

Interventions for adherence enhancement in HIV prevention trials

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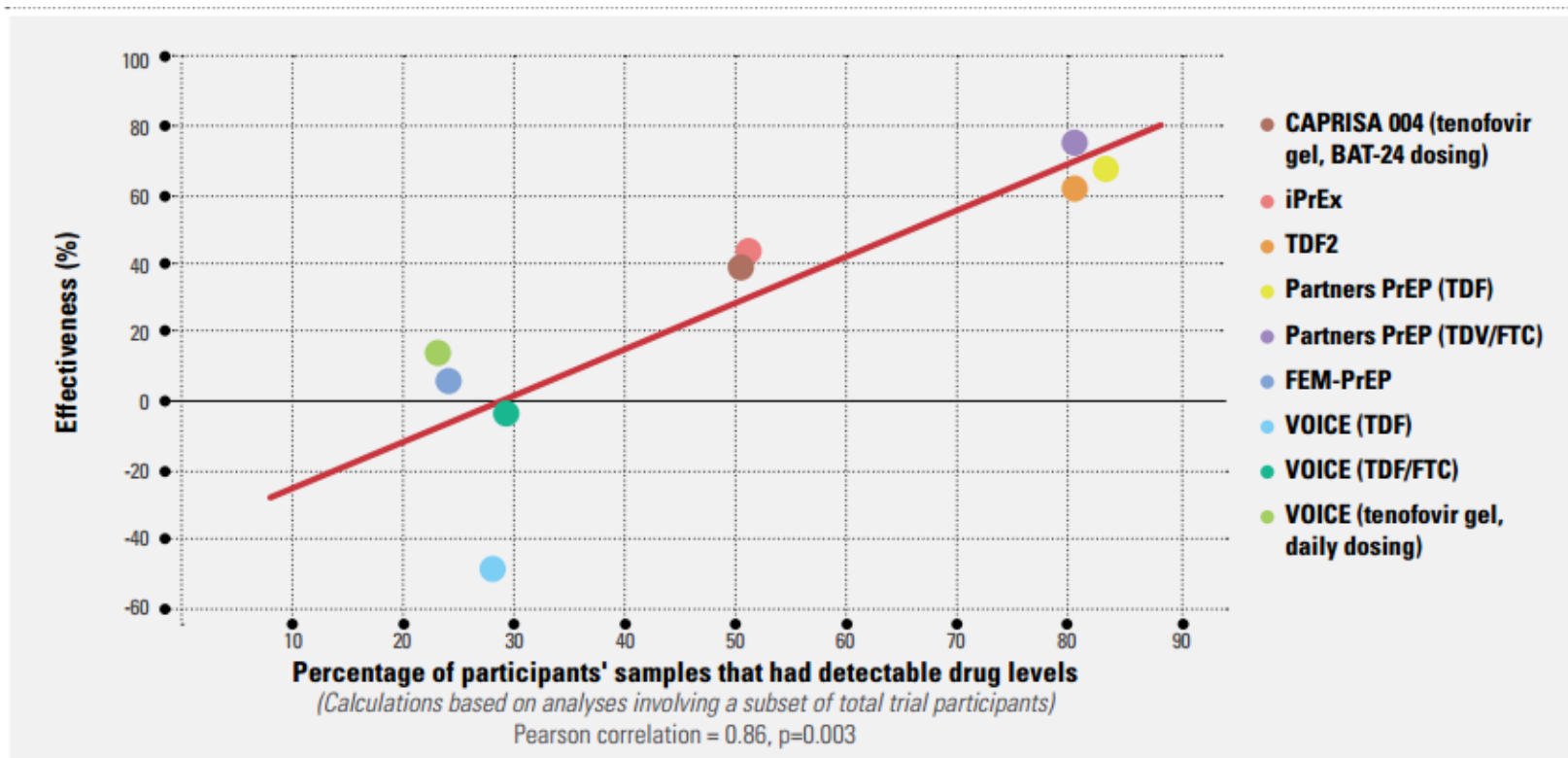
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ASCPT meeting, San Diego, March 12 2016

Outline

1. The problem: non-adherence
2. Is everyone non-adherent?
3. Adherence exploration in VOICE and beyond: an evolution
4. OLE and next generation of trials
5. Sources of non-adherence & linked interventions

PrEP Effectiveness as a function of adherence

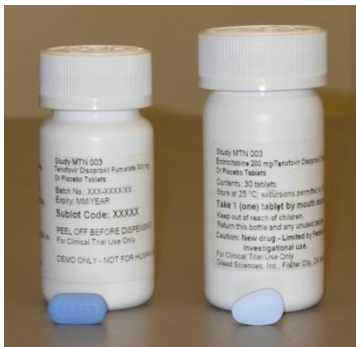


AVAC 2013, adapted from Salim. S. Abdool Karim, CAPRISA

“PrEP protects women from HIV acquisition when taken with sufficient adherence” (Thomson et al., Curr. Op. HIV AIDS 2015)

VOICE Final Results

- No demonstrated effectiveness of any of the 3 products, in the context of high HIV incidence



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Tenofovir-Based Preexposure Prophylaxis for HIV Infection among African Women

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ABSTRACT

BACKGROUND

Reproductive-age women need effective interventions to prevent the acquisition of human immunodeficiency virus type 1 (HIV-1) infection.

METHODS

We conducted a randomized, placebo-controlled trial to assess daily treatment with oral tenofovir disoproxil fumarate (TDF), oral tenofovir-emtricitabine (TDF-FTC), or 1% tenofovir (TFV) vaginal gel as preexposure prophylaxis against HIV-1 infection in women in South Africa, Uganda, and Zimbabwe. HIV-1 testing was performed monthly, and plasma TFV levels were assessed quarterly.

RESULTS

Of 12,320 women who were screened, 5029 were enrolled in the study. The rate of retention in the study was 91% during 5509 person-years of follow-up. A total of 312 HIV-1 infections occurred; the incidence of HIV-1 infection was 5.7 per 100 person-years. In the modified intention-to-treat analysis, the effectiveness was 40.0% with

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*A complete list of members of the Vaginal and Oral Interventions to Control the Epidemic (VOICE) Study Team is provided in the Supplementary Appendix, available at www.nejm.org.

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VOICE trial bio-behavioral gap: Evidence of non-adherence by route of administration & by measures

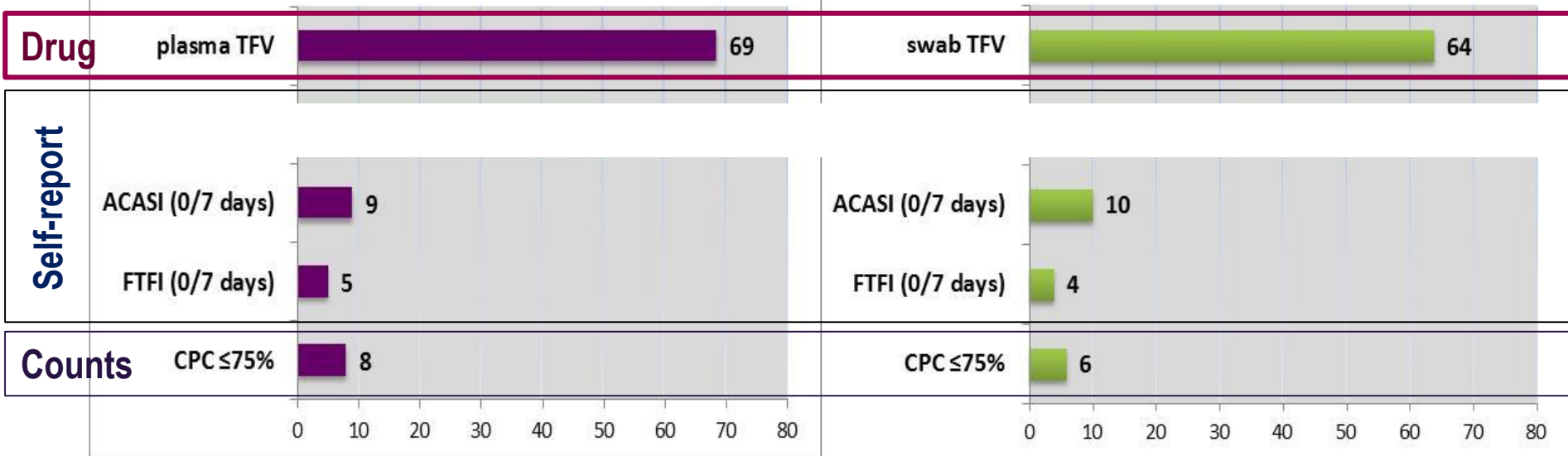


Random cohort sub-sample; among active arm VOICE participants



Oral Tablets, N=314

Vaginal Gel, N=158



% non-adherence (focus on past 7 days)

