CDC PrEP Trials

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7 February 2007
Why Test PrEP?

- Vaccines and microbicides years away
- Continuous oral prophylaxis approach effective in other settings
  - Malaria
  - HIV PMTCT
  - Animal HIV transmission models
- Easily combined with other prevention modalities
- Could be used by both genders and possibly against several routes of transmission
- Implementation feasible in the era of global ART access
Why TDF and TDF/FTC?

- Safety and resistance profile favorable
- Daily single dose widely available and at low cost in developing countries
- Macaque data supportive
# Efficacy Trial Design Differences Thailand and Botswana

<table>
<thead>
<tr>
<th>Thailand</th>
<th>Botswana</th>
</tr>
</thead>
<tbody>
<tr>
<td>- N=2000 IDU</td>
<td>- N=1200 heterosexuals</td>
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<tr>
<td>- 24 mo accrual, 12+ mo follow-up</td>
<td>- 15 mo accrual, 12+ mo follow-up</td>
</tr>
<tr>
<td>- TDF daily</td>
<td>- TDF+FTC daily</td>
</tr>
<tr>
<td>- 20-60 years old</td>
<td>- 18-29 years old</td>
</tr>
<tr>
<td>- 78% men, 22% women</td>
<td>- 50% men, 50% women</td>
</tr>
<tr>
<td>- 2% estimated incidence</td>
<td>- 5% estimated incidence</td>
</tr>
<tr>
<td>- DOT for majority</td>
<td>- DOT not available</td>
</tr>
<tr>
<td>- DEXA not done</td>
<td>- DEXA on a subset</td>
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</tbody>
</table>
Collaborative Effort
Thailand and Botswana

- Conducted at sites with long-standing MOH collaborations and local scientific leadership
  - Thailand-US Collaboration (TUC)
    - Dr. Kachit Choopanya, PI
  - BOTUSA
    - Dr. Poloko Kebaabetswe, co-PI
- Strong, multisectoral support for trials
- Supported by CDC scientists in-country and in Atlanta
Trial Design Similarities
Thailand and Botswana

- Randomized, double-blind, placebo-controlled trials
- Safety endpoints
  - Laboratory
  - Clinical interview, exam, medical records
- Efficacy endpoints
  - HIV seroconversion
- Risk behavior counseling and assessments
- Adherence counseling and assessments
- Seroconverter assessments
  - Resistance
  - Effect on disease progression
# Study Procedures

<table>
<thead>
<tr>
<th>Visit</th>
<th>What happens</th>
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<tbody>
<tr>
<td>Monthly visits</td>
<td>- Bring in unused pills, bottle, med diary</td>
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<tr>
<td></td>
<td>- Receive adherence, risk reduction, and pre- and post-test HIV counseling</td>
</tr>
<tr>
<td></td>
<td>- Have an oral HIV test</td>
</tr>
<tr>
<td></td>
<td>- Women: urine pregnancy test</td>
</tr>
<tr>
<td></td>
<td>- Receive new supply of pills</td>
</tr>
<tr>
<td>Quarterly and semi-Annual visits</td>
<td>Same as monthly visit, plus:</td>
</tr>
<tr>
<td></td>
<td>- Expanded interviews, some by ACASI</td>
</tr>
<tr>
<td></td>
<td>- Safety labs</td>
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</table>
Efficacy Endpoint

- HIV incidence in TDF and placebo arms

- Measured by:
  - Monthly oral transudate (Oraquick)
  - Reactive Oraquick tests confirmed by:
    - EIA in laboratory
    - WB in laboratory
    - Plasma viral load
Safety Endpoints

- Rates of grade 3-4 laboratory toxicities and clinical adverse events
- Defined by DAIDS grading tables
Behavioral Safety

- Risk behavior by volunteer may increase because he/she thinks they are protected.
- Medication counseling:
  - Don’t know if tenofovir will prevent HIV infection.
  - Don’t know if volunteer is on active drug or placebo.
- Sexual risk reduction counseling/condoms.
- Thailand:
  - Drug use risk reduction counseling/services.
- Botswana:
  - Repeat comprehension test every six months and re-educate as needed.
Safety Assessments

- **Laboratory Monitoring**
  - Bone (Calcium, phosphorus)
  - Renal function (BUN, creatinine)
  - Liver function (ALT, AST, bilirubin)

- **Clinical Monitoring**
  - Interviews
    - Reported interval medical care
    - Reported interval hospitalizations (abstract records)
  - Periodic physical exams
Retention

- Both sites
  - Remuneration strategy
  - Active follow-up
- Thailand
  - Permissions to follow volunteers when incarcerated
- Botswana
  - Full-time retention staff
  - Facilitate transfers between sites
Thailand Trial
Why IDUs in Bangkok?

