Open Label Extension studies: Findings from Partners PrEP Study

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PARTNERS PrEP STUDY

MTN microbicide trials network

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

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

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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

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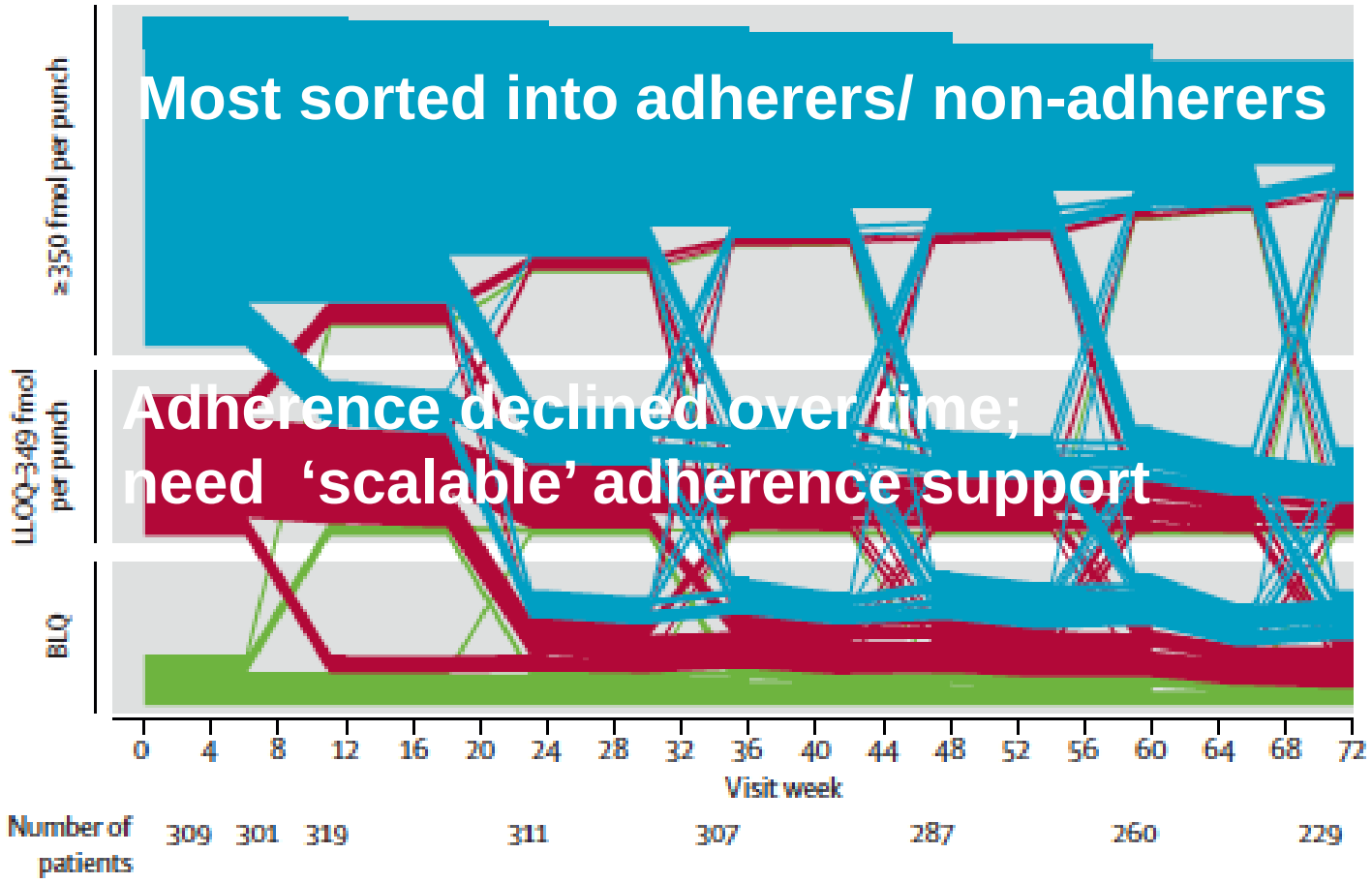
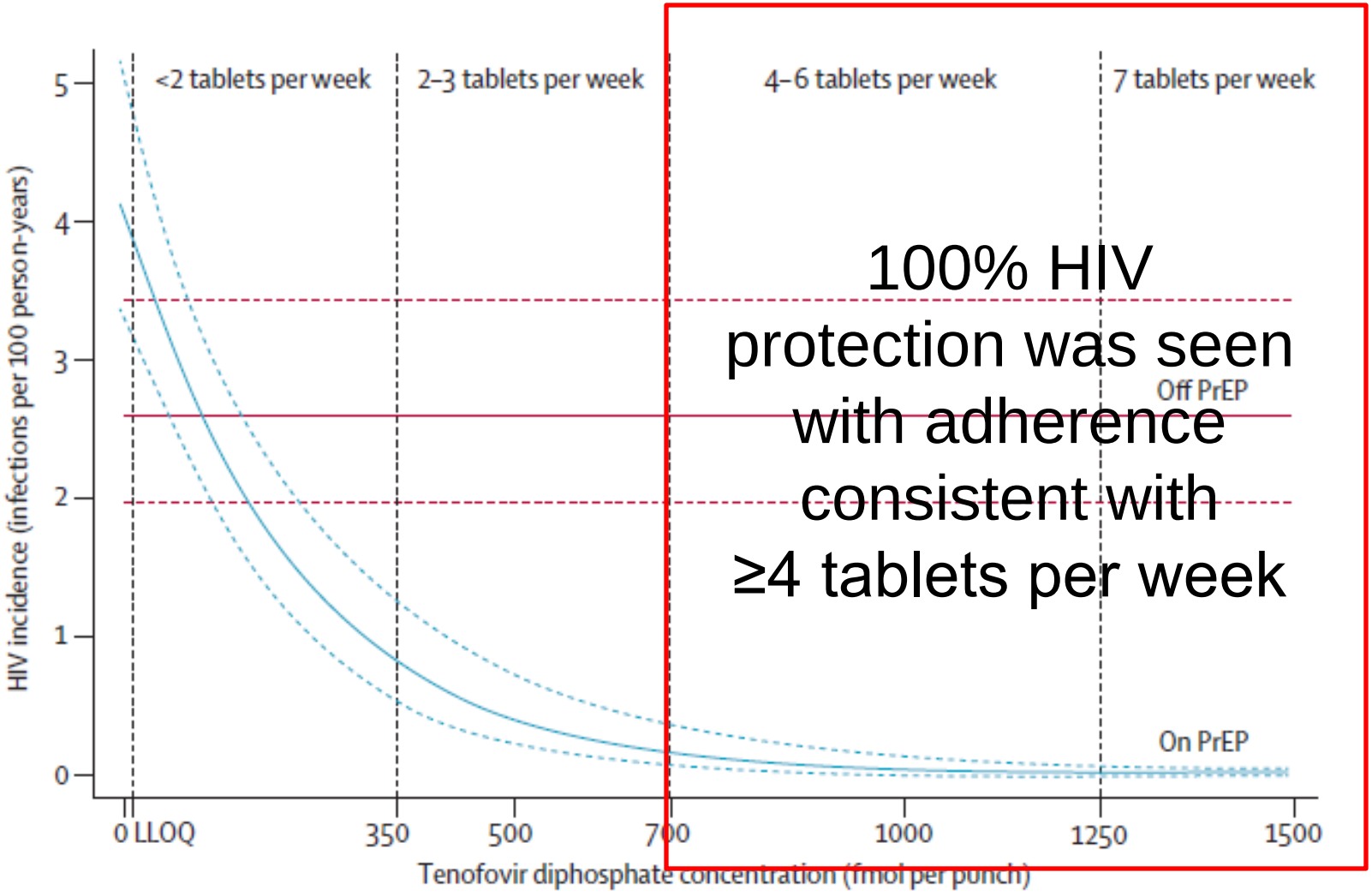
iPrEX OLE; Lessons about adherence



