How good is good enough: Do phase 3 trials predict effectiveness?

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MTN
microbicide trials network

Reminder of our goals for topical & oral ARVs for HIV prevention

- **Right drug**

(safe, effective, minimal resistance)

- **Right place**

(sufficient concentrations at site of exposure)

- **Right time**

(short onset of activity & long half-life
to optimize efficacy with variable adherence)

Celum CROI 2011

How good is “good enough” in HIV prevention?

- No single or predictable answer
- Depends in part on public health priorities, alternative options & resources
- Depends in part on perspectives, priorities & resources of the users, researchers, funders & program implementers

Efficacy of a biomedical prevention intervention: What does it really mean?

- **Ideal**: Phase 3 trials provide accurate estimate of biologic efficacy
- **Reality**: Not so simple
  - Less than optimal adherence dilutes efficacy
  - Often not known how high adherence is needed for efficacy
  - Not everyone in the trial is equally at risk and exposed to HIV

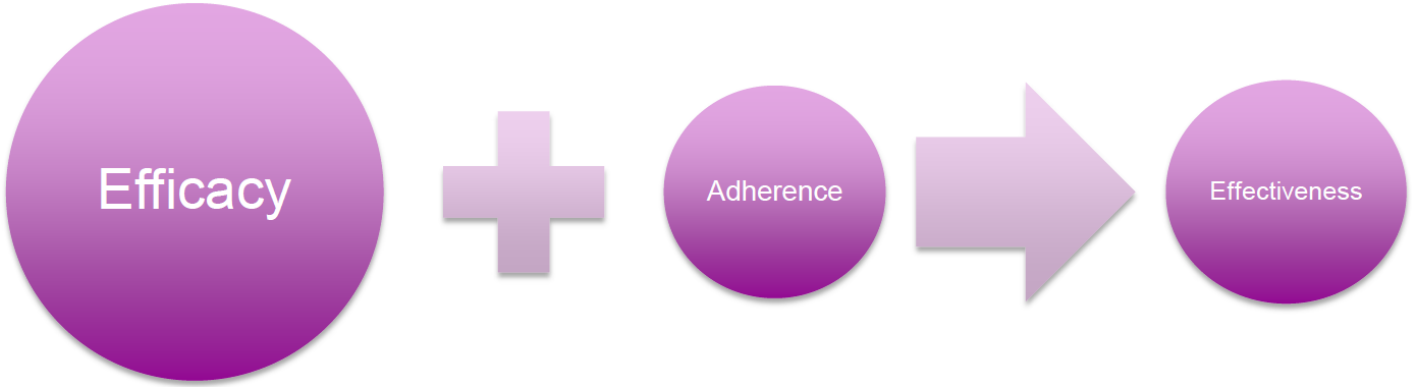
Efficacy, adherence & effectiveness

The clinical trialist's dream

Biologic 'truth' **Human behavior** **Observed outcome**

Efficacy, adherence & effectiveness

