Open Label Extension studies: 
Findings from Partners PrEP Study

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What can be learned from open label extension projects

- Uptake of PrEP after efficacy is known
  - Do those most at risk adopt it?
- Adherence of PrEP
  - Does adherence increase when people know they are receiving PrEP?
- Extended safety
- Risk behavior
- HIV incidence
- Resistance in seroconverters
## PrEP Open label studies

- Provide *research participants* access to PrEP for 1 year
- In context of known efficacy, assess adherence, risk behavior, HIV seroconversion, resistance & AEs

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Population</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bangkok Tenofovir Study Follow-Up</td>
<td>Thailand</td>
<td>People who inject drugs</td>
<td>500 expressed interest, with expected completion late 2014.</td>
</tr>
<tr>
<td>iPrEx OLE</td>
<td>Brazil, Peru, Ecuador, South Africa, Thailand, US</td>
<td>MSM/TGW</td>
<td>1529 (65%) enrolled; results in Lancet ID 2014</td>
</tr>
<tr>
<td>TDF-2 Follow-Up</td>
<td>Botswana</td>
<td>Heterosexual men and women</td>
<td>Enrolled 232 people; results expected late 2014</td>
</tr>
<tr>
<td>Partners PrEP</td>
<td>Kenya &amp; Uganda</td>
<td>Heterosexual HIV discordant couples</td>
<td>Re-randomized placebo arm to TDF or FTC/TDF; 12 months follow-up</td>
</tr>
</tbody>
</table>
iPrEX OLE

- High uptake
  - 76% of 1603 iPrEX participants
  - Higher uptake among men reporting condomless receptive anal sex (81%)

- Higher adherence during periods of risk
  - As well as among older & more educated men

- 49% lower HIV incidence in PrEP users compared to those who did not take PrEP

- Modeling: High efficacy among those taking >4 pills/week

Grant et al Lancet ID 2014
iPrEX OLE; Lessons about adherence

Most sorted into adherers/ non-adherers

Adherence declined over time; need ‘scalable’ adherence support

Grant et al  Lancet ID 2014
Enough is not necessarily perfection: iPrEx OLE

100% HIV protection was seen with adherence consistent with ≥4 tablets per week

Grant et al. Lancet ID 2014
Design & findings from Partners PrEP open label extension phase
Partners PrEP Design

4747 HIV discordant couples
(HIV+ partner CD4 >250, not on ART)

Randomize HIV- partners
(normal liver, renal, hematologic function)

TDF once daily  FTC/TDF once daily  Placebo once daily

All receiving HIV prevention services

Follow couples for 24-36 months

1° endpoint: HIV infection in HIV-negative partner
Co- 1° endpoint: Safety
Continuation of Partners PrEP Study

- In July 2011, the study’s independent DSMB recommended **public report of results & discontinuation of placebo arm**
  - Active arms continued & placebo arm re-randomized to PrEP
  - To collect additional comparative data on safety & efficacy

Study start
July 2008

DSMB recommends discontinuation of placebo arm
July 2011

Study conclusion
December 2012
Primary efficacy results – July 2011

- Primary analysis: modified intention-to-treat (mITT)
  - Excluding infections present at randomization (5 TDF, 3 FTC/TDF, 6 placebo)

<table>
<thead>
<tr>
<th></th>
<th>TDF</th>
<th>FTC/TDF</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of HIV-1 infections</td>
<td>17</td>
<td>13</td>
<td>52</td>
</tr>
<tr>
<td>HIV-1 incidence, per 100 person-years</td>
<td>0.65</td>
<td>0.50</td>
<td>1.99</td>
</tr>
<tr>
<td>HIV-1 protection efficacy, vs. placebo</td>
<td>67%</td>
<td>75%</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>(44-81%)</td>
<td>(55-87%)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

Effect of TDF (67%) and FTC/TDF (75%) were statistically similar to each other (p=0.23)

Baeten et al NEJM 2012
Partners PrEP Open Label Extension

- 89% of 1418 placebo participants consented to re-randomization to TDF or FTC/TDF

