Adherence & Effectiveness: Lessons from CAPRISA 004, iPrEx & Partners PrEP (& HSV-HIV trials)

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Top lessons from adherence in biomedical HIV prevention trials

- Why adherence is critical to measuring efficacy in clinical trials
- Measurement of adherence
  - Lessons learned from non-PrEP studies: HPTN 039, Mwanza HSV and HIV prevention study, Partners in Prevention HSV/HIV Transmission Study
  - Lessons from CAPRISA 004 & iPrEX
- Counseling about adherence
  - Lessons learned from CAPRISA 004, iPrEX & Partners PrEP
- Recommendations for ‘the way forward’

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Lesson 1:

Adherence matters

in assessing efficacy of user-dependent prevention methods

What he thought he heard.

Cartoon courtesy of Susan Buchbinder

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ELSEVIER

Contraception 83 (2011) 10–15

Contraception

Review article

Apples and oranges? Interpreting success in HIV prevention trials

Lori L. Heise[a,*], Charlotte Watts[a], Anna Foss[a], James Trussell[b,c], Peter Vickerman[a], Richard Hayes[d], Sheena McCormack[e]

- Efficacy vs effectiveness

> *effectiveness* is reserved for the effect that can be achieved in practice, taking into account limited coverage, constrained resources and inconsistent or imperfect use.

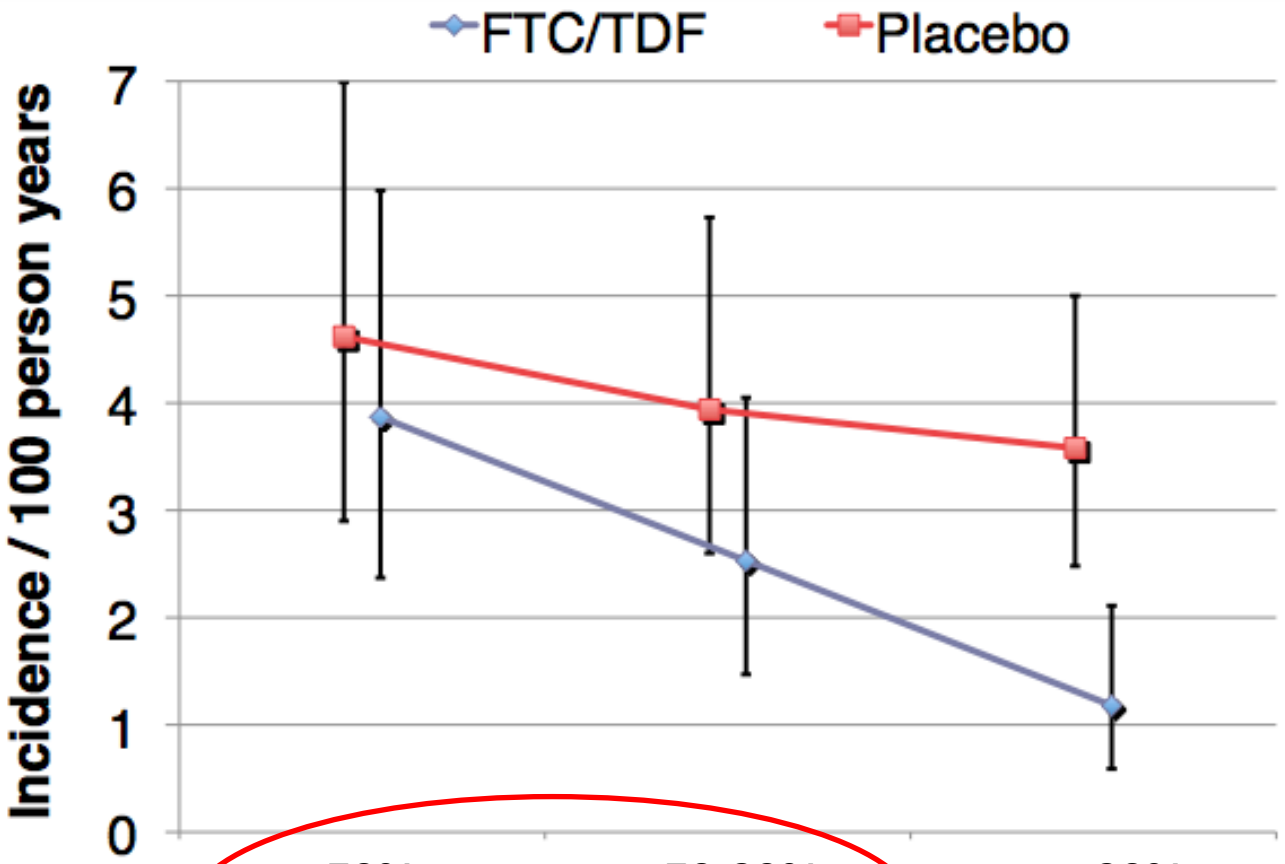
- Efficacy ≈ effectiveness for vaccines where can objectively measure adherence (receipt of vaccines)
- For user-dependent interventions (eg PrEP), phase III trials measure both biologic efficacy & adherence
  - Provide unbiased measure of efficacy across average users
  - 40% efficacy with <100% adherence implies higher efficacy