- Explosive HIV epidemic among IDUs 1988
- Prevalence increased from < 1% to 40%
- Estimated 37,000 IDUs in Bangkok
- HIV prevalence ~50%
- Annual incidence > 4%
- More than 800 new HIV infections/year
- New prevention tools urgently needed
- Tenofovir may be such a tool
Tenofovir - Methadone Interaction

- Open-label study of 14 HIV-negative persons on methadone maintenance*
- Subjects received 14 days oral Tenofovir 300mg PO and methadone with DOT
- Pharmacokinetics, physical exam, labs, withdrawal questionnaire
- No change in pharmacokinetics of methadone
- No relevant change in exam, labs, or withdrawal symptoms

*Smith et al. Tenofovir DR does not affect the pharmacokinetics or Pharmacodynamics of methadone. IAS Conference, Paris, 2003
Thailand Trial Schema

Phase II

Safety

Interim

Final

Phase III
Proven Trial Capacity
AIDSVAX B/E HIV Vaccine Trial

- Conducted in 17 BMA clinics
- 4,943 IDUs screened; 34% HIV positive
- 2,546 IDUs enrolled
- > 95% follow-up
- > 45,000 study visits
- > 40,000 blood draws
- > 500,000 case report forms
HIV Incidence Rate by Study Visit AIDSVAX B/E Trial

Incidence rate* (%)

Annualized HIV incidence: 3.4% per year

Study visit (month)

Incidence rate = new HIV infections per 100 person years per 6 month interval
Risk Reduction Activities

- Risk reduction education assessed with comprehension test
- Drug use and sexual risk reduction counseling
- HIV voluntary counseling and testing
- Condoms
- Bleach with instructions / demonstration
- Methadone maintenance and detoxification program on site
Adherence

- Counseling at each monthly visit
- Directly-observed therapy (DOT) offered
- Assessed by clinic records (DOT) and ACASI quarterly
Pregnancy - Thailand

- 22% women, very few pregnancies
Where are we now?

- Recruitment somewhat slower than anticipated but on schedule to complete enrollment in mid-2007
- Incidence somewhat lower than projected
  - Strong anti-drug use campaign
  - Changes in drug use patterns
  - Successful prevention activities?
- Retention good
The findings and conclusions in this presentation have not been formally disseminated by the Centers for Disease Control and should not be construed to represent any agency determination or policy.

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Botswana Trial
Why Botswana?

- High HIV incidence and prevalence
- Support for trial at multiple levels of society
- Government provides essentially free health care and ARV care for citizens
- Essentially no resistance to TDF detected among persons on HAART
- Has the infrastructure to implement PrEP if found to be effective
Trial Clinic Sites
Botswana Trial Schema

Phase II

TDF

N=71

Safety

Phase III

Final

Interim

TDF/FTC

Phase III

Final

Interim

Interim
### Estimating Incidence Botswana

<table>
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<tr>
<th>Age Group</th>
<th>HIV Prevalence (%)</th>
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<tr>
<td>15-19 yo</td>
<td>10%</td>
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<tr>
<td>20-24 yo</td>
<td>15%</td>
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</table>

*Seroincidence testing*  
2600 women in 2 antenatal clinics

- Vironostika “detuned” assay
- Adjusted downward for uncertainty
  - Clade C
  - Related but somewhat different population
  - Trial participation effects

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Risk Reduction Activities

- Individualized sexual risk reduction counseling quarterly
- Free male and female condoms
- STI diagnosis and treatment quarterly with partner notification and treatment
Adherence

- Individualized adherence counseling monthly
- Measure rates of medication adherence
  - Daily medication diary
  - Self-report (past 3 days, ACTG format)
  - Pill counts at each visit
- After unblinding, check reported adherence against drug levels in
  - Seroconverters
  - Selected non-seroconverters
TDF/FTC PK/PD studies

- Plasma and intracellular levels in all participants at 3 month visit
  - 15 minutes before and 2 hours after daily dose
  - Used to build population PK model

- Plasma and intracellular levels in 30 volunteers at 3 month visit
  - 15 minutes before and 1, 2, 4, and 8 hours after daily dose
  - Estimate traditional PK dynamics in local population

- Use data from both models to assess PD relationship to:
  - Reported adherence
  - Seroconversion event
Community “Safety”

- Monitor community impact of trial
  - Assess awareness of and attitudes about
    - Trial
    - ARVs for prevention
    - Implementation strategies for PrEP
  - Monitor unprescribed access to ARVs for prevention
Lessons learned

- In the TDF safety trial (n=71)
  - Slower than expected recruitment
  - High adherence
  - Reported risk reduction and low STI incidence
  - High pregnancy rate
  - Good retention (with caveats)
  - Higher than expected osteopenia at baseline
Pregnancy rates – Botswana

- High pregnancy rate in the TDF safety study despite
  - Informed consent language
  - Contraceptive counseling
  - Provision of contraceptives when requested
- Led to significant losses in follow-up time
- Use of hormonal contraception made an eligibility criteria for women in the TDF2 trial
- Reporting to ARV pregnancy registry
- When sufficient safety data on TDF/FTC in pregnancy available, will consider allowing those who become pregnant to remain on study medication
Where are we now?