- With 50 endpoints between the 2 active PrEP groups (both before & after July 10, 2011)
  - 87% power to see a 67% difference between TDF & FTC/TDF (& 67% power to see a 50% difference)

- Additional 3569 person-years of follow-up & 26 HIV endpoints
Partners PrEP Study & OLE: Final efficacy results

- Primary analysis: modified intention-to-treat (mITT)
- Excluding infections present at randomization (5 TDF, 3 FTC/TDF, 6 placebo) & re-randomization (4 in placebo arm)

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<th>TDF</th>
<th>FTC/TDF</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of HIV-1 infections</strong></td>
<td>31</td>
<td>21</td>
<td>52</td>
</tr>
<tr>
<td><strong>HIV-1 incidence, per 100 person-years</strong></td>
<td>0.71</td>
<td>0.48</td>
<td>1.99</td>
</tr>
<tr>
<td><strong>HIV-1 efficacy, TDF/FTC vs. TDF</strong></td>
<td>0.67</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
<td>(0.39-1.17)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td></td>
<td>0.16</td>
<td></td>
</tr>
</tbody>
</table>

- **Effect of TDF (67%) & FTC/TDF (75%) statistically similar to each other (p=0.16)**

Baeten et al Lancet Inf Dis 2014
Partners PrEP Study & OLE: Both TDF & FTC/TDF are highly efficacious

- Comparable efficacy: Ruled out 60% or greater difference in risk from FTC/TDF compared to TDF

- 85% estimated efficacy of TDF & 93% of FTC/TDF, based on tenofovir detection in plasma

- Oral TDF is an alternative option for oral PrEP
  - Lower cost
  - Side effects
  - Less resistance (although rare overall with PrEP use & thus not a big factor in choice of PrEP agent)
Partners PrEP Study: Resistance

• 2 of 12 individuals retrospectively identified to be acutely infected at enrollment
  – 1 M184V & 1 K65R (Baeten et al NEJM 2012)
  – 0 of 4 placebo participants re-randomized to active PrEP

• Post-randomization infections (N=52)
  – No mutations among 48 with resistance data
PrEP selected resistance is short-lived

- Ultra-sensitive assays (454 sequencing) to detect persistence of PrEP-associated resistance
- All PrEP associated mutations during acute infection were no longer present by 6 months

Lehman et al, submitted
Partners PrEP Study & OLE: Safety

• Similar frequency of adverse events in active arms throughout follow-up compared to placebo group before July 10, 2011

• No significant differences in deaths, SAEs, serum creatinine & phosphorus abnormalities
Partners PrEP Study & OLE: Renal safety

- Evaluated mean eGFR & >25% decline in eGFR
- Median follow-up of 18 months
- Slight reduction in eGFR in PrEP arms: mean difference of -1.23 mL/min/1.73 m^2
- Appeared by 1 month, stable through 12 months, then waned
- >25% reduction in eGFR at 12 months: 1.3% for TDF & 1.2% for FTC/TDF (not stat significant different compared to 0.9% in placebo arm)

Mugwanya et al JAMA Int Med, in press
In the Partners PrEP Study, no increase in unprotected sex in serodiscordant couples, STIs, or pregnancy after July 2011 (when placebo stopped and all received active PrEP).

Mugwanya et al., Lancet Infect Dis, 2013
Goals of PrEP for HIV prevention

**Drug Development**
- Right drug (safe, potent)
- Right place (high genital concentrations)
- Right time (quick onset, long t1/2)

**Implementation**
- Right population (at risk, motivated to use)
- Right timing (during ‘seasons’ of highest risk)
- Right delivery (cost-effective & efficient)
# PrEP demonstration project questions in research-naïve populations

<table>
<thead>
<tr>
<th>Topic</th>
<th>Question</th>
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<tbody>
<tr>
<td><strong>Targeting</strong></td>
<td>Who to prioritize for PrEP? How to deliver?</td>
</tr>
<tr>
<td><strong>Uptake</strong></td>
<td>Do those who might benefit most from PrEP want it?</td>
</tr>
<tr>
<td><strong>Adherence</strong></td>
<td>Who takes PrEP? Do they take it <em>often enough</em> to be effective?</td>
</tr>
<tr>
<td><strong>Sexual behavior</strong></td>
<td>Is PrEP use associated with risk compensation?</td>
</tr>
<tr>
<td><strong>Impact</strong></td>
<td><em>HIV incidence? Resistance? Incremental cost effectiveness?</em></td>
</tr>
</tbody>
</table>
PrEP & ART for serodiscordant couples