CAPRISA 004: Adherence is critical for efficacy against HIV

- High (>80% gel adherence) n=336 (38%)
  54% efficacy
- Intermediate (50-80% adherence) n=181 (20%)
  38% efficacy
- Low (<50% gel adherence) n=367 (42%)
  28% efficacy

Abdool Karim et al, Science 2010

Recorded Adherence and Efficacy



	<50%	50-90%	>90%
% of Visits	18%	33%	49%
Efficacy	**16%**	**34%**	**68%**
95% CI	-54 - 54	-20 - 64	36 - 84

Why do we care?

- In order to:

- Determine whether efficacy of user-dependent methods (e.g., PrEP) is related to biologic activity of the product or user adherence

-For regulators & policymakers, answer “how good is good enough?” for licensure & implementation

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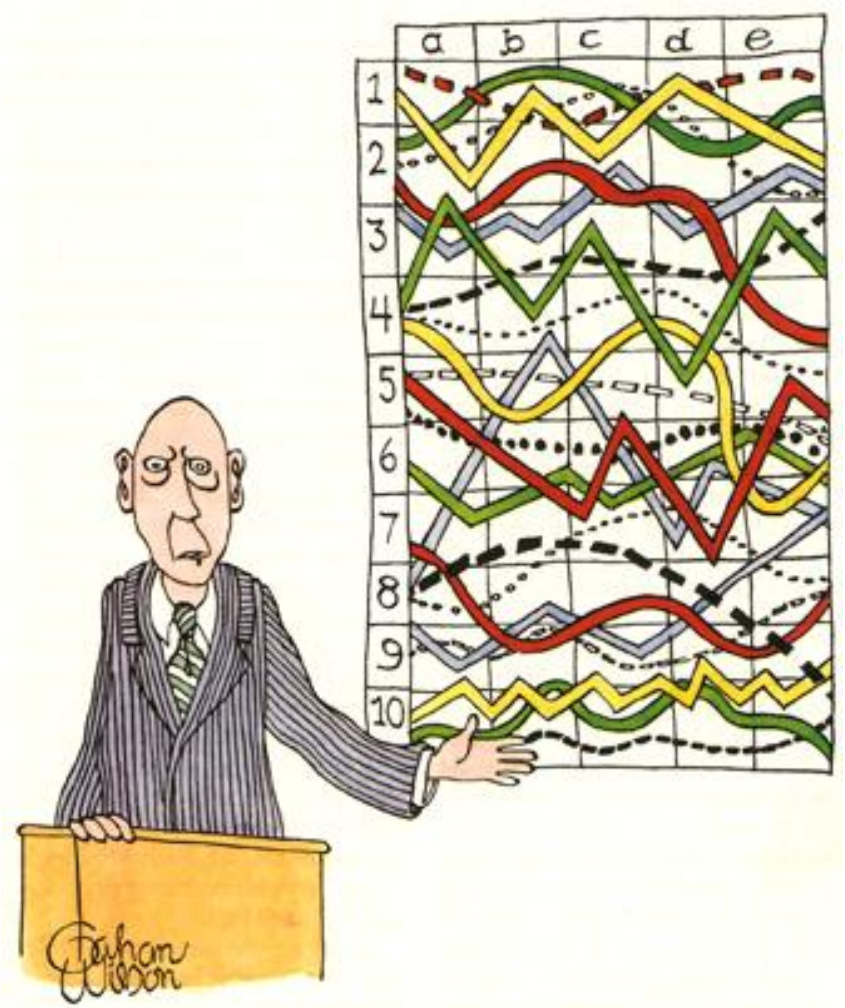
Lesson 2: ***Adherence measurement matters*** *in understanding & comparing efficacy of user-dependent prevention*



"I'll pause for a moment so you can let this information sink in."