Biologic 'truth' **Human behavior** **Observed outcome**



The clinical trialist's reality

The dreaded outcome: No adherence = no HIV protection

Baeten MTN 2015

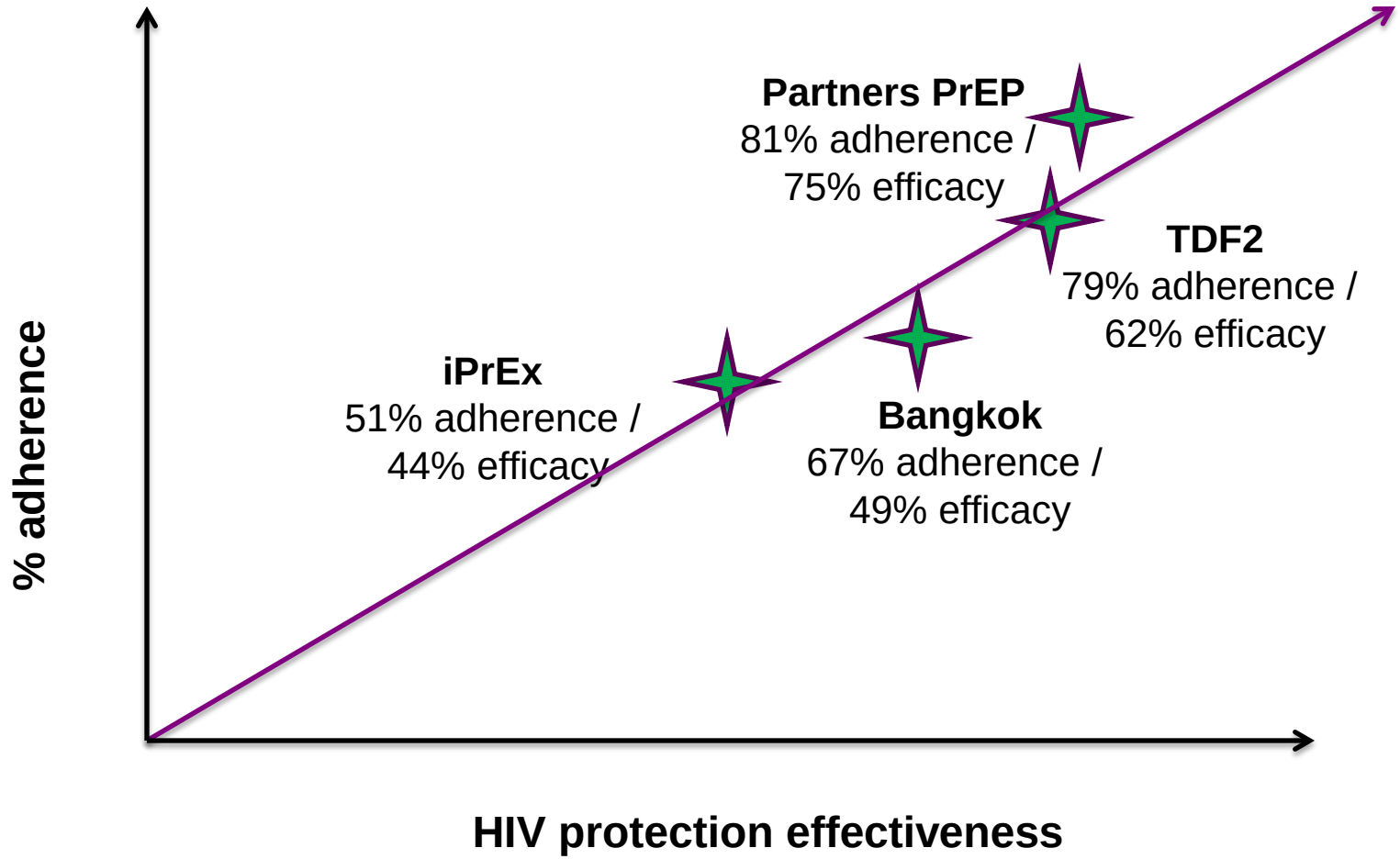
Assumptions (& dogma): Efficacy << effectiveness

- Clinical trials involve highly selected populations, frequent visits, intensive counseling & monitoring
- Implementing efficacious interventions involves less selected populations & simpler delivery
- Reaching the ‘right’ population is difficult
  - Most at risk are often stigmatized
  - May not recognize their risk
  - May not be motivated or able to adopt & use biomedical HIV prevention
- Adherence will be lower than in trials

Lessons from oral PrEP

- Efficacy in 4 trials ranged from 44% to 75%
- Adherence was a major factor in efficacy results
- Factors associated with low uptake and adherence in oral PrEP trials in young African women
  - Motivation to participate in the trial
  - Accuracy of risk perception
  - Belief in benefit when potentially randomized to placebo or product of uncertain efficacy
  - Concerns: stigma, side effects, partner reaction

When taken, oral PrEP works



The degree of HIV protection in PrEP trials was directly related to the proportion of subjects who were adherent to PrEP.

