women on dapivirine ring for at least 1 year follow-up</td>
<td>1500 women on dapivirine ring for 2 year follow-up</td>
</tr>
<tr>
<td>Participant follow-up</td>
<td>2 years + 6 weeks following ring discontinuation</td>
<td>Minimum 1 year + 4 weeks following ring discontinuation</td>
</tr>
<tr>
<td>Research sites</td>
<td>7 IPM research center partners in South Africa and Uganda</td>
<td>15 MTN research centers in Malawi, South Africa, Uganda, Zimbabwe</td>
</tr>
</tbody>
</table>

## Results

### Overall results
- The Ring Study: 31% effective, confidence interval 1-51
- ASPIRE: 27% effective, confidence interval 1-46

### Secondary analysis that excluded data from 2 sites with lower retention and adherence
- The Ring Study: 37% effective, confidence interval 12-56
- ASPIRE: 37% effective, confidence interval 12-56

### Results by age stratification (post hoc analysis)

#### Women over 21 years of age
- The Ring Study: 37% effective, confidence interval 3.5-59
- ASPIRE: 56% effective, confidence interval 31-71

#### Women 18-21 years of age
- The Ring Study: No statistically significant effect
- ASPIRE: No statistically significant effect

### HIV incidence
- The Ring Study: 4.1% among women in active arm
- 6.1% among women in placebo arm
- ASPIRE: 3.3% among women in active arm
- 4.5% among women in placebo arm
Factors that may impact efficacy

Behavior Adherence

STI/HIV Risk

Semen
Hormones
“Inflammatory state”
STI
Microbiota

Drug
PK/PD
What happens to drug PK/PD following sex: PRO 2000 Experience

<table>
<thead>
<tr>
<th>Visit 1</th>
<th>Visit 2</th>
<th>Visit 3</th>
<th>Visit 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>No drug</td>
<td>No drug</td>
<td>Drug</td>
<td>Drug</td>
</tr>
<tr>
<td>No coitus</td>
<td>Coitus</td>
<td>No Coitus</td>
<td>Coitus</td>
</tr>
<tr>
<td>Endogenous Activity</td>
<td>Impact of Sex on Endogenous Activity</td>
<td>PK/PD Following Vaginal Application</td>
<td>Impact of Sex on PK/PD</td>
</tr>
</tbody>
</table>
Loss in Antiviral Activity (PD) and Drug Recovered (PK) in postcoital

Keller and Herold, PLoSOne, 2010
Semen abrogates endogenous anti-E. coli and anti GBS activity of CVL (Nakra and Herold, JID 2016)
Modeling Effects of Semen with Next Generation Drugs

T cells treated with drug x 24 h (ring in place); challenged directly with HIV (no wash) Washed with medium or washed with 10% seminal fluid without adding more drug as might occur if ring is removed around sex; challenged with HIV
MTN 011: Impact of Sex on Tenofovir Gel PK/PD

<table>
<thead>
<tr>
<th>Gel</th>
<th>Visit</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>No gel</td>
<td>Baseline</td>
<td>Clinic</td>
</tr>
<tr>
<td>No gel</td>
<td>Post-Sex Baseline</td>
<td>Hotel</td>
</tr>
<tr>
<td>-1 h</td>
<td>Gel-1/Sex</td>
<td>Hotel</td>
</tr>
<tr>
<td>-1 h</td>
<td>Gel/No sex</td>
<td>Clinic</td>
</tr>
<tr>
<td>-24 h</td>
<td>Gel-24/Sex</td>
<td>Hotel</td>
</tr>
<tr>
<td>-24 h</td>
<td>Gel-24/No sex</td>
<td>Clinic</td>
</tr>
<tr>
<td>BAT</td>
<td>Gel-1.Sex/Gel+1</td>
<td>Hotel</td>
</tr>
</tbody>
</table>

- Target sampling ~2 h post-sex
- No sex sampling matched to preceding gel/coitus visits
- Washout of ~ 10 days between gel visits
- 24 couples completed -1 h matched visits; 22 the -24 h; 23 BAT
Study Participants

<table>
<thead>
<tr>
<th>Females</th>
<th>Cleveland (n=11)</th>
<th>Pittsburgh (n=13)</th>
<th>All Sites (N=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age: Mean (SD)</td>
<td>28.6 (6.0)</td>
<td>30.3 (9.1)</td>
<td>29.5 (7.7)</td>
</tr>
<tr>
<td>Currently married</td>
<td>4 (36%)</td>
<td>5 (38%)</td>
<td>9 (38%)</td>
</tr>
<tr>
<td>Attended college</td>
<td>10 (91%)</td>
<td>10 (77%)</td>
<td>20 (83%)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>10</td>
<td>9</td>
<td>19</td>
</tr>
<tr>
<td>Black</td>
<td>0</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Asian</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