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So, if we care about adherence, how do we measure it?

- How to measure adherence?
  - Self-report by interview
  - Self-report by CASI
  - Pill counts
  - Electronic monitoring
  - Drug levels in blood, hair
- Adherence measurement is complex & needs to be standardized so can interpret efficacy & adherence across studies

Different measures of adherence reported in recent HIV prevention trials

Study	Measure used	Value
HPTN-039	overall median % dispensed drug taken overall median adherence including 'non-adherence' % of quarterly visits with ≥ 90% adherence	94% 86% 73%
Mwanza trial	% of person-years with ≥ 90% adherence median adherence	51% 92%
Partners HSV2	% of doses taken % drug dispensed % of participants with ≥ 90% coverage*	96% 85% 71%
iPrEx	mean rate of self-reported pill use % of tablets returned at next visit % of tablets returned by next 2 visits median rate of pill use	89%-95% 66% 86% 89%-95%

*coverage defined as % doses taken * % doses dispensed

Kathy Baisley, LSHTM, work in progress

A tale of two trials:
Pill count measures in HPTN 039 & Mwanza HSV suppression trials

	HPTN 039 (monthly)	Mwanza (quarterly)
Numbered bottles/packets	Yes, unique ID, recorded when dispensed and returned	Yes, but not unique (batch number) & recorded only when dispensed
Counts of returned pills	Matched to visit dispensed	Assumed to have been dispensed at previous visit
Interim visits	Yes	Yes
Other counts between visits	No	Yes, at participant's home 3-4 weeks after scheduled visit
Treatment interruption allowed	Yes	Yes, but not for pregnancy
Self report of missing tablets	Yes, every visit	Yes, at 9–30m visits
End of study interview	Yes, 13 to 31 months after final visit	Yes, at final visit

Kathy Baisley, LSHTM, work in progress

HPTN 039 & Mwanza: Adherence calculations (the details matter!)

	HPTN 039	Mwanza
Method	Pill counts at each visit, self report if not returned	Pill counts at each visit, self report if >105%
Period over which adherence is calculated	Days elapsed since last visit	Days elapsed since last visit
Calculated as	(pills dispensed – pills returned) / days elapsed*2	(pills dispensed – pills returned) / days elapsed*2
Include periods off treatment	for some measures	Yes
Missed visits	Adherence calculated at next attended visit	Adherence calculated at next attended visit
Aggregated?	Yes, by quarter	No
Categories	<90%, 90-105%, >105%, unknown	<75%, 75-89%, 90-100%, unknown

Kathy Baisley, LSHTM, work in progress

Adherence measurement questions

- How much over-adherence to allow in 100%
  - None?
  - Up to 105%?
  - Fixed number of tablets (e.g.1-4)?
- How to handle missing pill counts?
- How to handle ‘ultra-high’ adherence?
- How to handle missed visits or time off treatment?
- Participant self-reports
  - Should we use self report to fill in gaps?
  - How reliable is it - should we even bother asking these questions?

Lesson 3:
Pill counts overestimate adherence

The Scream, by Eduard Munch, capturing the clinical trialist's response

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Why does self-report & pill count overestimate adherence?

- Participants have their reasons, including
  - motivation to stay in the study
  - misinterpreting consent forms about study termination ‘if can’t follow procedures’
  - appreciation of benefits of being in a study
  - learning ‘the right answer’ (i.e., social desirability bias)

Lesson 4:
Populations may differ regarding adherence

"The top doesn't come off. It's preventative medicine."