PrEP works for high-risk persons

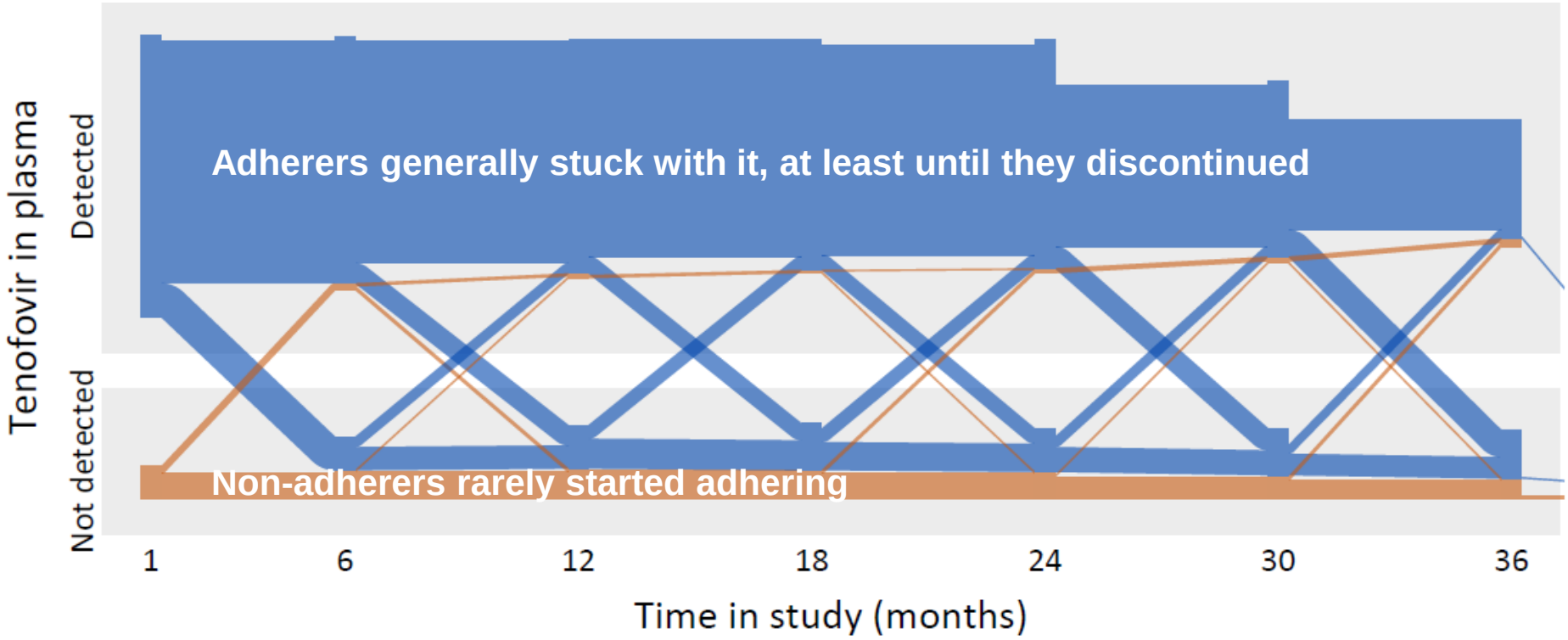
- Subgroup analyses of PrEP trials show that PrEP is effective for those at greatest HIV risk:
  - Heterosexuals (Partners PrEP) Murnane et al. AIDS 2013; Heffron et al. AIDS 2014
    - *Reporting sex without condoms*
    - *With an STI*
    - *With an HIV+ partner who has a high plasma HIV viral load*
    - *Women <30 years of age*
    - *Women using DMPA for contraception*
  - MSM/TGW (iPrEx) Buchbinder et al. Lancet ID 2014; Solomon et al. Clin Infect Dis 2014
    - *Used cocaine*
    - *Had syphilis*
    - *Had anal sex with an HIV+ partner*
- HIV protection estimates for these subgroups were often as high or higher than for the trial population as a whole, because adherence was often greater for higher-risk persons

Lessons about adherence in PrEP trials

- Serodiscordant couples were highly motivated for HIV prevention
  - Recognition of risk; desire for pregnancy; support from partner (Ware JAIDS 2012)
  - Early adherence predicted adherence at 12 months (Donnell JAIDS 2014)

