HIV PRE-EXPOSURE PROPHYLAXIS:
WHAT DO WE KNOW?

Angela DM Kashuba
UNC Chapel Hill

Presented at the 13th Int. Workshop on Clin. Pharmacology of HIV Pharmacology – 2012, Barcelona Spain
Controlling and Ending the HIV/AIDS Pandemic

- Aggressively seek, test, and treat infected individuals
- Prevent new infections
- “Cure” existing infections
HIV Prevention Principles

- Multiple strategies needed to assemble a complete toolkit
- No one prevention strategy will be appropriate to, or accepted by, everyone
## Four Prevention Opportunities for Sexual Transmission

<table>
<thead>
<tr>
<th>UNEXPOSED</th>
<th>EXPOSED (coital)</th>
<th>EXPOSED (postcoital)</th>
<th>INFECTED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavioral, Structural interventions</td>
<td>Vaccine, Topical Mic., PrEP</td>
<td>Vaccine PEP</td>
<td>Treatment Of HIV Reduced Infectivity</td>
</tr>
<tr>
<td>Circumcision Condom</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Timeline:*
- **YEARS**
- **HOURS** within 72h – 28d
- **MONTHS - YEARS**
The PrEP Challenge

To get the *right drug*
To the *right place*
In the *right concentration*
For the *right length of time*
The PrEP Challenge

To get the **right drug**
To the **right place**
In the **right concentration**
For the **right length of time**
The Right Place

Similar cell populations; different structure and proportion: 
implications for topical and oral dosing

Presented at the 13th Int. Workshop on Clin. Pharmacology of HIV Pharmacology – 2012, Barcelona Spain
The Right Place.....
Early Events in HIV Infection

The Right Place.....

$\alpha_4\beta_7$ CD4$^+$ T Cells with CCR5$^{\text{high}}$ Are Most Susceptible to Productive HIV Infection

Activated CD4$^+$ T cell

CCR5$^{\text{high}}$

$\alpha_4\beta_7^{\text{high}}$

Infected activated CD4$^+$ T cell

Fauci A. WAC 2010
**The Right Time**

1-3 hours  
HIV Translocates Through Mucosal Epithelium (Hu 2000, Greenhead 2000)

18-48 hours  

2-4 days  
Newly infected cells seen in submucosa (Maher 2005)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route of Infection</th>
<th>Outcome</th>
<th>Reference</th>
</tr>
</thead>
</table>
| TNF SC | Vaginal            | Full protection  
If 30mg/kg TNF SC within 36 hrs x 28 days;  
Partial protection if started at 72 hrs | Otten, J Virology 2000 |

*replication-competent HIV may reside in cervical tissue cx up to 8d (Collins 2000)*
## PrEP: The Right Concentration

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route of Infection</th>
<th>Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF SC</td>
<td>IV</td>
<td><strong>Full protection</strong></td>
<td>Tsai, Science 1995</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(TNF SC 20-30 mg/kg BW QD X 4 weeks (given 48 hrs pre or within 24 hours post exposure)</td>
<td>Van Rompay AIDS 1998, JID 2001</td>
</tr>
<tr>
<td>TNF SC</td>
<td>Oral</td>
<td><strong>Full protection</strong></td>
<td>Van Rompay, JID 2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TNF 30mg/kg pre and post, or just pre</td>
<td></td>
</tr>
<tr>
<td>TDF PO</td>
<td>Oral</td>
<td>Not protected</td>
<td>Van Rompay, JID 2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.037mg daily dose (equivalent to 0.011–0.018 mg/kg QD SC)</td>
<td></td>
</tr>
<tr>
<td>TDF PO (daily or weekly)</td>
<td>Rectal</td>
<td>Partial protection</td>
<td>Subbarao, JID 2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TDF 22 mg/kg body weight PO QD</td>
<td></td>
</tr>
<tr>
<td>TNF/FTC SC</td>
<td>Rectal</td>
<td><strong>Full protection</strong></td>
<td>Garcia-Lerma, CROI 2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TNF 22 mg/kg SC + FTC 20 mg/kg SC QD</td>
<td></td>
</tr>
<tr>
<td>TDF/FTC PO</td>
<td>Rectal</td>
<td>Partial protection</td>
<td>Garcia-Lerma, CROI 2007</td>
</tr>
<tr>
<td></td>
<td></td>
<td>full protection only with TNF 22 mg/kg SC + FTC 20 mg/kg SC QD</td>
<td></td>
</tr>
</tbody>
</table>

Presented at the 13th Int. Workshop on Clin. Pharmacology of HIV Pharmacology – 2012, Barcelona Spain
PrEP: The Right Concentration

Monkey-Human Exposure Comparison

- **Van Rompay AAC 2004**
  - TFV 30mg/kg SC
  - TFV 10mg/kg SC
  - TFV 2.5mg/kg SC