- Both PrEP and ART protect against HIV
  - ART is clearly the priority for HIV+ partners with lower CD4 counts (and, when possible, for all persons with HIV)
  - Not all HIV+ partners will choose to or can start ART immediately

- Staged use of PrEP, as a bridge to ART, might be one effective and cost-effective public health strategy
  (Hallett et al. PLoS Med 2011; Mitchell et al. STI World Congress 2013)
Partners Demonstration Project

• Subset of Partners PrEP Study sites in Kenya and Uganda

• Open-label demonstration project among new, high-risk HIV-1 serodiscordant couples
  • Provide PrEP, provide ART – assess interest, uptake, and sustained use (adherence)
  • Quantitative and qualitative research to better understand facilitators, preferences, and barriers
Primary Aims

1. Evaluate the ability to do targeted enrollment of higher-risk HIV-1 serodiscordant couples into a longitudinal HIV-1 prevention study.


3. Ascertain initiation of and adherence to PrEP among HIV-1 uninfected partners, when implemented as a bridge to ART.

4. Ascertain initiation of and adherence to ART among HIV-1 infected partners.

5. Assess factors influencing preferences, uptake and adherence for antiretroviral-based HIV-1 prevention.

6. Assess the feasibility of PrEP discontinuation in couples in which the HIV-1 infected partner initiates ART.

Using a risk score to define couples at highest HIV risk

<table>
<thead>
<tr>
<th>Age of HIV-1 uninfected partner</th>
<th>20 years or less</th>
<th>21-30 years</th>
<th>More than 30 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of children</th>
<th>0</th>
<th>1-2</th>
<th>3 or more</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Male HIV-1 uninfected partner uncircumcised</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Married and/or cohabiting</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Unprotected sex within partnership, prior 30 days</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HIV-1 plasma viral load, HIV-1 infected partner</th>
<th>50,000 copies or higher</th>
<th>10,000-49,999 copies</th>
<th>Less than 10,000 copies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

A score of 5 was associated with an HIV incidence of 5/100 person-yrs.
Partners Demonstration Project: High demand among high risk couples

- Enrollment of 1012 high risk couples Nov 2012-August 2014
  - Only 3% of eligible couples did not enroll
- 47% of couples have a risk score ≥7
- Higher risk than Partners PrEP Study:
  - Younger, fewer couples have children, more frequent unprotected sex
Partners Demonstration Project:
High PrEP Adherence

• ≈80% adherence by clinic-based pill counts
  – Limited data beyond month 12

• Similar adherence results with MEMS caps

• 86% with detectable tenofovir in plasma

• Comparable level of adherence to Partners PrEP Study

Haberer et al IAPAC 2014
Conclusions:
Open Label Extension studies

• Provides scientific value about uptake, adherence, safety, risk behavior, HIV incidence & resistance when people are offered a known efficacious product

• Meets our ethical obligation to study participants by providing an effective product to study participants for a time-limited period

• Learn about delivery, uptake, adherence & impact of effective biomedical HIV prevention products to inform implementation
Thank you

- Jared Baeten
- Renee Heffron
- Partners PrEP & Partners Demonstration Project Teams
- Sharon Hillier & Ian McGowan & MTN colleagues
- Funders:
  - Bill & Melinda Gates Foundation
  - NIH
  - USAID
- Study participants
Partners PrEP Study Team

