Pre-Exposure Topical Microbicides and Oral Prophylaxis Trials:
Rationale, Designs & Issues

Connie Celum, MD, MPH
Patrick Ndase, MBChB, MPH
May 2007 Regional MTN Meeting
Importance of HIV prevention

• Antiretroviral treatment alone will not be able to stem this epidemic

• No intervention is likely to be fully protective
  ♦ Need multiple approaches to HIV prevention (eg., male circumcision, HSV-2 suppression, PrEP)
  ♦ Need short-term interventions while working towards effective HIV vaccines and microbicides

• Need interventions that target reduced HIV infectiousness & decreasing HIV susceptibility
Interventions unlinked from timing of risk behavior

- HSV-2 suppression
- Pre-exposure Prophylaxis (PrEP)
- HAART to Treat HIV in Infected Persons
- Topical microbicides
- HIV vaccines
Rationale for Oral Chemoprophylaxis for HIV Prevention

- Vaccines & microbicides in early testing
- Continuous oral prophylaxis works against malaria and HIV PMTCT
- Efficacy demonstrated in animal models
- Can be combined with other prevention strategies
- Could be used by both genders
- Potentially could be effective against vaginal, anal, & parenteral transmission
Why test TDF and Truvada?

- Single daily dosing
- Potent NRTIs
- Safe profile (in HIV+)
- Limited resistance generated (in HIV+)
- Generic production underway
- Macaque data are encouraging re efficacy, low resistance
Macaque PrEP studies

- Tenofovir delayed time to infection
- Truvada (tenofovir/FTC) may have greater efficacy (in small animal studies)
- Studies underway in macaques:
  - PrEP with frequent, low dose challenges
  - Effect of PrEP on resistance in breakthrough infections
  - Compare viral set-point in those monkeys which received TDV vs TDV/FTC and among those, with and without resistant mutations
Design of PrEP Trials in Humans

- Placebo controlled, double-blind, randomized

- Primary endpoint is efficacy
  - In context of condoms, counseling & STI treatment

- Safety endpoints
  - Phosphorus (bone mineralization) & fractures
  - Kidney (renal insufficiency, Fanconi syndrome)
  - Hepatitis flares in persons with chronic Hepatitis B

- Adherence

- Risk behavior by arm and over time

- In seroconverters
  - Resistance to TDF or FTC/TDF
  - Effect on disease progression
## Existing Trials: Number of HIV Events

<table>
<thead>
<tr>
<th>Study Location (Sponsor)</th>
<th>PrEP Strategy</th>
<th>Risk Group</th>
<th>N</th>
<th>Power</th>
<th>Effect size</th>
<th>Number of Events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Completed Trial</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>West Africa (FHI/Gates)</td>
<td>Tenofivir</td>
<td>Women</td>
<td>1,200</td>
<td>90%</td>
<td>70%</td>
<td>30 events (2 TDF and 6 Placebo)</td>
</tr>
<tr>
<td><strong>Ongoing Trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thailand (CDC)</td>
<td>Tenofivir</td>
<td>IDUs 78% M 22% F</td>
<td>2,000</td>
<td>87%</td>
<td>67%</td>
<td>~50 events</td>
</tr>
<tr>
<td>Botswana (CDC)</td>
<td>Truvada</td>
<td>Heterosexual 50% M 50% F</td>
<td>1,200</td>
<td>80%</td>
<td>65%</td>
<td>~45 events</td>
</tr>
<tr>
<td><strong>Planned Trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peru/Ecuador (NIH)</td>
<td>Truvada</td>
<td>MSM</td>
<td>A: 1,400</td>
<td>87%</td>
<td>70%</td>
<td>~52 events</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>B: 3,200</td>
<td>90%</td>
<td>60%</td>
<td>~85 events</td>
</tr>
<tr>
<td><strong>Aborted Trial</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malawi (FHI/UNC/Gates)</td>
<td>Tenofivir</td>
<td>Heterosexual Men/Women</td>
<td>700 M 400 W</td>
<td>80%</td>
<td>80%</td>
<td>13 events (45 events)</td>
</tr>
<tr>
<td>Cambodia (NIH/Gates)</td>
<td>Tenofivir</td>
<td>Women</td>
<td>960</td>
<td>87%</td>
<td>67%</td>
<td>31 events</td>
</tr>
</tbody>
</table>
## Summary of PrEP trials

<table>
<thead>
<tr>
<th>Location</th>
<th>Sponsor</th>
<th>Pop’n</th>
<th>PrEP drug</th>
<th>Status</th>
<th>Approach to preg</th>
<th>Approach to BF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase II</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ghana</td>
<td>FHI/USAID &amp; Gates</td>
<td>936 high risk women</td>
<td>TDF</td>
<td>Completed</td>
<td>- no req’t for contraception</td>
<td>- BF excluded</td>
</tr>
<tr>
<td>US</td>
<td>CDC</td>
<td>400 MSM</td>
<td>TDF</td>
<td>Enr ends fall 2007</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Phase III</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thailand</td>
<td>CDC</td>
<td>2000 IDUs</td>
<td>TDF</td>
<td>Enrollment finished 2007</td>
<td>Non-barrier cont req’d</td>
<td>- BF excluded</td>
</tr>
<tr>
<td>Botswana</td>
<td>CDC</td>
<td>1200 young heterosexuals</td>
<td>Truvada</td>
<td>Enrollment resumed Mar 07</td>
<td>Non-barrier cont req’d</td>
<td>- BF excluded</td>
</tr>
<tr>
<td>Andes</td>
<td>NIAID</td>
<td>1400 MSM</td>
<td>Truvada</td>
<td>Enrollment May 2007</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Africa</td>
<td>BMGF (pending)</td>
<td>3900 HIV discordant couples</td>
<td>TDF &amp; Truvada</td>
<td>If funded, start fall 2007</td>
<td>Contraception offered (not req’d)</td>
<td>BF allowed</td>
</tr>
<tr>
<td>Africa</td>
<td>USAID/ BMGF</td>
<td>4000 high-risk women</td>
<td>Truvada</td>
<td>Start late 2007</td>
<td>Non-barrier cont req’d</td>
<td>- BF excluded?</td>
</tr>
</tbody>
</table>
Andean MSM PrEP Trial (IPrEX)