Cartoon courtesy of Susan Buchbinder

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Partners PrEP Adherence Ancillary Studies

In collaboration with David Bangsberg, Jessica Haberer, Christina Psaros, Steve Safren, & Norma Ware

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1000-1500 HIV discordant couples in Partners PrEP from 3 Ugandan sites

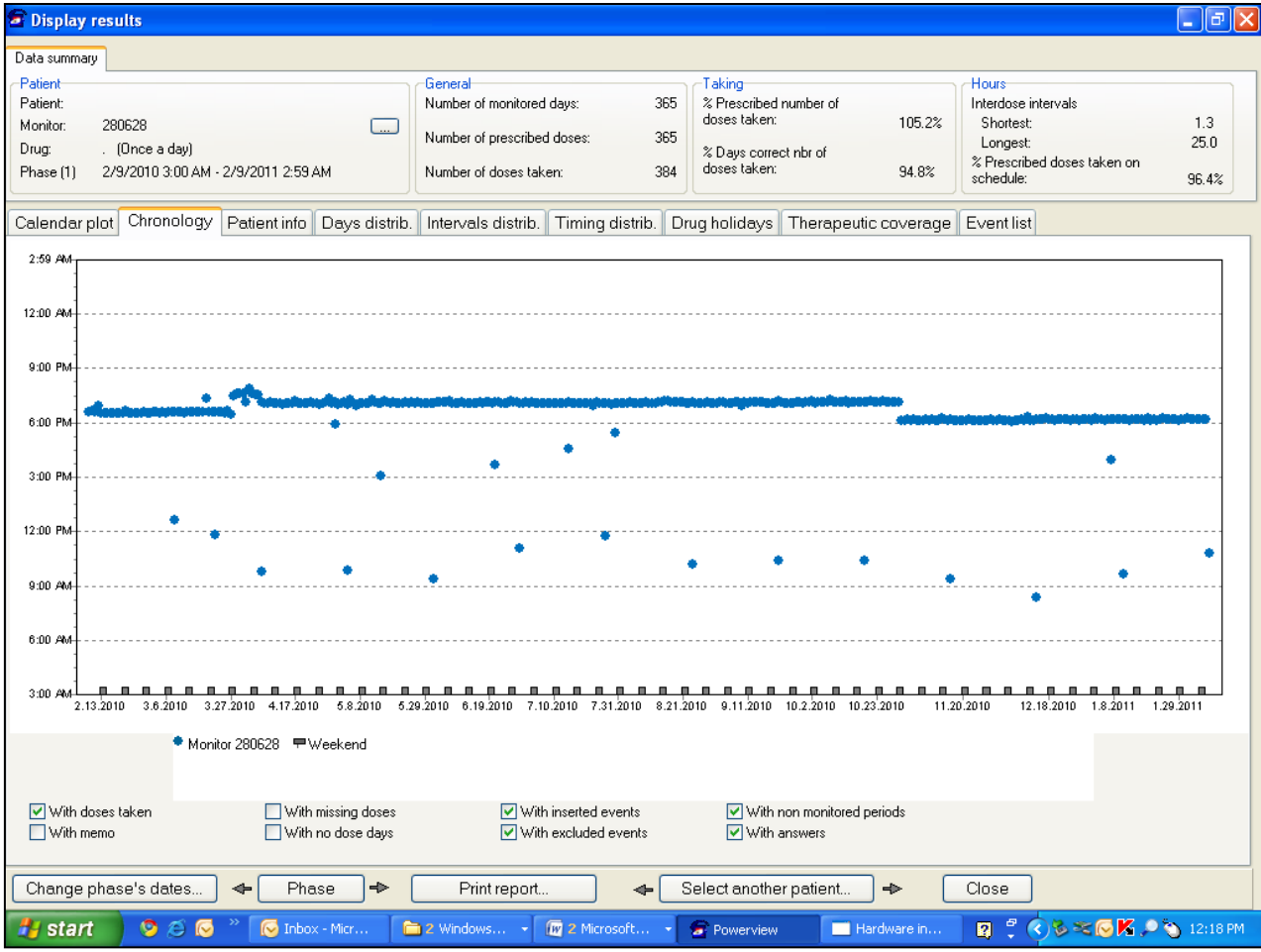
↓

1) Enhanced adherence measurements

- MEMSCaps to monitor daily pill-taking patterns vis a vis monthly pill counts
- Unannounced home visits for pill counts
- In-depth interviews
- Tenofovir levels: plasma, intracellular (subset) to measure recent adherence in HIV- partner & drug sharing in HIV+ partner