• Sites:
  – Eldoret, Kenya (Moi U, Indiana U): Edwin Were (PI), Ken Fife (PI), Cosmas Apaka
  – Jinja, Uganda (Makarere U, UW): Patrick Ndase (PI), Elly Katabira (PI), Fridah Gabona
  – Kabwohe, Uganda (KCRC): Elioda Tumwesigye (PI), Rogers Twesigye
  – Kampala, Uganda (Makarere U): Elly Katabira (PI), Allan Ronald (PI), Edith Nakku-Joloba
  – Kisumu, Kenya (KEMRI, UCSF): Elizabeth Bukusi (PI), Craig Cohen (PI), Josephine Odoyo
  – Mbale, Uganda (TASO, CDC): Jonathan Wangisi (PI), Akasiima Mucunguzi
  – Nairobi, Kenya (KNH/U Nairobi, UW): James Kiarie (PI), Carey Farquhar (PI), Grace John-Stewart (PI), Harrison Tamooh
  – Thika, Kenya (KNH/U Nairobi, UW): Nelly Mugo (PI), Kenneth Ngure
  – Tororo, Uganda (CDC, TASO): Jim Campbell (PI), Jordan Tappero (PI), Aloysious Kakia

• University of Washington Coordinating Center:  
  Connie Celum (PI and Co-Chair), Jared Baeten (Co-Chair and Medical Director), Deborah Donnell (Statistician), Justin Brantley, Tami Cloutier, Robert Coombs, Amy Dao, Shauna Durbin, Mira Emmanuel-Ogier, Lisa Frenkel, Carlos Flores, Harald Haugen, Renee Heffron, Ting Hong, Jim Hughes, Erin Kahle, Johanna Karas, Becky Karschney, Lara Kidoguchi, Meighan Krows, Matt Leidholm, Jai Lingappa, Toni Maddox, Angela McKay, Julie McElrath, Allison Mobley, Susan Morrison, Nelly Mugo, Andrew Mujugira, Vikram Nayani, Patrick Ndase, Apollo Odika, Hilda O’Hara, Dana Panteleeff, Jennifer Revall, Marothodi Semenya, John Sparkman, Kathy Thomas, Ellen Wilcox

• Adherence Ancillary Study: David Bangsberg, Jessica Haberer, Norma Ware, Monique Wyatt, Steve Safren, Christina Psaros, Craig Hendrix, Namandjé Bumpus

• DF/Net (data center): Lisa Ondrejcek, Darryl Pahl, Jae Chong

• CLS (laboratory oversight): Wendy Stevens, Charlotte Ingram, Ute Jentsch, Mukthar Kader, Nombulelo Gqomane, Feroza Bulbulia, Jan van den Heuvel

• ClinPhone/Perceptive Informatics (randomization)

• Gilead (study drug donation): Jim Rooney

• Bill & Melinda Gates Foundation (study funder): Stephen Becker

• HIV serodiscordant couples who tested, screened, & participated
Conclusions

• Demonstration projects are essential first step for understanding demand and delivery of innovations such as ARV-based prevention
• Risk score useful in identifying at risk couples who will benefit most from ARV-based prevention
• Demand for PrEP is high in couples
• PrEP discontinuation is feasible (typically when HIV+ partner on ART for 6 months)
• PrEP and ART can work together to provide couples with maximum protection against HIV transmission

Partners Demonstration Project Team

Investigators

- University of Washington Coordinating Center: Jared Baeten (protocol co-chair), Connie Celum (protocol co-chair), Deborah Donnell (protocol statistician), Renee Heffron (project director), Ruanne Barnabas, Bettina Shell-Duncan, Jenn Morton, ICRC Operations, Data and Administration teams
- Kabwohe, Uganda (KCRC): Elioda Tumwesigye, Steven Asiimwe, Edna Tindimwebwa
- Kampala, Uganda (Makerere University): Elly Katabira, Nulu Bulya
- Kisumu, Kenya (KEMRI): Elizabeth Bukusi, Josephine Odoyo
- Thika, Kenya (Kenyatta National Hospital, UW): Nelly Mugo, Kenneth Ngure
- MGH/Harvard: David Bangsberg, Jessica Haberer, Norma Ware
- Johns Hopkins: Craig Hendrix, Mark Marzinke
- Fred Hutchinson Cancer Research Center: Dara Lehman
- DF/Net Research (data management)

Funders

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- US Agency for International Development (contract AID-OAA-A-12-00023)

Research participants

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