- Ethics approvals for TDF2 trial obtained
- Staff training completed
- External monitoring site initiation visit completed
- Anticipate screening to start Feb 15
Providing access if PrEP proven to work

- Open-label study for trial participants
- Consider bridging studies
- Beginning local and Atlanta-based discussions about planning for possible implementation
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Statistical Analysis Issues:
CDC PrEP Trials

Ramses Sadek, Ph.D.
Roman Gvetadze, MD
CDC/NCHSTTP/DHAP
Botswana study: Design

- Time to event analysis for efficacy
- Efficacy = 100% * (1 - RR)
- 1:1 randomization
- Uniform enrollment rate
- Annual 15% loss to follow up
- One interim and one final analysis
- 80% power, alpha = 0.025
- Effect size 65%, 10% lower CI
## Botswana study: Total sample size

80% power, 0.025 alpha (one-sided)

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<tr>
<th>Background HIV rate</th>
<th>Expected Efficacy</th>
<th>Lower efficacy bound</th>
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<td>402</td>
<td>466</td>
<td>547</td>
<td>788</td>
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</table>
Botswana study: Power curves

Lower efficacy bound = 0.1; Total sample = 1200

Power vs. Expected Efficacy

Background HIV rate
- 0.03
- 0.05
- 0.07
Botswana study: Expected person-time accrual, N=1200

**Final analysis:** 1325 p-y

**Interim analysis:** 662 p-y

- Annual loss=0%
- Annual loss=15%
Botswana study: Primary hypothesis

$H_0$: Truvada efficacy $\leq 10\%$

$H_A$: Truvada efficacy $> 10\%$

86% power to detect a specific efficacy alternative of at least 65%
Botswana study: Endpoints expected at interim and final analyses, per study group (Placebo/Treatment)

<table>
<thead>
<tr>
<th>Expected efficacy</th>
<th>Interim analysis (662.5 person-years)</th>
<th>Final analysis (1325 person-years)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Background HIV incidence</td>
<td>Background HIV incidence</td>
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<tr>
<td></td>
<td>0.03</td>
<td>0.05</td>
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<tr>
<td>0.5</td>
<td>10 / 5</td>
<td>17 / 8</td>
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<td>10 / 4</td>
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<td>17 / 7</td>
</tr>
<tr>
<td>0.65</td>
<td>10 / 3</td>
<td>17 / 6</td>
</tr>
<tr>
<td>0.7</td>
<td>10 / 3</td>
<td>17 / 5</td>
</tr>
</tbody>
</table>
Botswana study: Sample size calculation

\[
N = \left[ \frac{Z_\alpha \sqrt{\phi(\bar{\lambda}, \eta_e)Q_e^{-1} + \phi(\bar{\lambda}, \eta_c)Q_c^{-1}} + Z_\beta \sqrt{\phi(\lambda_e, \eta_e)Q_e^{-1} + \phi(\lambda_c, \eta_c)Q_c^{-1}}}{|\lambda_e - \lambda_c|} \right]^2
\]

\[
\phi(\lambda, \eta) = \lambda^2 \left\{ \frac{\lambda}{\lambda + \eta} \left[ 1 - \frac{e^{-(T-R)(\lambda+\eta)} - e^{-T(\lambda+\eta)}}{R(\lambda+\eta)} \right] \right\}^{-1}
\]

T – overall length of trial
R – length of enrollment period
\(\lambda_e, \lambda_c\) – HIV hazards in experimental (E) and control (C) groups
\(\eta_e, \eta_c\) – losses to follow-up
Q_e, Q_c – allocation proportions

_Lachin and Foulkes. Biometrics 1986; 42._
Botswana study: Group sequential plan (testing for efficacy)

- O’Brien-Fleming design;

- Interim analysis at 50% f-up or 50% infections:
  - stop for efficacy if $Z > 2.963$, or $p < 0.001523$;
  - continue otherwise;

- Final analysis at study completion:
  - declare efficacy if $Z > 1.969$, or $p < 0.024477$
Thailand study:
Design

- Time to event analysis for efficacy
- Efficacy = 100% \( \times (1 - RR) \)
- 1:1 randomization
- Uniform enrollment rate
- 5% loss to follow up
- One interim and one final analysis
- At 67% efficacy, alpha = 0.025, 2% incidence rate, and 10% lower CI, power = 92%
Thailand study: Primary hypothesis

$H_0$: Tenofovir efficacy $\leq 10\%$

$H_A$: Tenofovir efficacy $> 10\%$

92% power to detect a specific efficacy alternative of at least 67%
Thailand Study: Power calculation via simulation

- 2000 person-years per group
- 5% dropout rate
- Poisson model
- 1% - 3% background HIV rate
- 50% - 80% efficacy
- 10% lower efficacy bound
- 1000 replications per simulation
## Thailand Study: Power, incidence and efficacy for n=2000

<table>
<thead>
<tr>
<th>Expected efficacy</th>
<th>HIV incidence</th>
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<tr>
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<td>0.600</td>
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<td>0.8</td>
<td>0.880</td>
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</table>
Thailand Study: Power curves

Lower efficacy bound = 0.1; Total sample = 2000

The graph depicts the relationship between expected efficacy and power with different background HIV rates. The x-axis represents the expected efficacy, while the y-axis shows the power. Different symbols and colors are used to indicate different background HIV rates (0.01, 0.02, 0.03).
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