New adherence support intervention implemented mid-trial

VOICE starts
9/2009

VASP
implemented
5/2011

Oral TDF
futility results
9/2011

Vaginal TFV
futility results
11/2011

VOICE ends
8/2012

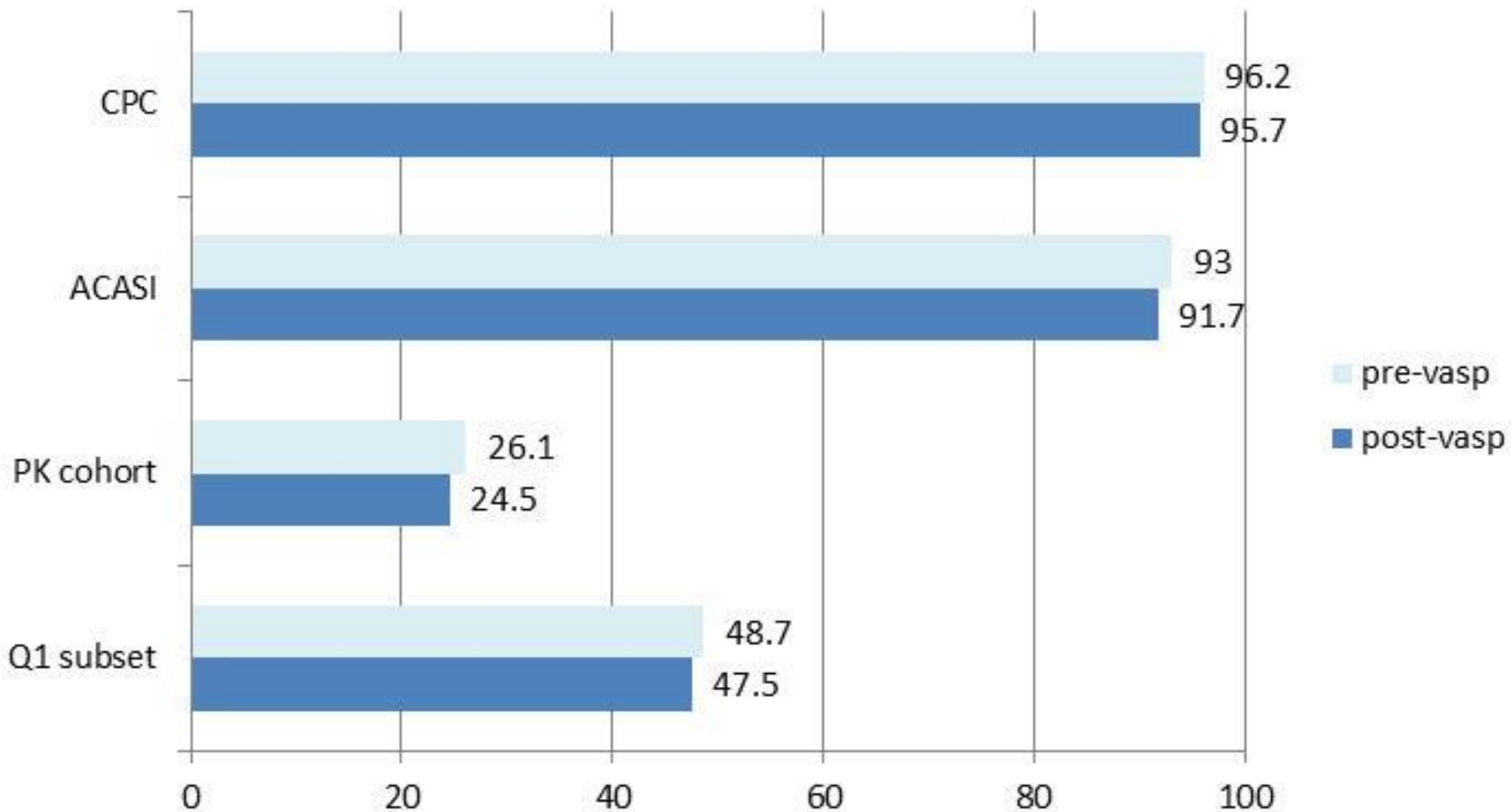
Original Adherence Support Program (ASP)

- Used product count from pharmacists to inform the counseling session; reconciled product count and self-reported adherence.
- Asked the participant how often she had been able to use the product and then based counseling on reported level of adherence.
- Adherence plan/strategies based on overcoming **barriers** to product use.
- Used reported adherence (none, some, or all of the time) to determine the focus of the session.
- Reinforcement of product use instructions (10 key messages) by the **adherence counselor**.
- Positive reinforcement of good adherence.
- Goals focused on perfect adherence.

VOICE Adherence Strengthening Program (VASP)

- Counselors did **NOT** review product count prior to counseling session or probe about discrepancies in product count versus self-report.
- Counseling focused on participant's experiences using the product, and what makes using product easier or harder, regardless of how much she used it.
- Adherence plan/strategies based on addressing **adherence-related needs**.
- All sessions followed same format regardless of self-reported adherence/non-adherence.
- Product use instructions (10 key messages) removed from the counseling session and instead reviewed by other staff as needed.
- Maintain a neutral counseling approach.
- Goals focused on making product use manageable.

VASP: Adherence support intervention: too little, too late



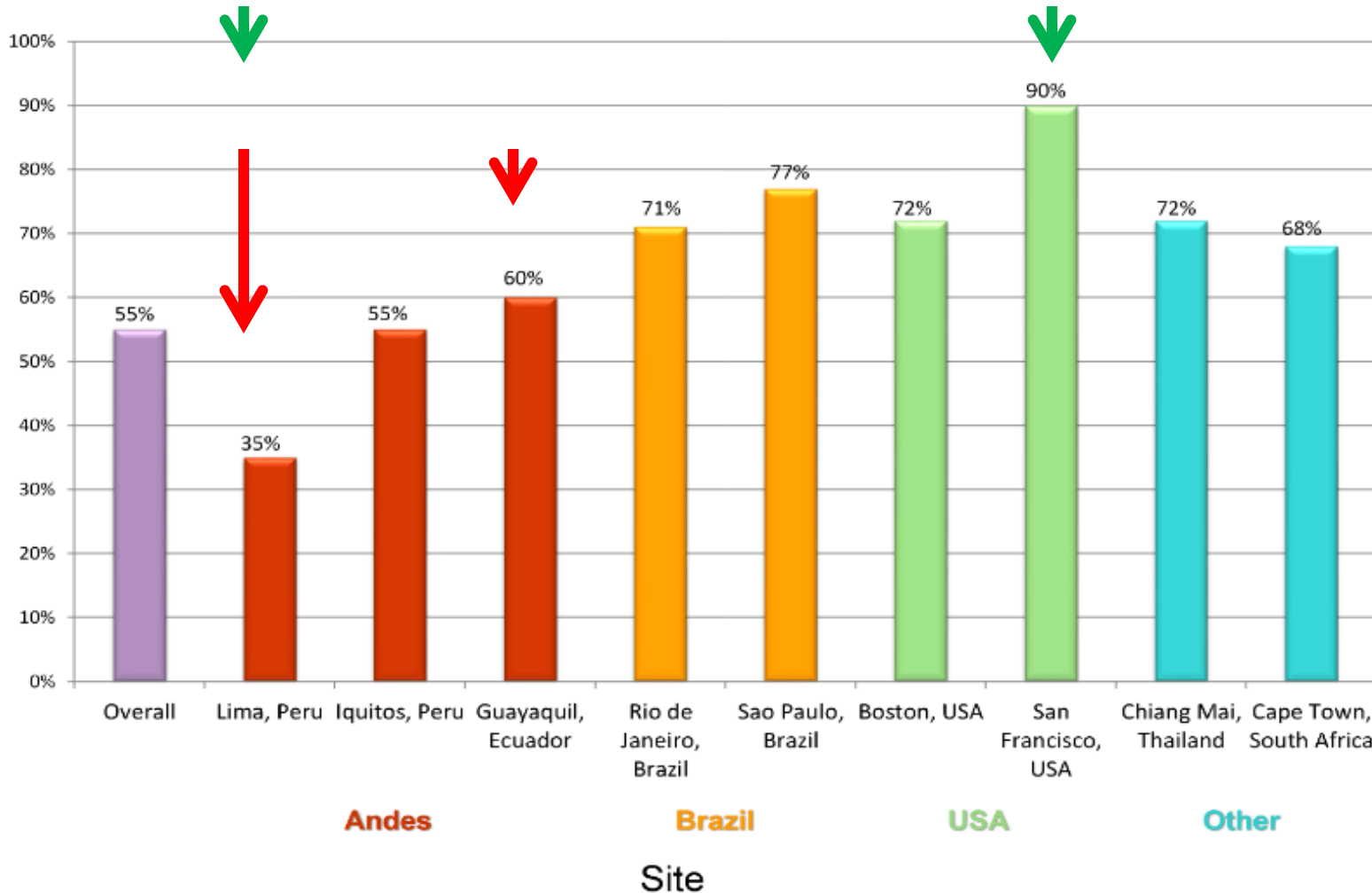
van der Straten, AIBE 2015

Clinic Product Count (CPC; n=2,958); Audio-Computer Self Interview (ACASI; n=3,111); Pharmacokinetic (PK) cohort (n=379); Q1 subset (n=78)

2. Is everyone non-adherent?

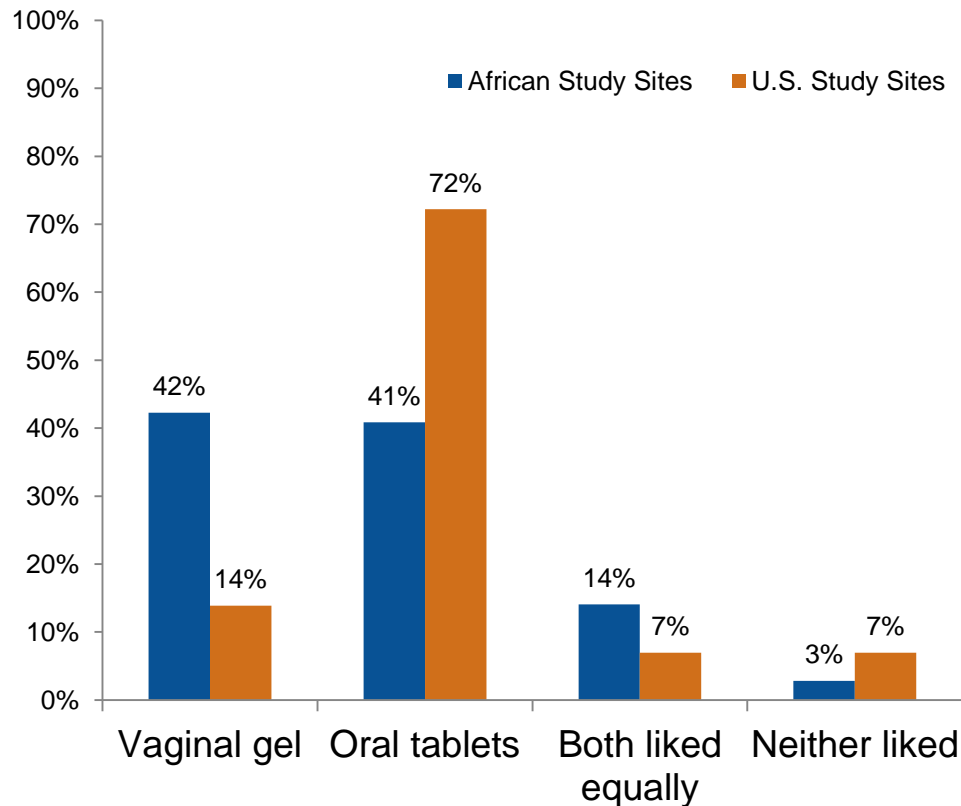


Important variations **across** regions but also **within** regions (across sites)