- 1400 MSM (likely to be increased to 2300) randomized to Truvada or placebo
- Will have 85 endpoints
- Efficacy of PrEP estimated to be 60%, sufficient statistical power to rule out low efficacy (<30%)
- Will do bone scans on subset
- Will evaluate cellular immune responses against HIV
- Will evaluate effect of Truvada discontinuation on hepatitis B flares
HIV discordant couples: Significance, Challenges, & Prevention Needs

- Majority of HIV transmissions in Africa occur in HIV discordant couples

- Identification of these couples is challenging

- Partners Study required large community outreach activities
  - ~48,000 couples tested for HIV (e.g., at VCTs); ~15% HIV discordant
  - 6,126 HIV discordant couples pre-screened for study eligibility
  - 3,148 couples enrolled (HIV+ partner HSV-2+ with CD4>250)

- HIV-negative women in discordant couples seek prevention strategies that allow them to safely become pregnant
Partners PrEP Scientific Objectives: Proof-of-Concept in HIV discordant couples

### Primary Objectives:
- Efficacy of PrEP: Power to assess predicted 60% efficacy
  - 90% power for pooled PrEP arms vs placebo
  - 82% power for each active arm vs placebo
  - Power to ‘rule out’ < 30% efficacy
- Safety (overall and specific rates of SAEs)

### Secondary Objectives:
- Rates of resistance in breakthrough infections (& their partners)
- PrEP efficacy by gender
- Impact of source partner HIV viral load on PrEP efficacy
- Study drug adherence
- Risk compensation
Proposed PrEP trial among HIV-negative partners in HIV discordant couples

3900 HIV- discordant couples with HIV+ partner >250

Randomize HIV- partners with normal liver, renal, hematologic function

Truvada once daily
Tenofovir once daily
Placebo once daily

Follow couples for up to 2 years

1° endpoint: HIV infection in HIV-negative partner
(estimated 3% in placebo arm)
Minimum Efficacy for Cost Effectiveness
By Lab Monitoring Required for Safety

Cost per HIV case averted

- High >50%
- Mod >40%
- Low >35%

Cost/User

Assume: Lowest Price, TDF, 5% inc.
High: q1mo, HBV+Chem.
Mod: q3mo, Cr/Chem
Low: q12mo, Cr/ALT

ARV Rx / person

Efficacy

Courtesy of Bob Grant
A few of the challenges ahead, if PrEP trial is funded

- More intensive protocol with additional lab testing & adverse event evaluation than for acyclovir suppression and microbicides trials
- Need well-trained, prepared sites to be able to recruit & retain couples, monitor safety, manage side effects, be able to refer ineligible couples for care
- Requires extremely vigilant site coordination, many logistics, and highly motivated, cohesive site team
- Need extensive community preparation & understanding of concept
Once you get the funding, you think it’s going to be like this....

Western Utah Range Country
But then it ends up being like this...

The Trollstigen (Troll's Path), Isterdalen, Norway
Community challenges with ART based oral & topical microbicides Trials

Patrick Ndase MBChB, MPH
MTN Regional Physician
Community challenges with ART based oral & topical microbicides

- Context: Not clear what results will be for current products under trial (two failed products)
- More transparency about the why and the how of moving into ART based microbicide research
  - Inevitably need to engage community in regard to previous failures & successes
  - May require a more proactive approach with both community & media
- Extensive community consultation (Cabs, IRB, gov’t treatment activists etc) to develop appropriate central & site specific communication education plans
- Partnerships and planning to rapidly integrate results (involvement of potential implementers)
Understanding HIV prevention trials
- Particularly concept of using ARVs to prevent rather than treat HIV (prevention paradox)

Drug sharing
- Bigger issue in Household with HIV + members

Resistance in breakthrough infections
- Lots of discussion, limited data
- Valuable lessons to be learnt from CDC Truvada trial in Botswana

Follow-up and treatment of seroconverters
- Standard in HIV microbicide trials (MTN 015 – sero-converter protocol)
Access & Programmatic Issues for PrEP

- Access of ARVs for HIV+
  - Controversy assoc with PrEP when ARV supply isn’t sufficient to treat HIV+ cases

- Cost of scale up, if topical or oral ART works
  - Will be expensive relative to other potential strategies (acyclovir suppression, diaphragm, male circumcision)

- Need for pharmaco-vigilance surveillance
  - Unprescribed ARV use & resistance at population level

- Ways to monitor impact on risk behavior and HIV incidence
  - Assumption that change in behavior could offset as much as 50% effectiveness in PrEP