PrEP: adherers adhere

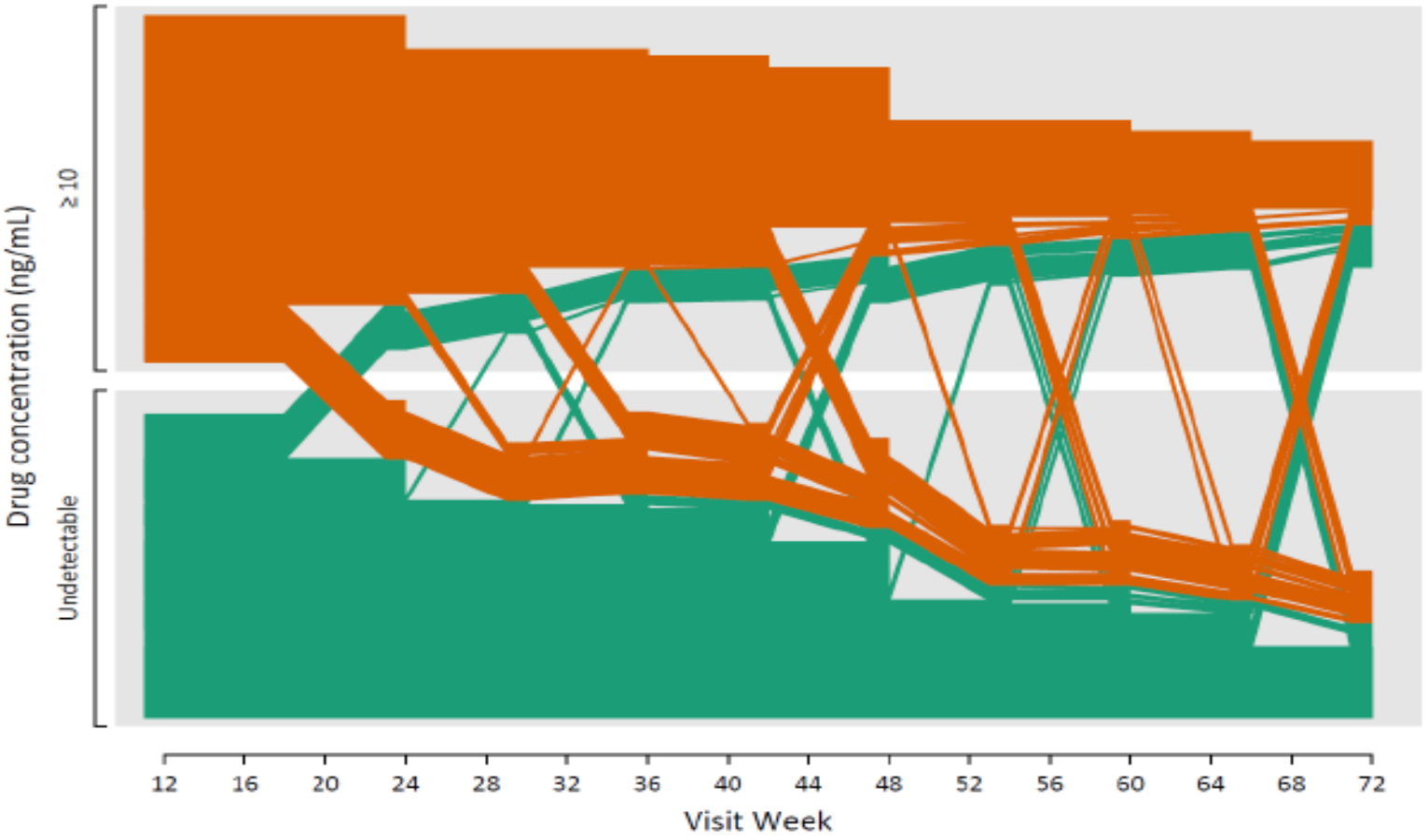
- Longitudinal analysis of tenofovir detection in blood samples from Partners PrEP has shown that, for those who were taking PrEP, adherence was frequently consistent over time:



Partners PrEP Study, Baeten et al., Lancet ID 2014

PrEP: adherers adhere

- Similar results about early sorting into adherers & nonadherers were seen in iPrEx:



Liu et al., JAIDS 2014

iPrEx OLE: Adherence does not need to be perfect

- In iPrEx OLE, HIV incidence declined with greater tenofovir concentrations in blood spots.
- 100% protection was seen with levels consistent with taking ≥4 tablets/week, showing that consistent PrEP taking, even when not necessarily perfect, can be highly protective.