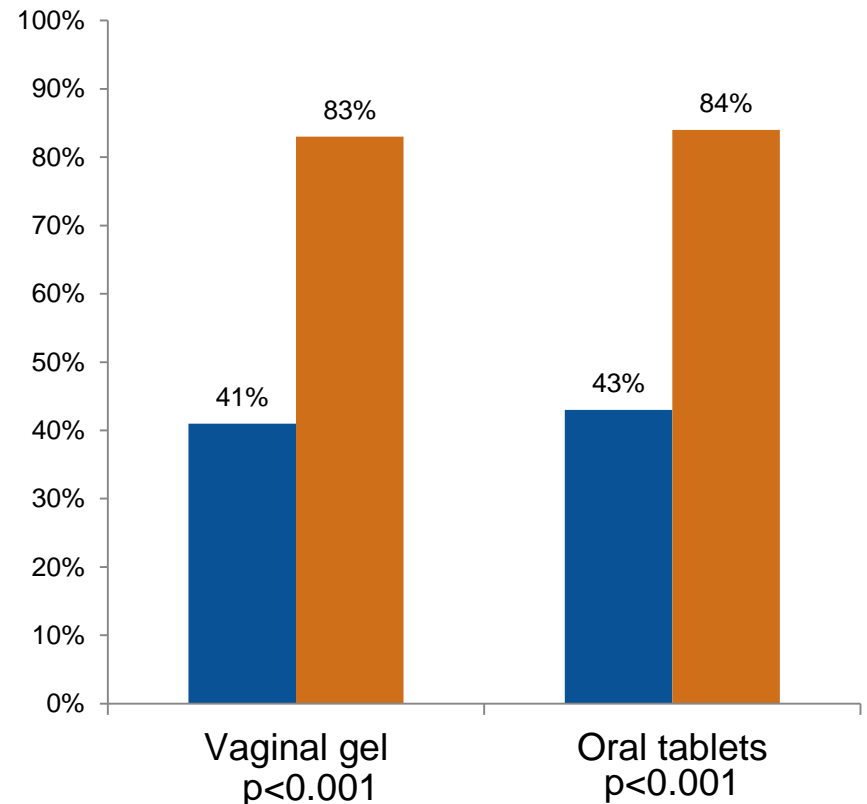
MTN-001: women's product preference (gel vs tablets) and adherence varies by geographical setting (N=144)

Women's product preferences in US vs Africa



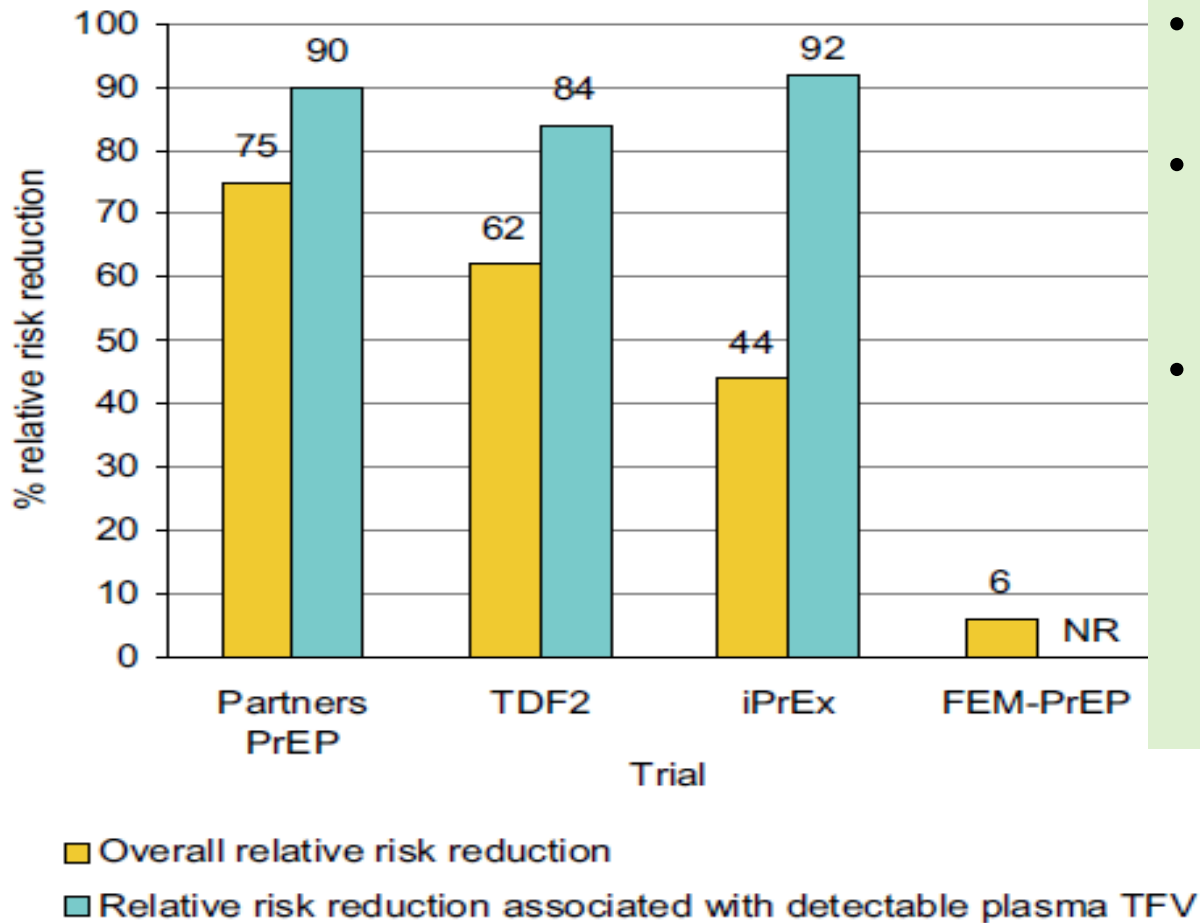
Minnis et al., AIBE 2012

Prior day plasma drug detection by product type and setting (N=141)



Minnis, et al., AIBE 2015

African successes: TDF2 and Partners PrEP

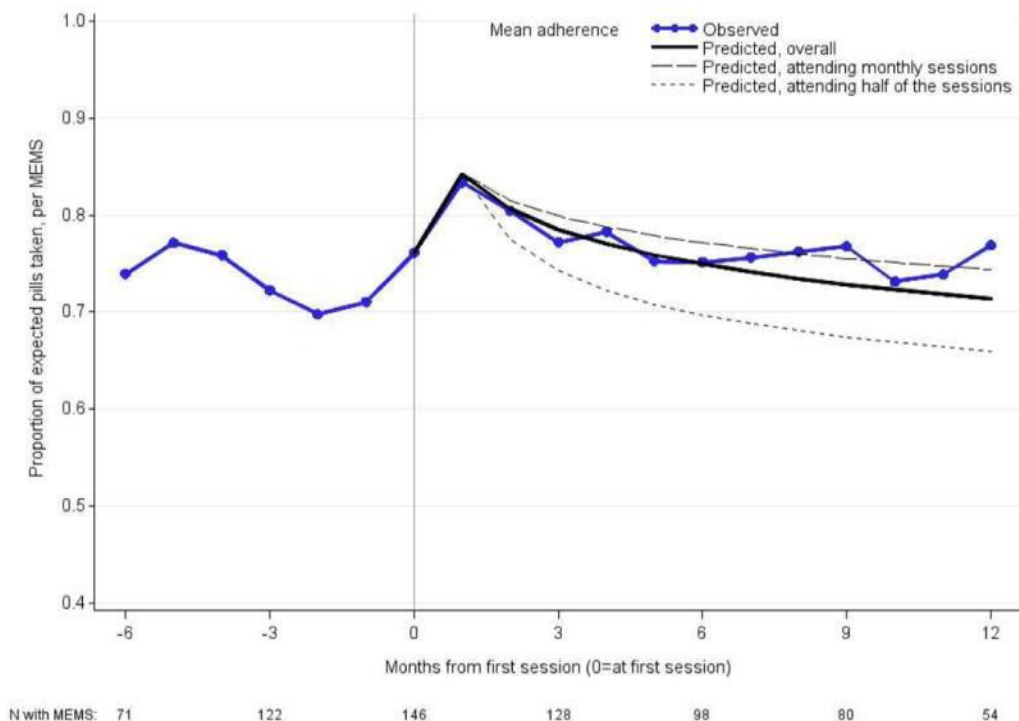


- TDF2: 62% protection in heterosexual ♀ & ♂
- Partners PrEP: 72% protection in hetero SDC
- More protection associated with adherence (plasma PK estimates)