Grant et al Lancet ID 2014

Enough is not necessarily perfection: iPrEx OLE



Grant et al. Lancet ID 2014

Design & findings from Partners PrEP open label extension phase

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Partners PrEP Design

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

↓

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

↙ ↓ ↘

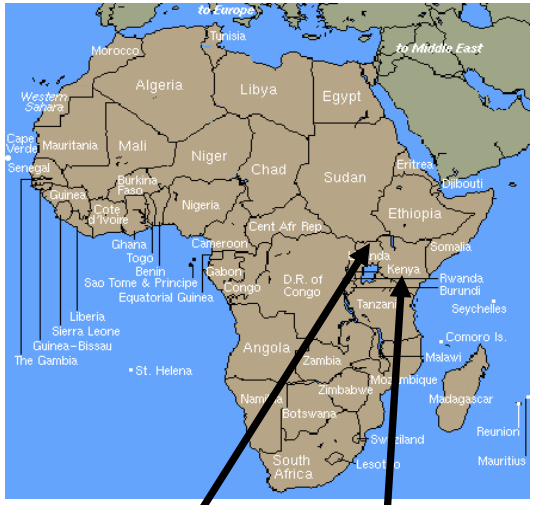
TDF once daily	FTC/TDF once daily	Placebo once daily

All receiving HIV prevention services

↓

Follow couples for 24-36 months

1° endpoint: HIV infection in HIV-negative partner
Co- 1° endpoint: Safety



Kabwohe, Kampala, Jin
Mbale, Tororo, **Uganda**

Eldoret, Kisumu, Nairobi, Thika, **Kenya**

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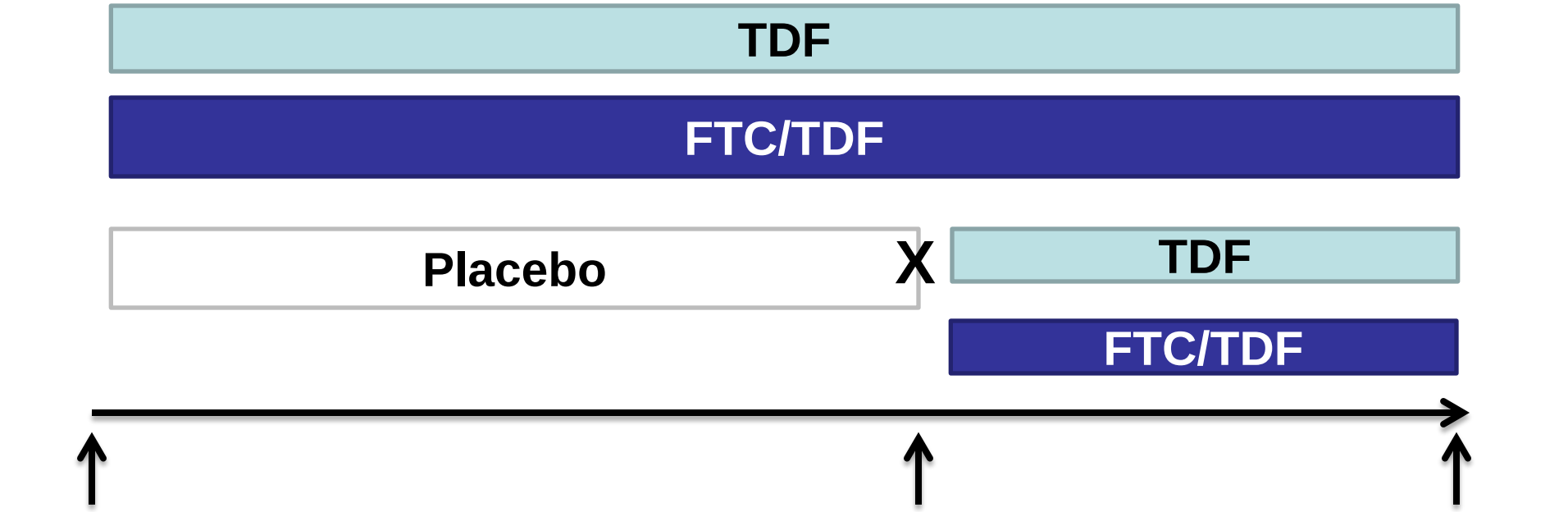
Continuation of Partners PrEP Study