	HIV incidence (per 100 person-years)	**Risk reduction** (versus off-PrEP)
Not on PrEP	3.9	-
On PrEP: 2-3 tablets/wk	0.56	84%
On PrEP: 4-6 tablets/wk	0.00	100%
On PrEP: 7 tablets/wk	0.00	100%

Grant et al. Lancet ID 2014

Lessons about adherence in PrEP trials

- Serodiscordant couples were highly motivated for HIV prevention
  - Recognition of risk; desire for pregnancy; support from partner (Ware JAIDS 2012)
  - Early adherence predicted adherence at 12 months (Donnell JAIDS 2014)
- Women also self-sorted into adherers & non-adherers
  - Although low proportion in VOICE overall used product, a minority were consistent users ((Marrazzo NEJM 2015)
  - Adherence impacted by concern about partners' reaction, stigma, uncertainty about ARVS for prevention, discussions with other women in trial (van der Straten 2014)
  - Women in FEM-PrEP voiced concern about losing benefits if disclosed non-adherence (Cornelli AIDS 2015)

PrEP: efficacy and effectiveness

Clinical trial efficacy	Implementation effectiveness
iPrEx: 44% *51% TFV in blood*	**PROUD:** 86% *near-perfect TFV in blood*
Partners PrEP: 75% *81% TFV in blood*	**Partners Demo:** 96% *85% TFV in blood*

McCormack Lancet 2015
Baeten CROI 2015

What PrEP looks like in real world delivery: PROUD Study

- Among MSM in the UK, delivery of PrEP (compared in a randomized trial to deferred access to PrEP in a public health clinic setting) *was so effective in preventing HIV that the deferred arm was discontinued early, when only 10% of the planned sample size had been enrolled*.

- **<u>RESULTS:</u> 86% HIV reduction (95% CI 58-96%, 3 vs. 19 infections)**

  – The PROUD population was at considerable HIV risk: in the year prior to enrollment 25% had gonorrhea, 10% had syphilis, 40% used PEP, & 74% had recreational drug use

PROUD Examining the impact on gay men of using Pre-Exposure Prophylaxis (PrEP)

MRC Clinical Trials Unit | Public Health England

McCormack et al. CROI 2015

What PrEP looks like in a delivery project: Partners Demonstration Project

- The Partners Demonstration Project is providing ***PrEP as a bridge to ART*** in an implementation study among Kenyan and Ugandan serodiscordant couples:

