

Project T

**A Safety Study of Pre-exposure Prophylaxis (PrEP)
with Daily Oral Tenofovir in HIV-negative MSM**

Rectal Microbicide Working Group Conference Call

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Outline

- Background on PrEP
- Review basics of Tenofovir
- Project T overview
- Important PrEP trial issues



PrEP is a promising new HIV prevention approach to explore

- PrEP = Pre-exposure Prophylaxis
- Antiretroviral medication could complement existing behavioral prevention strategies to further reduce HIV infections in HIV-negative individuals
- Concept of taking a pill against an infectious agent prior to exposure has proven effective in other situations:
 - Malaria
 - Prevention of Maternal to Child Transmission of HIV (PMTCT)
- Two critical questions:
 - Is PrEP safe?
 - Biological safety
 - Behavioral safety – behavioral disinhibition?
 - Does PrEP work?
 - How effective is PrEP in reducing HIV infections?
- Current PrEP trials will evaluate the safety and efficacy of daily oral tenofovir in various populations around the globe



Tenofovir (Viread) for PrEP

- Nucleotide reverse transcriptase inhibitor (NRTI)
- Blocks HIV replication by inhibiting reverse transcriptase enzyme
- FDA-approved for HIV treatment in 2001, used clinically in combination therapy in over 200,000 patients
- Favorable pharmacologic profile
 - Low incidence of side effects
 - Once daily dosing (300 mg)
 - No food requirement
 - Resistance slow to develop



Tenofovir: what we know about side effects in HIV positives

- Side effects generally mild and relatively rare
- Most common side effects include GI problems, dizziness, headache, and rash (5-15%)
- <1% of HIV-positive patients treated with tenofovir stopped treatment due to these side effects
- Rarely associated with kidney toxicity in people with HIV: usually resolve when tenofovir is stopped
- Studies in animals and HIV-positive individuals have shown small decreases in bone density, no increase in fractures



PrEP data from non-human primates

- Pre-/post-exposure TDF can prevent or delay infection with SIV/SHIV infection and alter viral set point in rhesus macaques
 - Depends on dose, timing and duration of TDF*
- Pre-/post-exposure TDF/FTC prevented SHIV infection in macaques using rectal challenge model*
- FTC alone provided partial protection to macaques rectally challenged with SHIV (trial ongoing)**

*Tsai CC et al. Science 1995

*Van Rompay KK et al. AHR 1998

*Subbarao S et al. 12th CROI 2005
2006

*Van Rompay KK, et al. AIDS 1998

*Van Rompay et al. Abstract LbOrB10, 2004

**J Garcia-Lerma, Abstract 32LB, 13th CROI



Project T Overview

- A CDC-sponsored phase II clinical trial of daily oral tenofovir in 400 HIV-negative MSM
- Specific aims
 - Establish clinical safety & tolerability of tenofovir in healthy HIV-negative MSM
 - Evaluate the effects of taking a daily HIV pill on risk taking behavior
- Other study questions:
 - Resistance patterns in seroconverters
 - Adherence to study drug
 - Social harms (embarrassment, stigmatization)