Figure 1. Relative risk reduction in acquiring HIV infection (compared to placebo) in PrEP trials

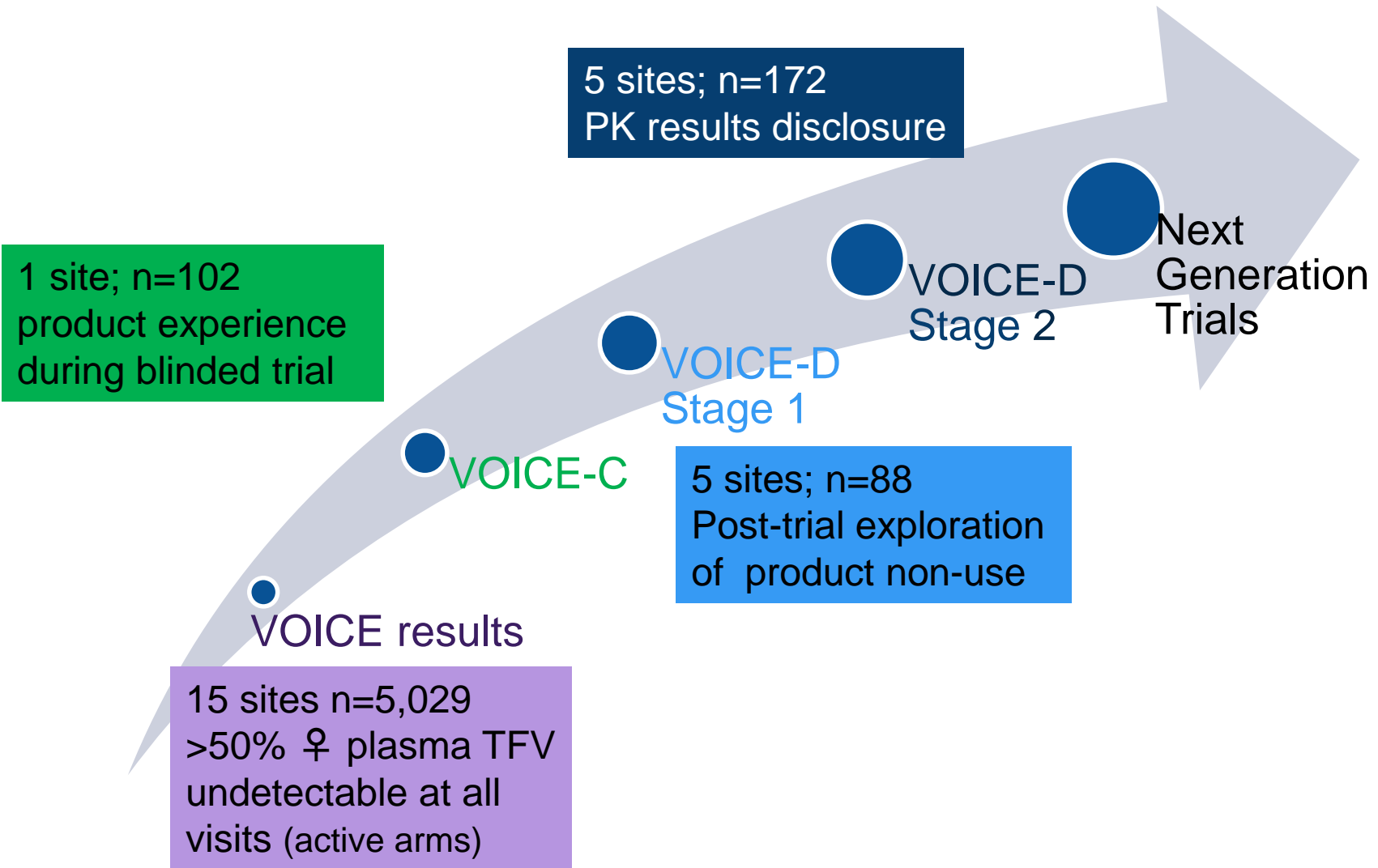
Note: Overall and by adherence measured as detectable plasma TFV
NR, not reported; TFV, tenofovir

Partners-PrEP adherence support intervention (N=1147)

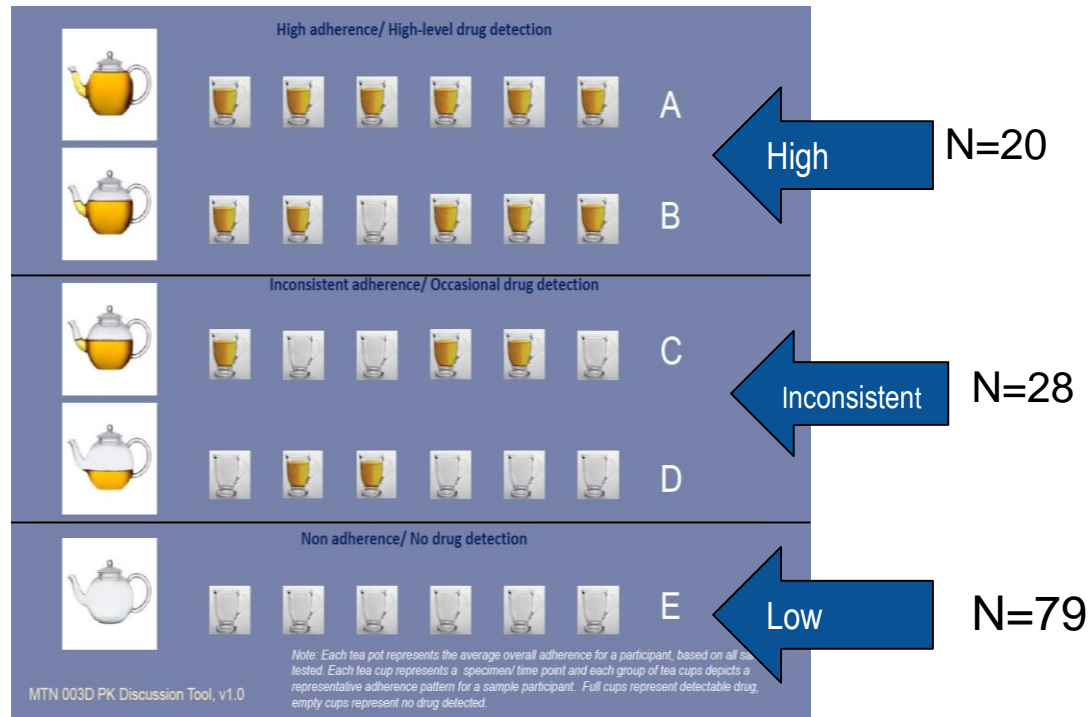


- 3 sites in Uganda
- <80% adherence per UPC triggered adherence intervention
 - N=168 (15%) received it
 - Median of 10 sessions
 - Mean adherence (MEMS)
 - 76% Pre-intervention
 - 84% Post-intervention ($p < .001$)
- Intervention components
 - Education & information
 - Motivational interviewing
 - Problem solving
 - Couple session
 - FU sessions as needed