- 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



Primary efficacy results – July 2011

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

	TDF	FTC/TDF	Placebo
Number of HIV-1 infections	**17**	**13**	**52**
HIV-1 incidence, per 100 person-years	0.65	0.50	1.99
HIV-1 protection efficacy, vs. placebo	**67%**	**75%**	
95% CI	**(44-81%)**	**(55-87%)**	
p-value	**<0.0001**	**<0.0001**	

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)

	TDF	FTC/TDF	Placebo
Number of HIV-1 infections	**31**	**21**	52
HIV-1 incidence, per 100 person-years	0.71	0.48	1.99
HIV-1 efficacy, TDF/FTC vs. TDF		0.67	--
95% CI		**(0.39-1.17)**	
p-value		**0.16**	

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

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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-upcompared to placebo group before July 10, 2011
- No significant differences in deaths, SAEs, serum creatinine & phosphorus abnormalities

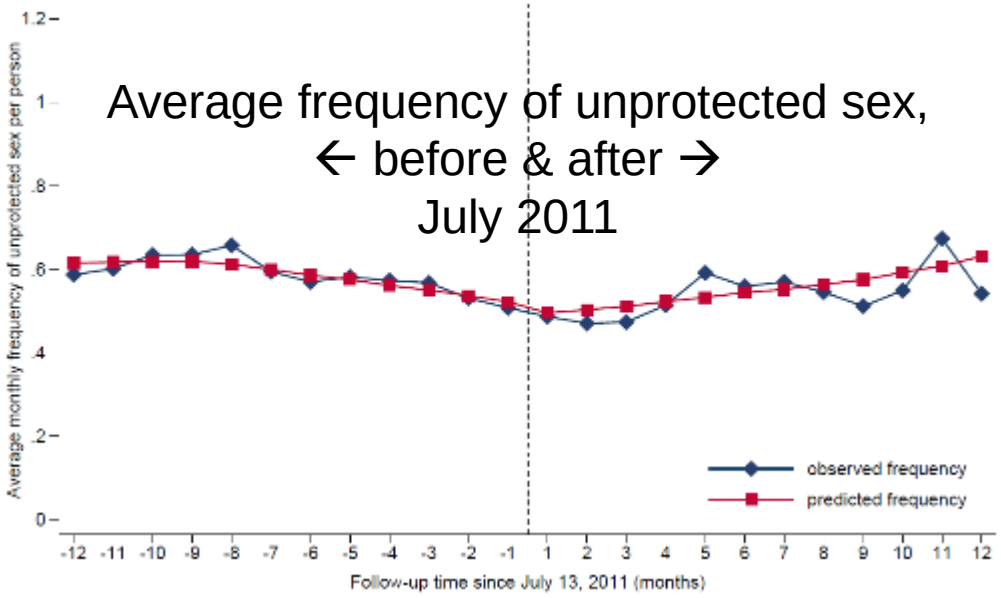
Partners PrEP Study & OLE: Renal safety

- 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

No elevated risk compensation after unblinding and receipt of active PrEP

- 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

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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

Topic	Question
Targeting	Who to prioritize for PrEP? How to *deliver*?
Uptake	Do those who might benefit most from PrEP *want* it?
Adherence	*Who* takes PrEP? Do they take it *often enough* to be effective?
Sexual behavior	Is PrEP use associated with *risk compensation*?
Impact	*HIV incidence? Resistance? Incremental cost effectiveness?*