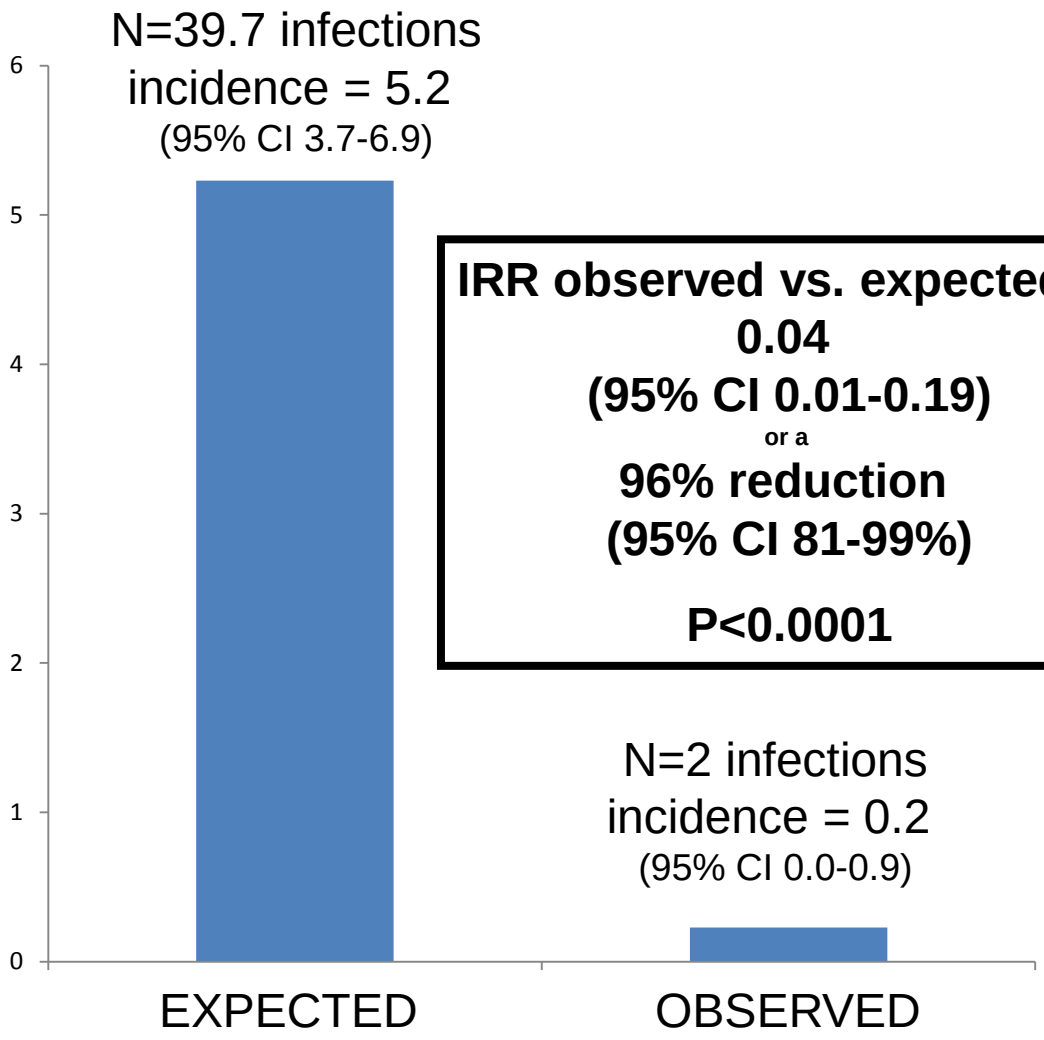
Adherence	Partners Demonstration Project (Delivery Setting)	Partners PrEP Study (Clinical Trial)
>80% adherence by MEMS cap monitoring	**77%**	**80-85%**
Tenofovir detected in blood samples	**87%**	**81%**

Importantly, the Demonstration Project population is at considerably higher behavioral risk than the clinical trial population.

Baeten et al. NEJM 2012; Haberer et al. PLoS Med 2013; Heffron et al. R4P 2014; Irungu et al. R4P 2014