3. Adherence exploration in VOICE and beyond: an evolution

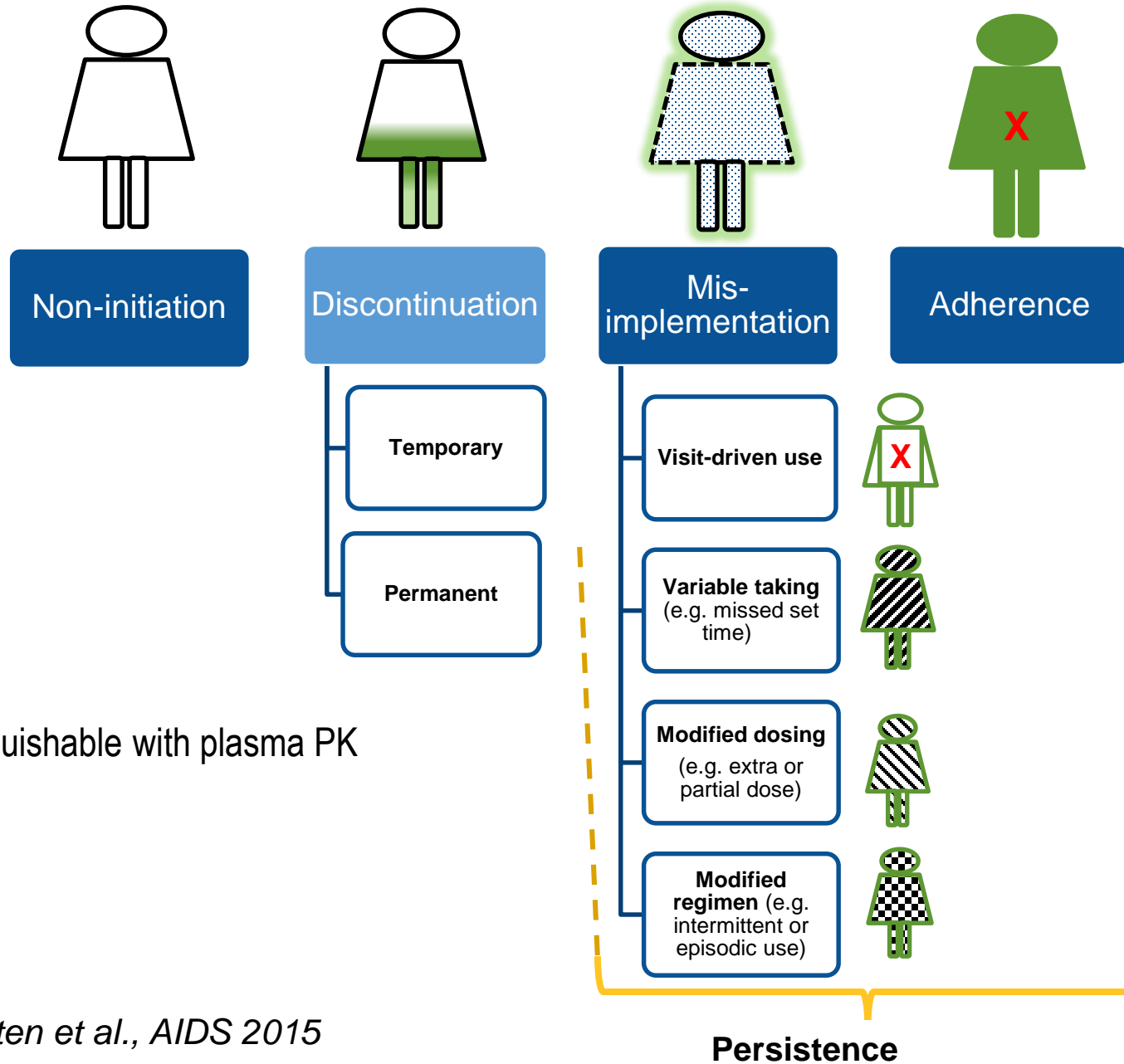


VOICE-D: TFV plasma PK result tool

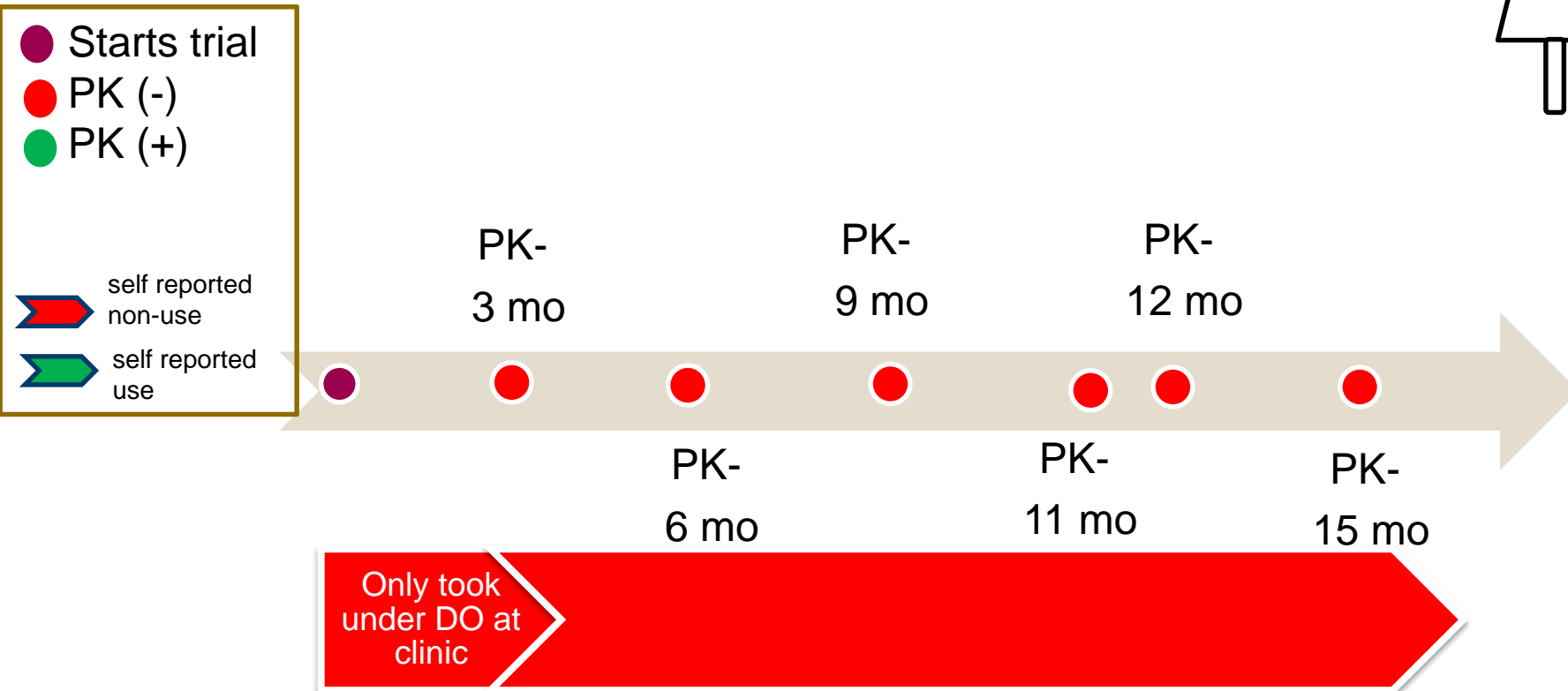
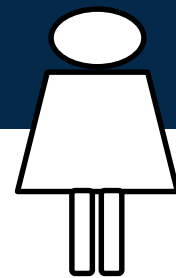


PK result “Teapot tool”

VOICE-D: Typology of Product Use Patterns



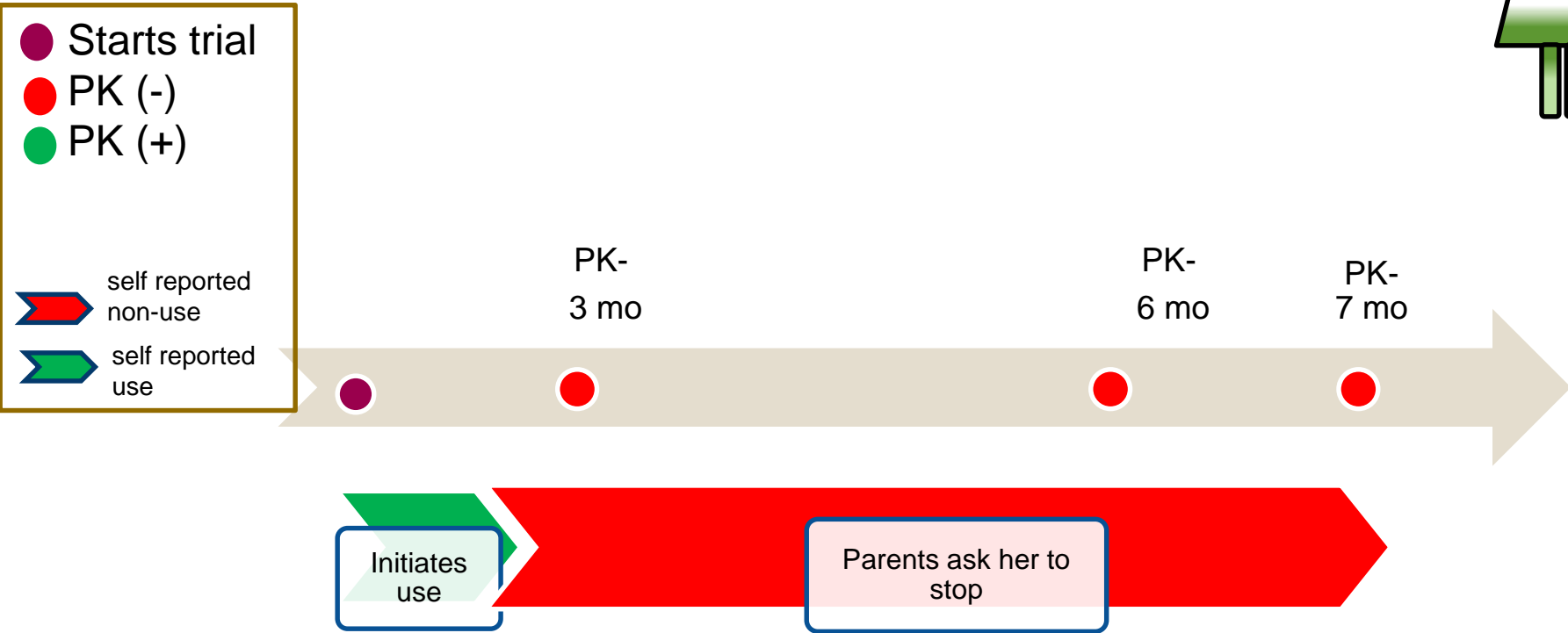
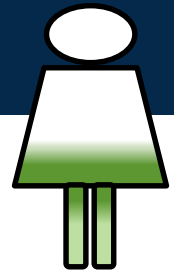
a. non-Initiation



I would explain it (PK results) easily; I am one of those who did not drink it. I only drank the ones we were given at the clinic to drink while we were being taught

(South Africa, 36 years old, **tablet group**, low PK, 15 months in VOICE)