- **Subbarao JID 2006, Garcia-Lerma PLoS 2008**
  - TDF 22mg/kg PO

Time (hrs)

0 2 4 6 8 10 12 14 16 18 20 22 24

TNF Concentration (ng/mL)

100000 10000 1000 100 10

Presented at the 13th Int. Workshop on Clin. Pharmacology of HIV Pharmacology – 2012, Barcelona Spain
<table>
<thead>
<tr>
<th>Study (Sponsor)</th>
<th>Study and Agent(s) (dose)</th>
<th>Population (Target N)</th>
<th>Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPRISA 004 (NIAID)</td>
<td>Phase IIB safety and effectiveness of Tenofovir gel (1%) versus placebo gel given in a coitally-dependent manner</td>
<td>Premenopausal women Age: 18 to 35</td>
<td>South Africa</td>
</tr>
<tr>
<td>iPrEX (NIAID/BMGF)</td>
<td>Phase III daily Truvada or placebo</td>
<td>MSM Age: 18 and up (3000)</td>
<td>Peru, Ecuador, Brazil, Thailand, South Africa, USA</td>
</tr>
<tr>
<td>Partners Study (BMGF)</td>
<td>Phase III daily TDF, or Truvada, or placebo</td>
<td>Discordant heterosexual couples Age: 18 to 60 (4000)</td>
<td>Uganda, Kenya</td>
</tr>
<tr>
<td>TDF2 CDC-NCHSTP-4940; BOTUSA MB06</td>
<td>Phase III daily Truvada or placebo</td>
<td>Men and Women Age: 18 to 29 (1200)</td>
<td>Botswana</td>
</tr>
<tr>
<td>FemPrEP FHI (USAID)</td>
<td>Phase III daily Truvada or placebo</td>
<td>High Risk Women Age: 18 to 35 (3900)</td>
<td>Kenya, Malawi, South Africa, Tanzania, Zimbabwe</td>
</tr>
<tr>
<td>VOICE/MTN 003 (NIAID)</td>
<td>Phase IIB safety and effectiveness of daily Tenofovir gel (1%), placebo gel, or daily TDF (300mg), Truvada, or oral placebo</td>
<td>Premenopausal women Age: 18 to 35 (2400 oral, 1600 gel)</td>
<td>South Africa, Zambia, Malawi, Uganda, Zimbabwe</td>
</tr>
<tr>
<td>Bangkok TFV Study US CDC-NCHSTP-4370</td>
<td>Phase II/III daily TDF or placebo</td>
<td>IDU Age: 20 to 60 (2000)</td>
<td>Thailand</td>
</tr>
</tbody>
</table>
### Recent Prevention Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Effect size (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment for prevention</td>
<td>96% (73; 99)</td>
</tr>
<tr>
<td>Tenofovir/Truvada for discordant couples</td>
<td>73% (49; 85)</td>
</tr>
<tr>
<td>Truvada for heterosexuals</td>
<td>63% (22; 83)</td>
</tr>
<tr>
<td>Truvada for MSMs</td>
<td>44% (15; 63)</td>
</tr>
<tr>
<td>Tenofovir vaginal (coital)</td>
<td>39% (6; 60)</td>
</tr>
<tr>
<td>Tenofovir oral (daily) for women</td>
<td>0% (-69; 41)</td>
</tr>
<tr>
<td>Tenofovir gel (daily) for women</td>
<td>0% (-49; 34)</td>
</tr>
<tr>
<td>Tenofovir oral (daily) for women</td>
<td>0%</td>
</tr>
</tbody>
</table>

- HPTN 052: Partners PrEP
- TDF2: CAPRISA 004
- iPrEX: VOICE
- FEM PrEP: VOICE

What is Driving the Results?

- Statistical issues (unlikely)?
- Biologic Issues?
- Pharmacologic issues?
- Behavioral Issues?

The Scream, Eduard Munch
Biologic

- Does PrEP not work in high-risk populations?
  - Are cofactors more prevalent in FEM-PrEP and VOICE?
    - STIs
    - Partners with acute infection
    - Use of hormonal contraception
    - Intravaginal practices
    - Genital inflammation
  - Possible, but currently hypothetical

---

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

- Can you have too much of a good thing?
  - CAPRISA 004 (39% efficacy): BAT 24
  - VOICE (0% efficacy): Daily Dosing
  - TFV 1% gel is hyperosmolar (3111 mOsmol/kg) and may disrupt epithelial integrity

Rohan et al. PLoS One 2010
TFV 1% gel provides 1000X higher TFV concentrations in the vaginal lumen compared to oral TDF

Oral TDF provides 100x higher TFV and TFV-DP concentrations in rectal tissue compared to vaginal and cervical tissue

Are discordant couples different (Partners PrEP vs FEM PrEP & VOICE)?

Risk perception and partner support affect adherence

HPTN 052 adherence implications

P Anderson

B Vrijens

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