2) Enhanced adherence intervention if adherence <80%

MEMS Caps



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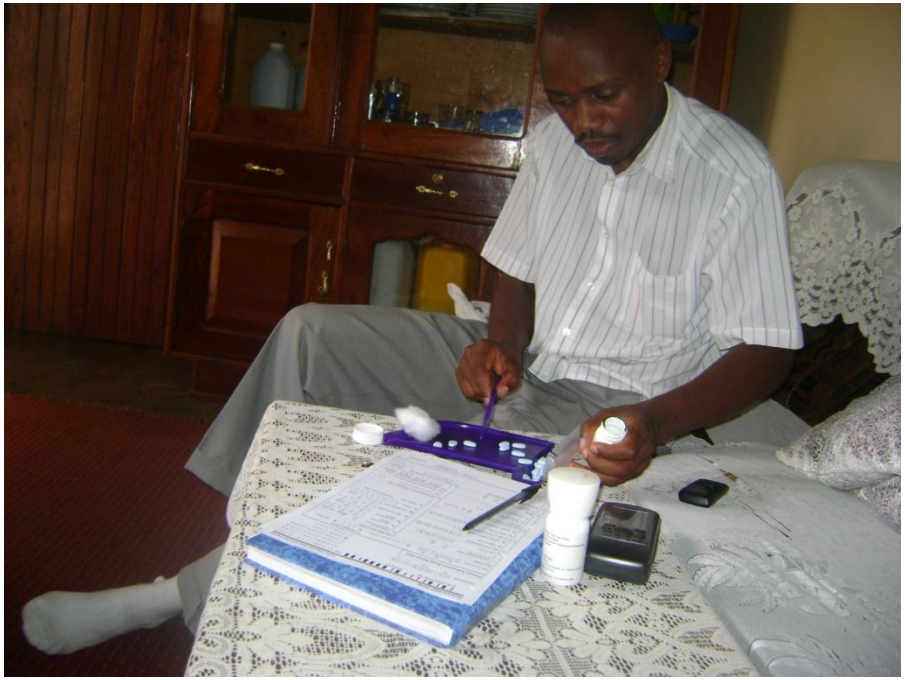
Partners PrEP: Home visits for unannounced pill counts in adherence substudy



Kampala

Partners PrEP: Ancillary study on drug adherence

- 978 couples enrolled to date
- >5100 unannounced home visits completed (!)
- To date, ~5% participants have had <80% adherence measured at any home visit
- MEMS data: high correlation with home visit pill counts, indicating high adherence (N=691)

Clinic-based pill counts	99.6% (IQR 96.1-100.9)
MEMS	101.9% (IQR 97.4-104.7)
Unannounced pill counts	99.1% (IQR 97.2-100.0)

Haberer et al, CROI 2011

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Lessons Learned: Partners PrEP and pill taking

- Additional procedures to implement adherence substudy were labor-intensive
  - Particularly the unannounced home visits for pill counts
- High correlation between unannounced home visits for pill counts & MEMS with clinic pill counts
- African HIV serodiscordant couples are highly motivated to take PrEP
- Couples' issues impact adherence
  - Intimacy, discord, sexual activity, HIV- partner reminded re PrEP by HIV+ partner taking Septrin

Lesson 4:
You can only intervene upon what you measure

Did you ever miss a dose or doses of study drug due to drinking alcohol?

☐ *yes* ☐ *no* → *Go to item 6 on page 2.*

5a. If so, how did alcohol result in you missing study drug? *Mark all that apply.*