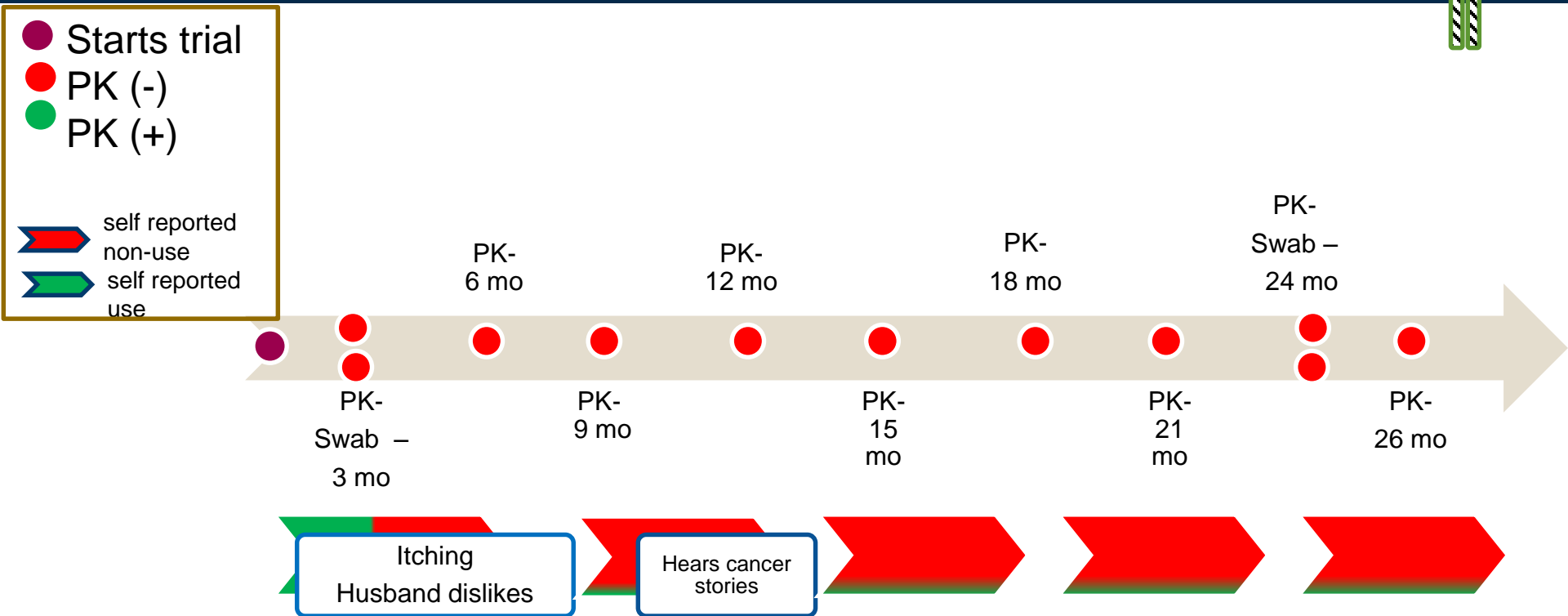
b. Discontinuation



[My parents] were concerned that I might use this thing and then get ill since this was a study.[...] I was afraid of it [tablets] when I had just started using it, when I also lacked understanding. I was afraid that they were testing it on us. [...]My mum said I must stop because I do not know if this will put me at risk, I then stopped.

(South Africa, 21 years old, **tablet group**, low PK, 7 months in VOICE)

c. Mis-implementation/ execution: modified dosing



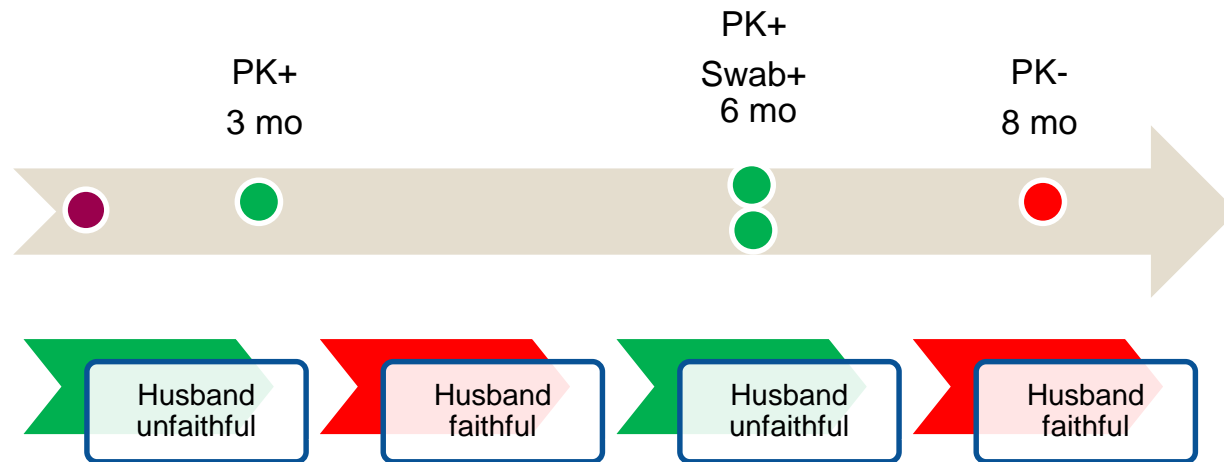
- I thought that if it had caused itching on the outside, what about inside the uterus?... That is why I decided to put it [gel] on the outside [genitalia].*
 - Maybe the other problem was when I wanted to urinate or to bathe, to tell the truth, I used to wash it away.*
- (Uganda, 30 years old, **gel group**, low PK, 26 months in VOICE)

c. Mis-implementation: modified regimen



- Starts trial
- PK (-)
- PK (+)

- self reported non-use
- self reported use



Well, what was happening was that when I did use the product... My husband will be acting promiscuous during those times. ...

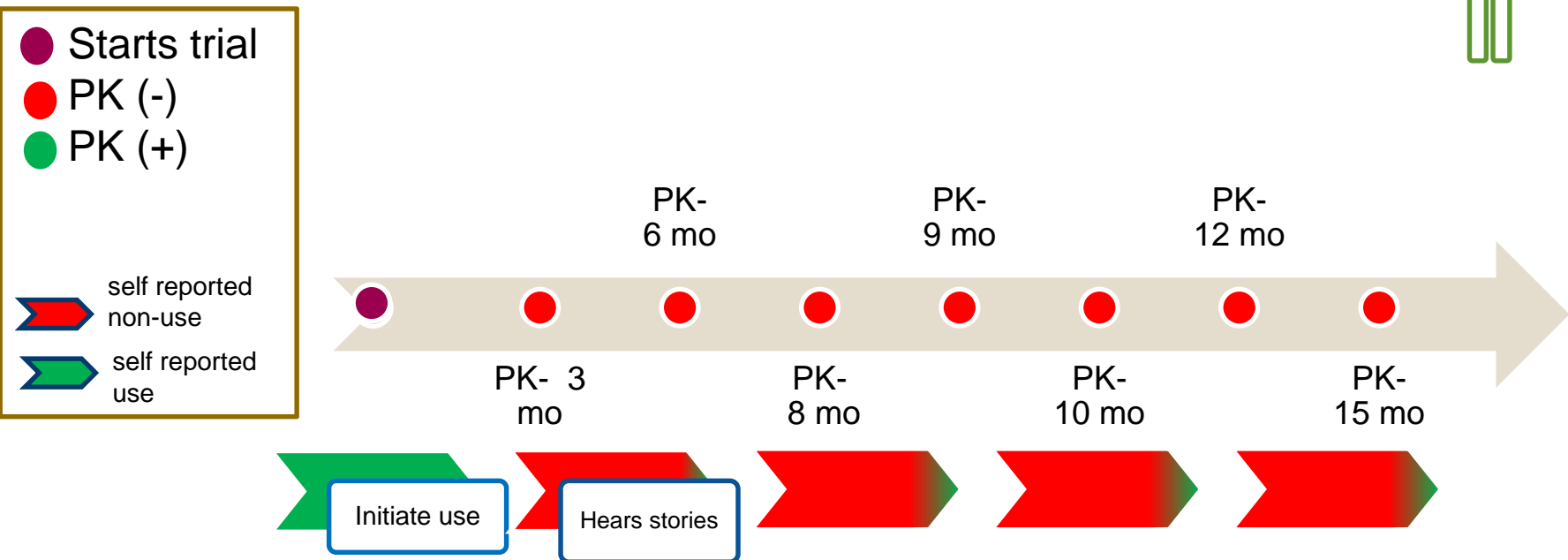
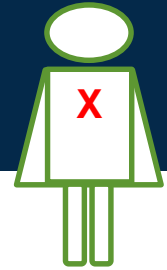
I: So, what then happened on the days that he was being faithful to you?

R: *[Laughing]. That's when I would stop using the products. [..]*

R: *I think I would have used gel everyday if my husband had continued sleeping around!*

(Zimbabwe, 31 years old, gel group, inconsistent PK; 8 months in VOICE)

c. Mis-Implementation: visit driven



I took them for a while [1 month]... I took them and they actually made me put on weight.... There was a lot of talk, and I said, “No, I’m not taking them anymore”. I stopped taking them; maybe I would take them once in a while... If I’m coming here [Clinic]....I’m only taking them so that when you [study staff] check me, you will find them.