- Median age males 29 (range 21-50)
- 58% males attended college
- 71% white; 96% of both M & F non-Hispanic
- 83% couples living together
TFV levels decrease after sex
CVL and Cervical Tissue

Note the variability in drug levels with doses applied at the clinic

Herold et al, Clinical Infectious Diseases® 2016;62(3):375–82
Semen/Sex Impact Endogenous Antimicrobial activity, PK & Efficacy

• Sex is associated with a significant decrease in luminal and tissue tenofovir and intracellular TFV-DP levels
• Effects may be greater for DPV (if ring removed pericoitally), which rapidly transits in and out of cells and binds avidly to semen
• Sustained delivery (or BAT dosing) would overcome effects
• Semen may also modulate infectivity of pathogens (enhance or inhibit) and immune responses
• Opinion:
  – Studies designed to measure PK/PD under conditions that more closely reflect how drugs will be used should be done prior to initiating Phase 2/3 trials
What about the microbiome?
Drugs are not released into culture medium
Hypothesis: Vaginal Microbiota Differ Across Populations and Modulate PK/PD

- Modulation of vaginal pH
- Bacteria can bind/absorb drugs and alter drug availability
- Bacteria release products that may degrade drugs or interfere with drug uptake
# Mechanisms of Drug Transport

<table>
<thead>
<tr>
<th>Drug</th>
<th>Structure</th>
<th>IC(_{50}) (µM)</th>
<th>Transport mechanism</th>
<th>Energy dependency</th>
<th>Saturability</th>
<th>Enzymes</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir (TFV)</td>
<td><img src="image" alt="TFV Structure" /></td>
<td>2.5</td>
<td>Endocytosis</td>
<td>ATP-dependent non-saturable</td>
<td></td>
<td></td>
<td>Taneva et al., AAC, 2015</td>
</tr>
<tr>
<td>TFV disoproxil fumarate (TDF)</td>
<td><img src="image" alt="TDF Structure" /></td>
<td>0.1</td>
<td>Passive diffusion</td>
<td>ATP-independent saturable Carboxylesterase-1 rate-limiting</td>
<td></td>
<td></td>
<td>Taneva et al., AAC, 2015</td>
</tr>
<tr>
<td>TFV alafenamide (TAF)</td>
<td><img src="image" alt="TAF Structure" /></td>
<td>0.05</td>
<td>Passive diffusion</td>
<td>ATP-independent saturable Cathepsin A rate-limiting</td>
<td></td>
<td></td>
<td>Taneva et al., (in prep)</td>
</tr>
<tr>
<td>Dapivirine (DPV)</td>
<td><img src="image" alt="DPV Structure" /></td>
<td>0.002</td>
<td>Passive diffusion</td>
<td>Unknown uptake/efflux mechanisms</td>
<td>Metabolized by CYP4503A4/5</td>
<td></td>
<td>To et al., <em>Biochem Pharmacol</em>, 2015</td>
</tr>
</tbody>
</table>
Summary Microbiota Studies

Tenofovir uptake is significantly reduced at pH > 5.5

Bacteria act as a sink and irreversibly bind DPV or accumulate TFV
No effect on TDF or TAF

- DPV is impacted by live and heat-killed bacteria - all species tested
- TFV is actively accumulated: most avidly by *L. crispatus*

Bacteria release products that interfere with TFV endocytosis in T cells
No effect on TDF, TAF or DPV uptake

- Inhibition by *G. vaginalis*; enhancement by *A. vaginae*
What about oral PrEP?

- Where does oral (systemic) PrEP act?
  - PBMC, lymph nodes or locally at tissue (vagina or cervix)
  - Levels in cervix significantly lower than plasma for many drugs suggesting not the site of action
  - Mechanism: TFV competes with deoxy ATP and FTC with dCTP for reverse transcription- tissue and cellular levels vary (gut versus cervix)

What about oral PrEP?

• Does the gut microbiome impact oral drug uptake/bioavailability?
  – Enteric coating of pills reduces impact of pH
  – Microbiome may alter expression of drug-metabolizing enzymes and transporters
    • Examples:
      – Digoxin is inactivated by enzyme expressed by *Eggerthelia lenta*
      – L-DOPA is sequestered by Helicobacter pyori
  – ?? PrEP drugs
Implications and Future Directions

• Understanding how intracellularly active drugs enter, egress and are metabolized informs potential efficacy
  – (TDF/TAF >>> TFV)

• Semen, pH, and microbiome impact PK/PD for some drugs by different mechanisms
  – Impact greatest when drug levels fall
  – Intermittent adherence

• Clinical studies to examine these effects could help streamline decisions about products and inform consumers
  – How long can I keep my ring out?

• Delivery systems could be optimized to overcome some of these effects