☐ *I was scared that alcohol wouldn't mix with my study drug (drug interaction)*

☐ *I forgot to take my study drug*

☐ *other:* _____

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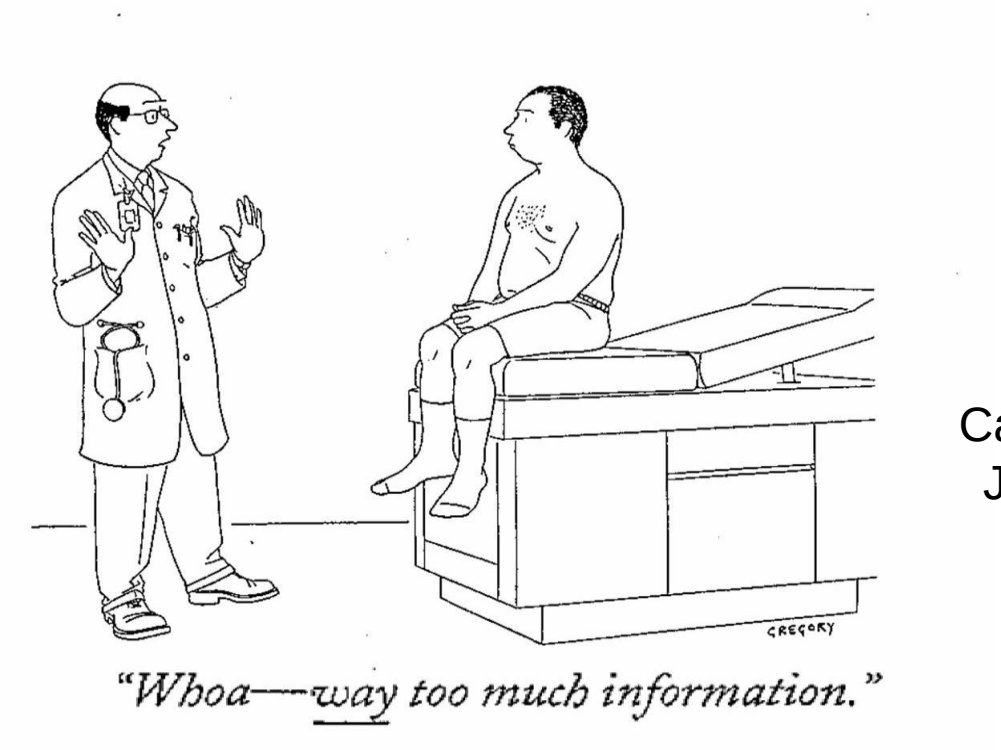
Corollary:
Ask about factors influencing PrEP use (e.g., alcohol, pregnancy intention) so can offer interventions (adherence aids, family planning)

- In assessment of adherence at HPTN 039 unblinding, 36% of Peruvian, 8% of US & 4% of African participants participants reported they missed study drug due to alcohol Jacob et al AIDS & Behavior 2010
- Often do not ask about fertility intention or carefully reassess contraceptive use and interest in studies among women & couples

Lesson 5:
Adherence counseling is critical & needs to be flexible



"Whoa—way too much information."

Cartoon courtesy of Jeanne Marrazzo

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Adherence Counseling

- Recognize that adherence is often harder than we think
- When we're busy, it's easy to become directive -- to talk and not listen
- Adherence messaging does not need to be done by all site staff who see participants
  - Participants have to feel they have room to be honest about adherence
- While adherence measurement needs to be standardized, adherence counseling does not
  - Make it flexible, responsive, personalized

Learning from CAPRISA 004 & iPrEX: ‘Next Step Counseling’

Partners PrEP adherence intervention

- Counselors: barriers to pill-taking include changes in sexual behavior, partner discord, travel, & life changes
- Participants: high levels of motivation to adhere to PrEP, often driven by altruism
- Adherence intervention for those with <80% adherence in prior 3 mos
  - Assessment of sexual & pill-taking behaviors, motivational interviewing, & optional couples session
- Encouraging preliminary data; adherence ↑ to >80% in 72% of those who went through intervention

Psaros, IAPAC 2011

The Way Forward: Adherence & the 'Achilles heel' of ARVs for HIV prevention

- **Will people at highest risk for HIV reliably use a gel? a pill?**
  - Adherence is challenging, even in clinical trials
  - Serodiscordant couples in Partners PrEP: intimacy, disclosure & partner support important to support pill-taking
  - Need objective measurements (MEMS & drug levels)
- **Many beliefs, too little understanding about risk perception & behavioral aspects of biomedical prevention**
- **Need to hit the 'sweet spot' in adherence counseling**
  - Listen to your participants
  - Give them permission to tell you what they did
  - Be neutral in your assessment

Thank You

- Jared Baeten, Andrew Mujugira & Partners PrEP Adherence Study Coordinators (Alex Kintu, Kenneth Mugwanya, Michael Enyakoit)
- David Bangsberg Jessica Haberer, Christina Psaros , Steve Safren, Norma Ware (MGH & Harvard)
- Rivet Amico (U of Conn), Bob Grant, Javier Lama & iPrEx team
- Jeanne Marrazzo , Mike Chirenje & VOICE Team
- Slim & Quarraisha Abdul-Karim & CAPRISA004 team
- Kathy Baisley, LSHTM
- Susan Buchbinder, SFDPH
- Deborah Donnell, FHCRC & UW ICRC

If you want to go fast, go alone.

If you want to go far, go together.

– African proverb