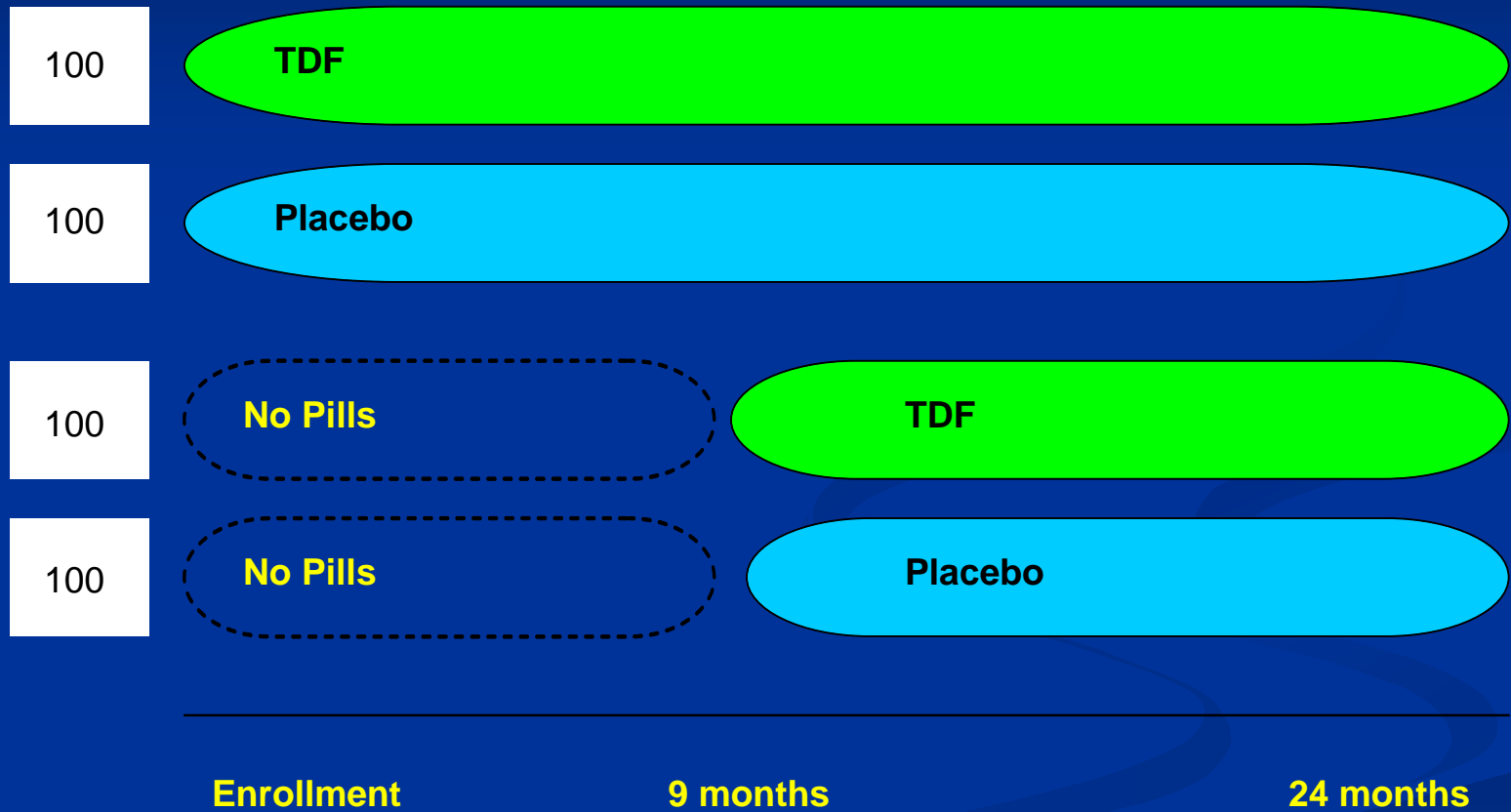


Project T Study Design

- Randomized, double-blinded, placebo-controlled trial of 400 HIV-negative MSM
- 2 sites in US (each will enroll 200)
 - San Francisco Department of Public Health (Buchbinder/Liu/Grant)
 - AIDS Research Consortium of Atlanta (Thompson)
 - Enrollment began in February 2005, halfway enrolled in SF
- Eligibility criteria include:
 - Healthy, sexually active HIV-negative MSM
 - Age 18-60
 - Normal kidney function and bone density at baseline
 - Not taking any medications toxic to the kidneys
- Community input (from CAB and other community members) has been critical in design and implementation of Project T



Study design: 2 immediate and 2 delayed arms to evaluate both biological and behavioral safety



Project T: study procedures

- Participant takes daily study pill (starting at enrollment or 9 months)
- Frequent study visits (every 3 months) for 2 years
 - Rapid HIV testing, risk reduction counseling, free condoms/lube
 - Clinical and laboratory monitoring for safety
 - ACASI (Audio Computer Assisted Self Interview) used to administer behavioral questionnaire
 - Adherence measurements
- Seroconverters followed for 1 additional year
 - Provided additional counseling, linkages for medical and psychosocial care
 - Resistance patterns and course of HIV infection (CD4, HIV RNA levels) will be followed



How will we help protect the safety of study participants?

- Extensive informed consent process
 - Reinforce no evidence TDF works to prevent HIV
 - May be getting placebo
 - Comprehension test
- Close monitoring for adverse events
- Free rapid HIV test at any time during study
- Clinician on call 24 hours/day to answer questions about study drug
- Independent safety review committee
- Ongoing community input (SFDPH CAB)



Project T Recruitment

- Street outreach, recruitment in bars, street corners, sex clubs
- Internet (craigslist), banner ads
- Referrals from other prevention studies
- Referrals from community based organizations
- Outreach to community clinics, providers and STD clinics
- TV/radio advertisements and press releases
- **Recruitment goal: 25% men of color**



Join a community working to fight AIDS



Project T

Project T will test whether HIV negative gay/bi men can safely take an HIV drug. If so, further studies may test it as an HIV prevention strategy. Participants will receive free STD & HIV testing and counseling, and \$35-50 per visit.

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HIV Research Section, SF Dept. of Public Health



Current clinical trials of PrEP with daily tenofovir in HIV-negative populations

Planned/Ongoing PrEP Trials [when results available]

- 400 MSM in US (CDC) – SF and Atlanta [2008]
- 1200 MSM in Peru (NIH) [2009]
- 400 high risk women in Ghana (FHI) [2006]
- 1200 young men and women in Botswana (CDC) [2008]
- 1600 injection drug users in Thailand (CDC) [2008]

Suspended/stopped PrEP trials

- 960 women in Cambodia (NIH/FHI)
- 400 women in Cameroon (FHI)
- 400 women in Nigeria (FHI)
- 400 men in Malawi (FHI)



Important PrEP trial issues

US Trials

- Community/provider concerns about behavioral disinhibition
 - Community forums and extensive educational outreach
 - Importance of studying behavioral safety in Project T

- Unapproved PrEP use – risk to individuals and community
 - Anecdotal reports of use in clubs, bath-houses
 - Preliminary survey by CDC – 25% heard of PrEP, 7% reported PrEP use
 - SFDPH conducting more rigorous survey to look at PrEP use in SF Bay Area

- Development of resistance

- Recruitment challenges

All Trials

- Importance of scientific coordination across PrEP studies

- Communications about PREP
 - Proactive communications strategy regarding trials
 - Manage expectations, prepare communities for results

- Access to PREP if safety and efficacy proven



Issues raised in international PrEP trials

- Ensuring informed consent of participants
- Provision of adequate prevention methods
 - HIV risk reduction counseling
 - Clean needles
- Provision of access to care for HIV seroconverters, during and after trial
- Treatment for trial related adverse events
- Concerns about tenofovir resistance
- Operational issues

Grant et al. Science Sept 2005

Page-Shafer et al. Lancet Oct 2005



Ways to help?

- Increase community support for domestic and international PrEP trials
- Assist with community education and communication, preparation for range of different results
- Suggestions to boost recruitment
- Others?