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

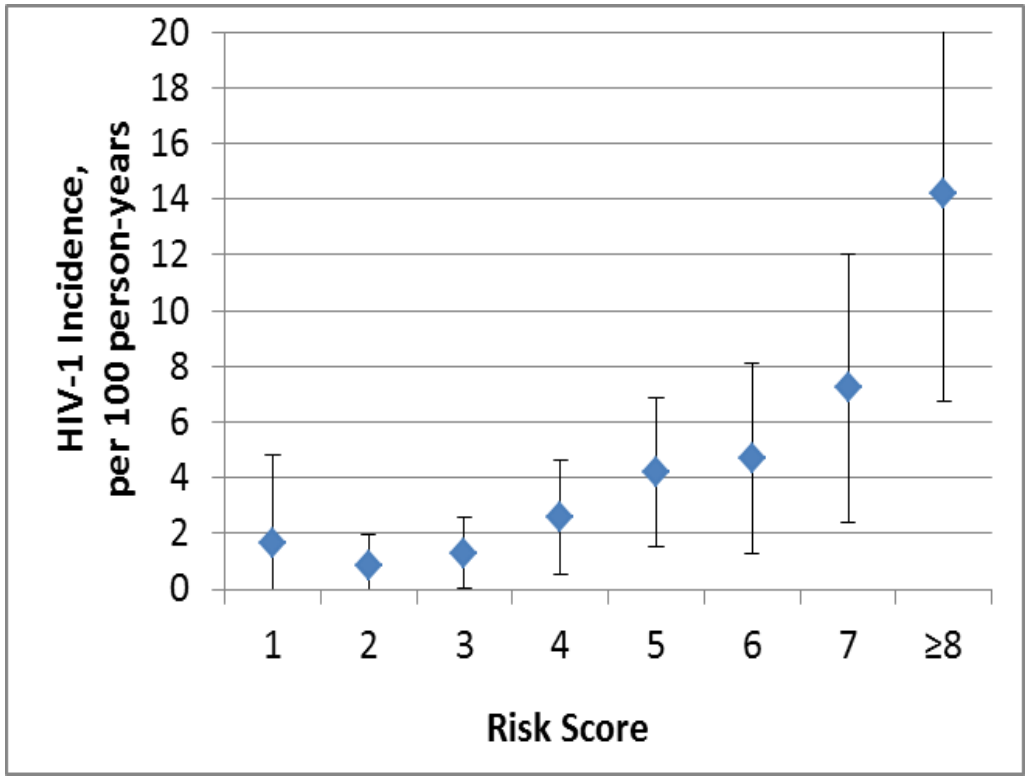
The Partners Demonstration Project is made possible by the United States National Institutes of Health, the Bill and Melinda Gates Foundation, and the generous support of the American people through the United States Agency for International Development. The contents are the responsibility of the University of Washington and study partners and do not necessarily reflect the views of any of the study sponsors or the United States Government.

Primary Aims

1. Evaluate the ability to do **targeted enrollment** of higher-risk HIV-1 serodiscordant couples into a longitudinal HIV-1 prevention study
2. Assess **user preferences** among high-risk HIV-1 serodiscordant couples for ART initiation for HIV-1 infected partners and PrEP for HIV-1 uninfected partners.
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
7. Assess **PrEP use** and birth outcomes among HIV-1 uninfected women who choose to continue PrEP **during pregnancy**

Using a risk score to define couples at highest HIV risk

Age of HIV-1 uninfected partner		
	20 years or less	4
	21-30 years	1
	More than 30 years	0
Number of children		
	0	2
	1-2	1
	3 or more	0
Male HIV-1 uninfected partner uncircumcised		
	Yes	1
	No	0
Married and/or cohabiting		
	Yes	1
	No	0
Unprotected sex within partnership, prior 30 days		
	Yes	2
	No	0
HIV-1 plasma viral load, HIV-1 infected partner		
	50,000 copies or higher	3
	10,000-49,999 copies	1
	Less than 10,000 copies	0
Total score		



A score of 5 was associated with an HIV incidence of 5/100 person-yrs

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Kahle et al JAIDS 2013

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

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MTN

Partners PrEP Study Team

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- **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**

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Partners Demonstration Project Team

Investigators

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- Johns Hopkins: Craig Hendrix, Mark Marzinke
- Fred Hutchinson Cancer Research Center: Dara Lehman
- DF/Net Research (data management)

Funders

- US National Institutes of Health (grants R01 MH095507, R01 MH100940, R01 MH101027, R21 AI104449, R21 TW009908, K99/R00 HD076679)
- Bill & Melinda Gates Foundation (grants OPP47674, OPP1056051)
- US Agency for International Development (contract AID-OAA-A-12-00023)

Research participants

The Partners Demonstration Project is made possible by the United States National Institutes of Health, the Bill and Melinda Gates Foundation, and the generous support of the American people through the United States Agency for International Development. The contents are the responsibility of the University of Washington and study partners and do not necessarily reflect the views of any of the study sponsors or the United States Government.