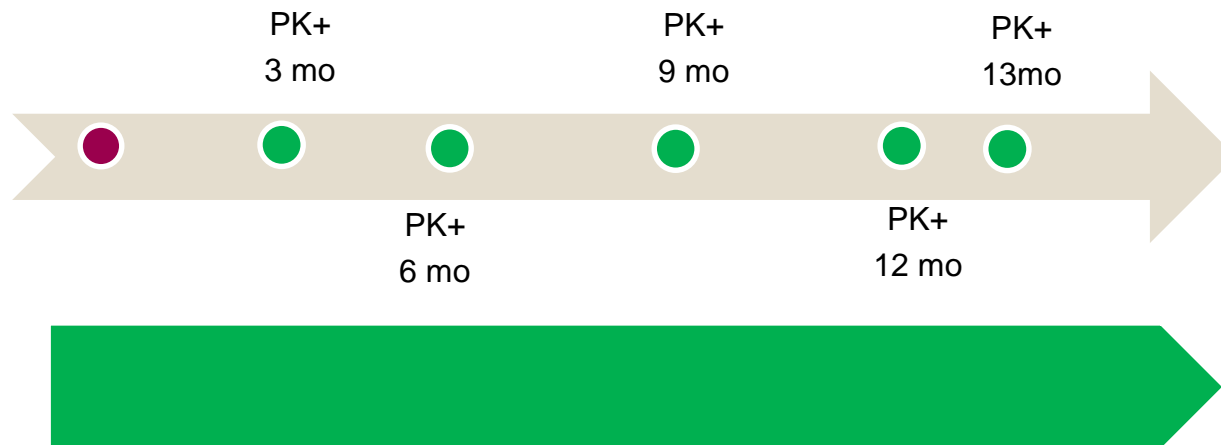
(South Africa, 23 years old, **tablet group**, low PK, 15 months in VOICE)

d. Adherence per PK data



- Starts trial
- PK (-)
- PK (+)

- self reported non-use
- self reported use



I didn't care if it would harm me because I was committed. [...] I used to tell [the other women] to look at me, I took the tablets and I never changed. I didn't have any side effects. I tried to encourage the others; I used to invite some of them to my house just to see that I was telling the truth. I was actually taking my tablets. And if you told the others that you were taking your tablets they would laugh at you but I would take it as ignorance.
(Zimbabwe, 37 years old, **tablet group**, High PK, 13 months in VOICE)

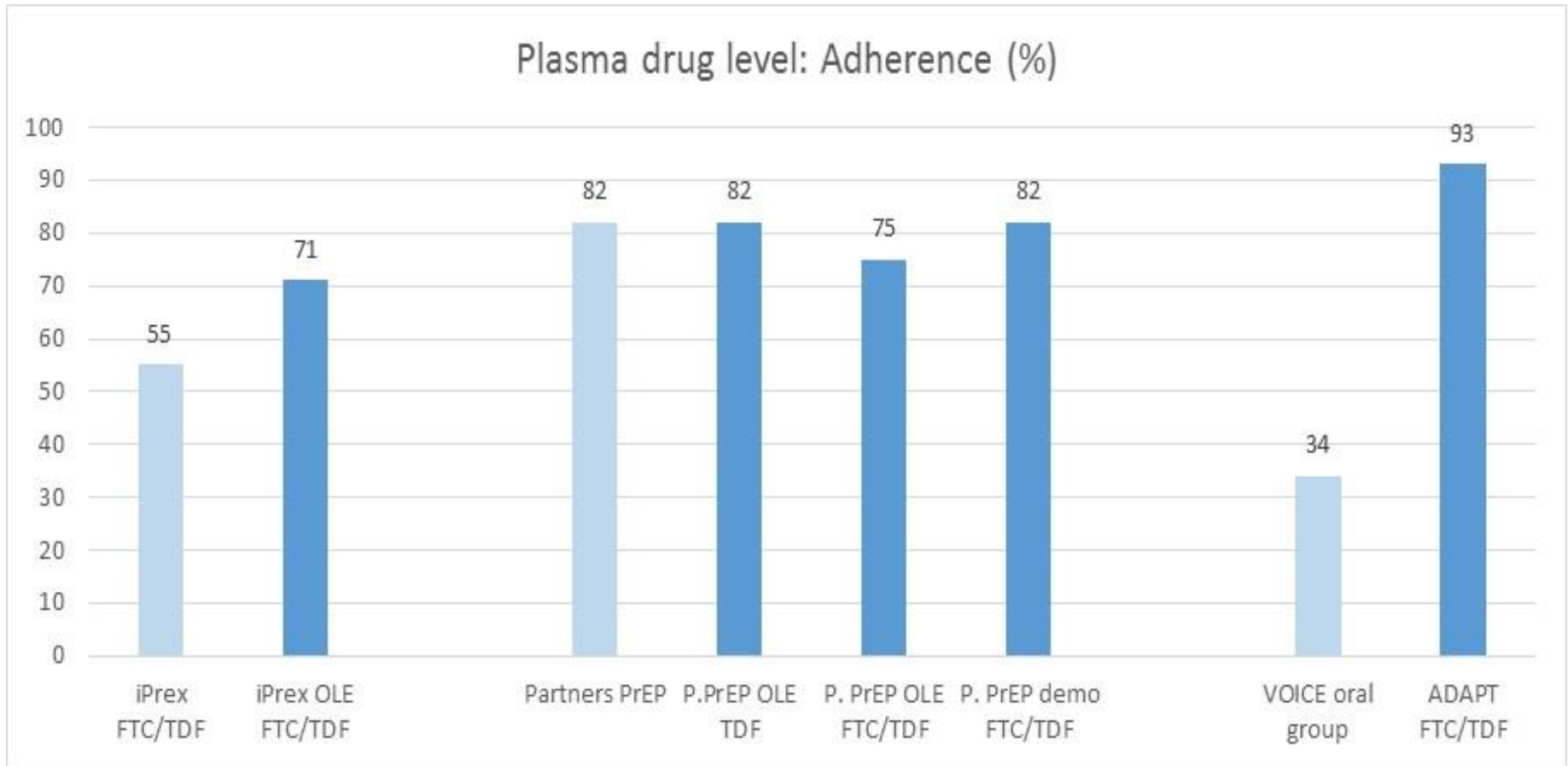
VOICE-D Stage 2 Key findings

- ❑ PK results feedback promoted more candid discussion of product (non-)use.
- ❑ Varied adherence patterns and sub-patterns were reported among those with evidence of non-use based on plasma PK.
- ❑ Patterns were shaped by product attributes, personal beliefs and circumstances (women adapted regimen to their own situations) as well as social influences: partners, peers (waiting room), family etc...
- ❑ Mis-implementation (poor execution) appeared more common than early discontinuation, suggesting that many participants may have remained partially engaged with product regimen.

4. OLE and next generation of trials

- Open-label extensions and studies
- HPTN 067 (ADAPT) open label oral PrEP trial (N= 179 ♀ Capetown SA)
- MTN-017 Phase II open label oral & rectal gel trial (N= 195 ♂ & TGW)
 - Real-time feedback from individual-level PK data
 - Embedded qualitative component
 - Product adherence reconciliation interviews
- MTN-020 (ASPIRE) phase III placebo-controlled vaginal ring trial (N=2629 ♀ in Sub-Saharan Africa)

Adherence increases in Open-label vs Placebo-Controlled studies



Marrazzo (2015) NEJM; van der Straten, CROI 2015; Bekker (2015) CROI ; Baeten (2016) personal communication; (2014) Lancet ID; (2102) NEJM; Liu (2014) JAIDS, Grant (2014) Lancet; (2013) IAS

ADAPT (HPTN-067): Open-label Truvada Trial in CPT

- 179 ♀, 30 week trial, 3 Truvada dosages (daily, time & event-driven)
- Highest adherence in daily arm (80% per plasma PK at week 30*)
- Ongoing Wisepill monitoring, weekly SMS/phone feedback
- Qualitative participants (IDI, FGD) in 2 waves mid-point and end of trial
- Congruence of themes with VOICE-C and D

Adherence challenges

- Non-disclosure/privacy
- Tablet attributes
- Side effects
- PrEP=ARV=HIV

Adherence facilitators

- Efficacy beliefs
- Concrete strategies
- Need protection/Risk
- Social support
- Understands regimen

Uptake challenges

- Community stigma & distrust
- Safety concerns
- Negative clinic exp.

Participation facilitators

- Package of care
- Financial/ reimbursement
- Connection with team
- Commitment/alignment