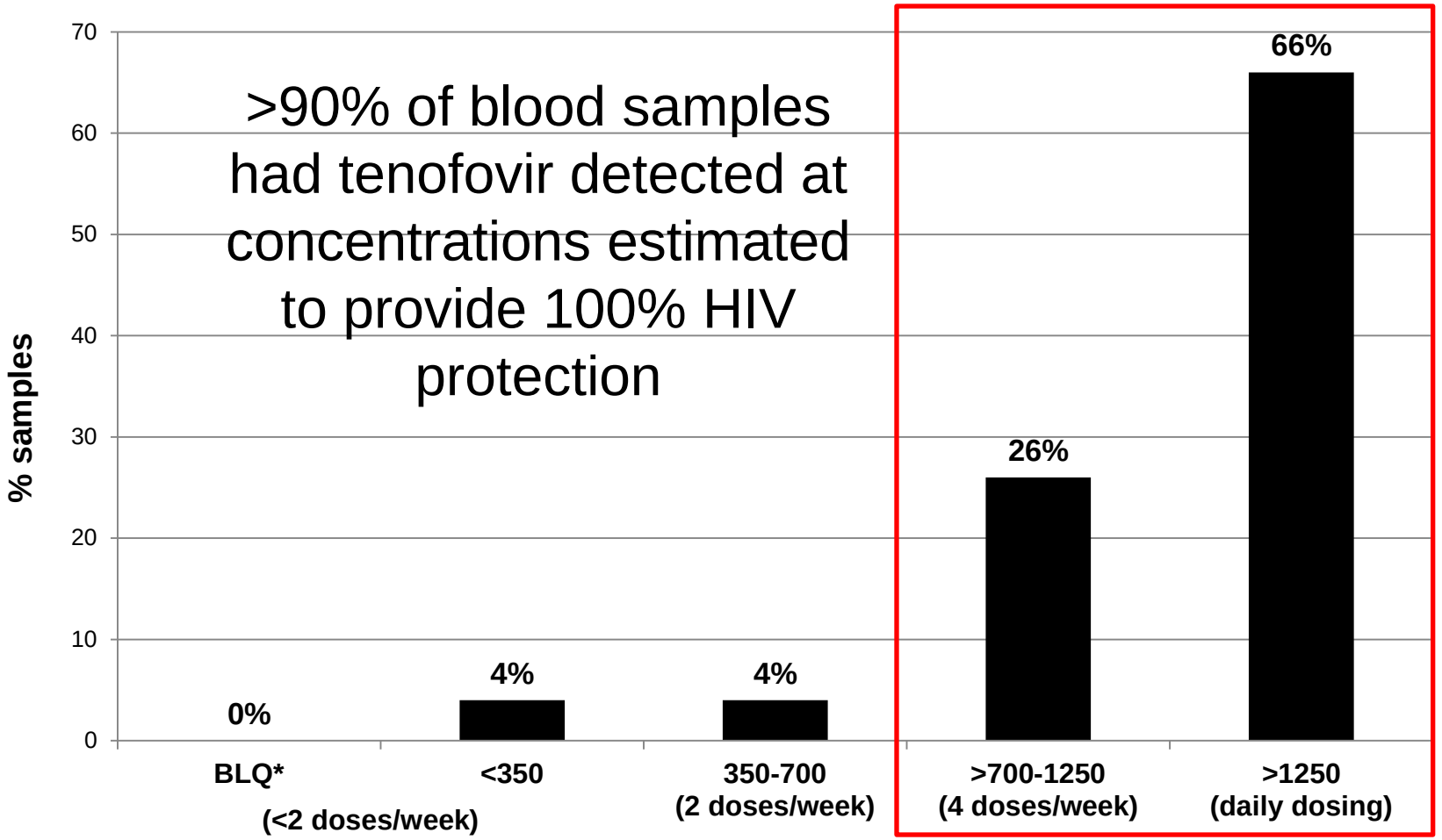
Partners Demonstration Project

- To date, only 2 HIV infections has been **observed** in 1013 high-risk serodiscordant couples, compared with nearly 40 infections that would be **expected** in a counterfactual simulation model.
- The observed incidence is a **96% reduction** compared to expected.



Baeten CROI 2015

What PrEP looks like in real world delivery: San Francisco Demo Project in MSM



Liu et al. IAPAC 2014

Learning from PrEP delivery in SF

- No HIV infections among 657 MSM who received PrEP through Kaiser San Francisco
  - Upper limit of 97.5% CI of **1%**
- Mean duration of PrEP use of 7.2 months
- 30% of PrEP initiators were diagnosed with an STI after 6 months of follow-up
- # of sexual partners unchanged in 74%, decreased in 15% & increased in 11%
- Condom use unchanged in 56%, decreased in 15% & increased in 3%

Volk CID 2015

Making sense of higher effectiveness of oral PrEP than efficacy in MSM & couples

- Effectiveness ≈ efficacy estimate of 90% among those with detectable drug during phase 3 trials
- MSM and couples at risk are:
  - Able to recognize their risk
  - Motivated for HIV prevention
  - Able to use PrEP sufficiently well to achieve high prevention benefits

Value of small, focused studies: ADAPT/HPTN 067

- 79% adherence at 30 weeks among women in Cape Town in daily oral PrEP arm
- Higher adherence in women on daily than less than daily dosing
- *Ubuntu* (a quality that includes the essential human virtues of compassion and humanity)
  - Motivation for research arising from qualitative research in ADAPT

Bekker CROI 2015

Amico IAS 2015

What PrEP offers people

- What PrEP-takers say PrEP offers (Gilmore et al. IAPAC 2014; Ware et al. JAIDS 2012; Ware et al. AIDS & Beh 2014)
  - Decreased anxiety
  - Increased communication, disclosure, trust
  - Increased self-efficacy
  - Increased sexual pleasure & intimacy

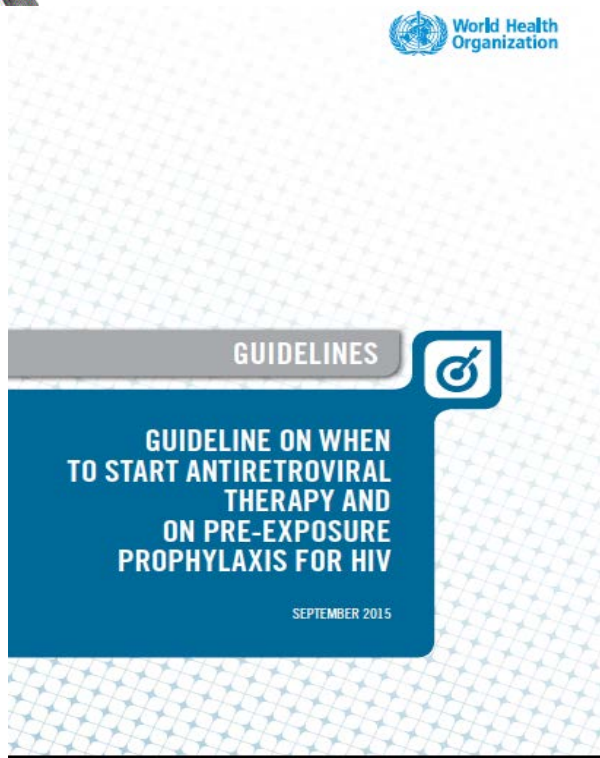
We all have our slips sometimes *where we're, like, engaged in sex and stuff like that and either we're intoxicated or we just feel a certain way about a person, you know,* ***we really don't take, you know, the safest route all the time****.* - iPrEx OLE participant (Gilmore et al. IAPAC 2014)

How good is good enough?

Moving forward with efficacy & effectiveness data

- PrEP as part of combination HIV prevention for young African women in PEPFAR DREAMS initiative

- WHO guidelines Sept 2015
  - **Oral PrEP with TDF should be offered as <u>an additional prevention choice</u> for people at substantial risk of HIV infection as part of combination prevention approaches**



Summary of how good is good enough & do phase 3 trials predict effectiveness?

- “Good enough” is relative to alternatives, priorities & resources
- Phase 3 trials do not always predict effectiveness
  - Value of ‘as treated’ analyses in phase 3 trials (i.e., efficacy estimates in those with detectable drug)
  - Effectiveness can be higher than efficacy (PROUD, Partners Demo project)
- Invaluable lessons can be learned from open label studies, demonstration projects and delivery studies

Summary: How good is good enough? Do phase 3 trials predict effectiveness?

- "Good enough" is relative to alternatives, priorities & resources
- Phase 3 trials do not always predict effectiveness
  - Value of 'as treated' analyses in phase 3 trials (i.e., efficacy estimates in those with detectable drug)
  - Effectiveness can be higher than efficacy (PROUD, Partners Demo project)
- Invaluable lessons can be learned from open label studies, demonstration projects and delivery studies
- We need prevention choices for women
  - HOPE is a critical next step after ASPIRE & the Ring studies, if efficacy is demonstrated

‘Hats off’ to the inspiring ASPIRE team

MTN microbicide trials network

ASPIRE
A Study to Prevent Infection with a Ring for Extended Use

National Institutes of Health

Statistical Center for HIV/AIDS Research & Prevention
SCHARP

fhi360

Johns Hopkins Research Project
Malawi

RHI

CAPRISA
CENTRE FOR THE AIDS PROGRAMME OF RESEARCH IN SOUTH AFRICA

MRC
SOUTH AFRICA

INTERNATIONAL PARTNERSHIP FOR MICROBICIDES

DESMOND TUTU HIV FOUNDATION

UNC PROJECT
Lilongwe, Malawi

University of Zimbabwe, School of Medicine

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Thanks to the Partners Demonstration Project Team

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PEPFAR

UNIVERSITY OF WASHINGTON
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