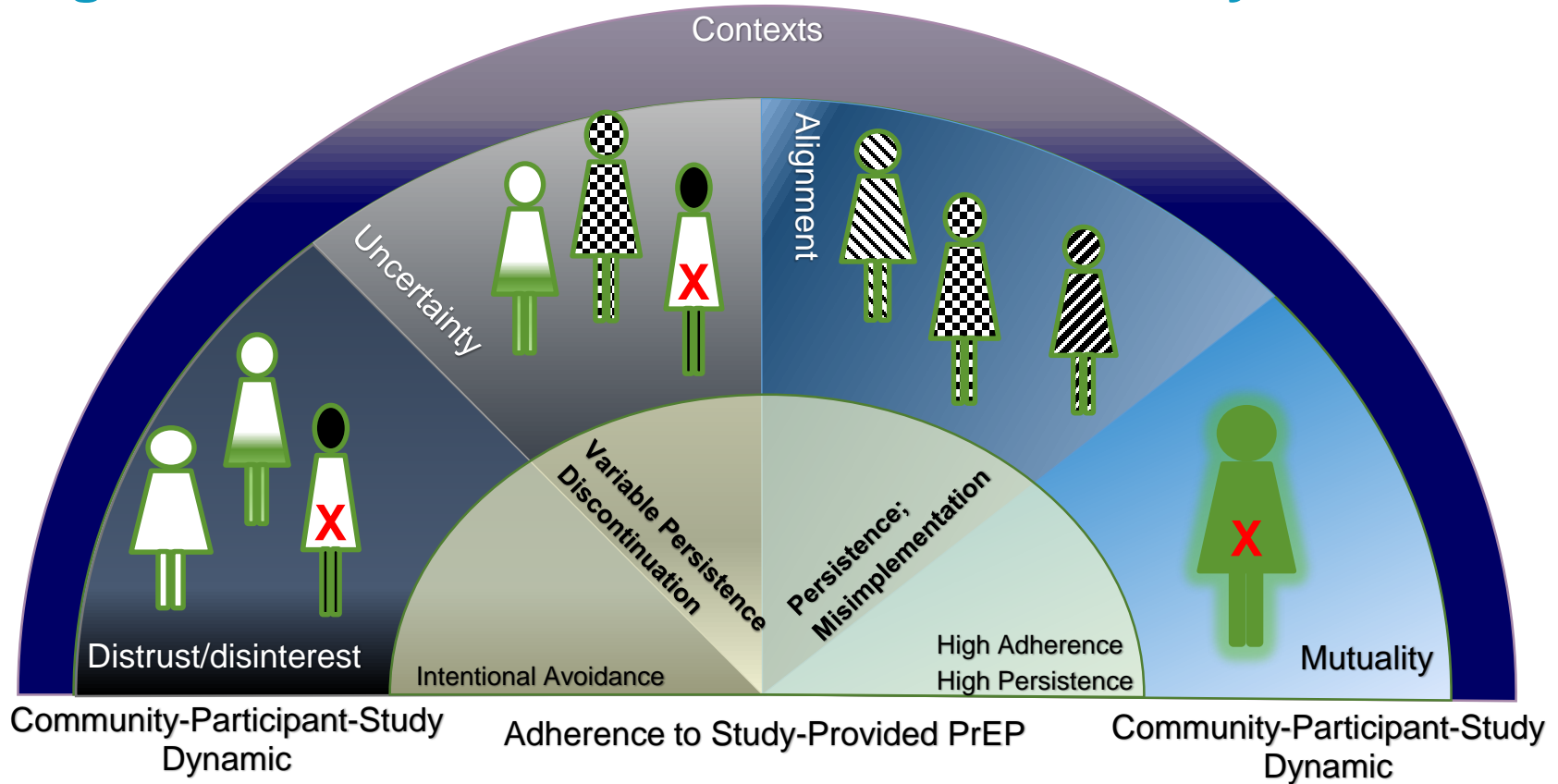


(*) in weeks where sex was reported

*Bekker, CROI 2015;
Amico IAS 2015*

ADAPT: "Ubuntu" or Model of mutuality

Congruence of VOICE-D themes and mutuality framework



Model identifies 4 unique dynamics ranging from distrust to mutuality -> implies different adherence interventions based on these 4 quadrants

ASPIRE: Phase 3 RCT (placebo controlled) of 25mg dapivirine vaginal ring

- 4 countries/ 15 sites:
RSA, Malawi, Uganda, Zimbabwe
- N=2,629 enrolled (6/14)
- End of study: 6/25/2015
- 12-33 months of ring use



Objective Adherence Assessment



- Dapivirine was measured in quarterly plasma samples. Levels **>95 pg/mL**, indicating >8 hours of continuous use, defined adherence.
 - While the study was ongoing, plasma results were reviewed by the study leadership, in a fashion that preserved study blinding, overall and for each site.
- After the first year of the study, residual dapivirine in returned, used rings was also measured; levels **<23.5 mg** (= 1.5 mg released) were used to define adherence.
- *Thus, these measures could exclude those who were non-adherent but overestimate adherence if a ring were inserted several hours prior to a clinic visit.*

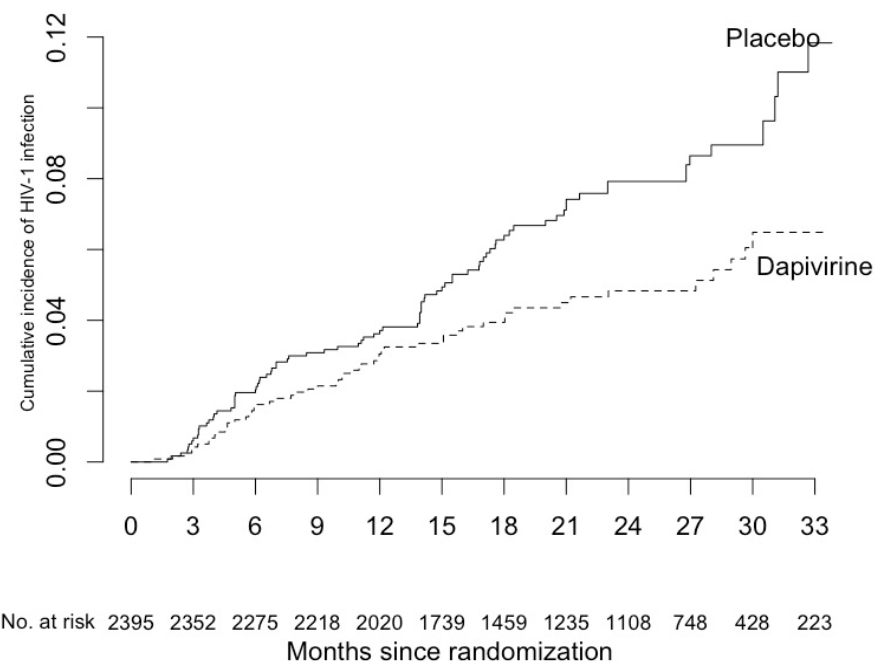
Monitoring and feedback

- Monitored **aggregate plasma PK data** at site level;
- **Site performance**: the protocol chairs review each site's data with the site IoR, as well as data for all other sites (in a coded fashion)
- Site-level feedback provided by IOR to participants
- Ongoing participants (& partner) **engagement activities** to increase: self-motivation, transparency and understanding (dispel stories), strengthen social bonds with peers & staff.
- Participant's reactions to biological data feedback:
 - CRFs at exit
 - Multisite qualitative component: embedded serial IDIs & exit FGDs

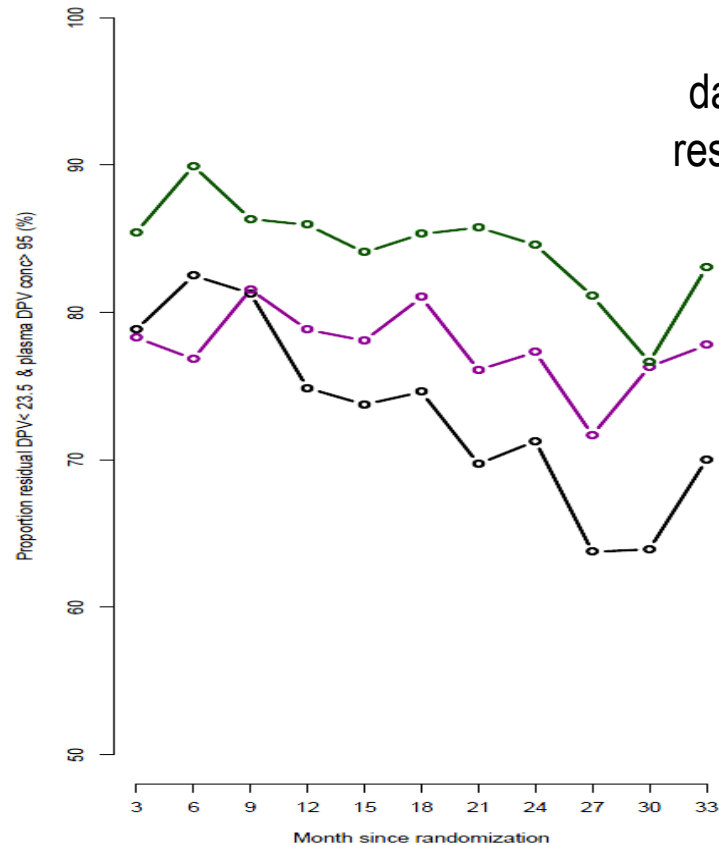
- mITT effectiveness (all 15 sites): 27% $p=0.046$
- After pre-specified exclusion of data from two sites with lower adherence and retention, the dapivirine ring reduced HIV-1 acquisition by 37%.

Primary HIV-1 effectiveness intention-to-treat analysis

| | Dapivirine | Placebo |
|---|------------------------------|---------|
| # HIV-1 infections | 54 | 85 |
| HIV-1 incidence, per 100 person-years | 2.8 | 4.4 |
| HIV-1 protection effectiveness 95% CI, p-value | 37% (12, 56) $p=0.007$ | |



- Additional age-stratified categories were explored. Lack of HIV-1 protection was limited to those ≤ 21 years of age.
- Objective measures of adherence were strongly related to age as well.
- **Among women >21 years of age, HIV-1 protection effectiveness was 56% (95% CI 31-71%, $p < 0.001$)**



5. Sources of non-adherence & linked interventions

- Lack of consequences
- Forgetting/ burden with product or regimen
- Low saliency/intrinsic motivation
- Low social support
- Real-time PK or EM and feedback (site or individual level)
- Reminder systems, easier regimens, LA-products
- (BE) incentives, rewards
- Couple focus, PrEP buddies
- Medical & research mistrust; rumors
- Investigational products, placebos
- Participant, partners & community engagement, trust building work
- Open-label trials, demo projects to assess effectiveness
- Accessing trials for ancillary benefits (HCT, health services)
- Improve health care system, access to and quality of services

Summary

- **VOICE:** low use, low trust and intervention was too little too late
- **VOICE-D**
 - Retrospective disclosure of drug results: acceptable & yielded candid discussions of a variety of (non-) use patterns
 - Insights in whereabouts of unused products (shared, sold, dumped, stock piled..)
 - Perceived benefits of real time drug feedback reinforced by those interviewed
- **OLE:** higher adherence than in blinded trials
- **ADAPT:** Open label trial -> use of Truvada in the context of known efficacy
 - Intensive monitoring & feedback (WP/SMS) to support adherence
 - Range of participants responses to the study itself and to Truvada
- **MTN-017:** Open label trial
 - Drug PK feedback at individual level is feasible in an open label trial
 - Feedback and adherence support counseling are acceptable/feasible.
 - Data convergence to understand the “full adherence picture”
- **ASPIRE:** modest HIV protection with monthly vaginal ring (↑ with age & adherence)
 - Aggregate drug level feedback to participants is feasible in a blinded RCT

Conclusion

Interventions for adherence enhancement in HIV prevention trials need:

- **Accurate measurement** and ongoing monitoring
- Real-time (or near-time) **objective feedback** to participants
- **Trust** between participants and researchers for greater reporting honesty and understanding of non-observable behaviors/events.
- Tailoring to the **type of non-adherence** (use typology), informed by a “mutuality framework”
- Identification of the **source(s) of non-adherence** (psycho-social, clinical or structural level) for improved impact.

Acknowledgements

- Microbicide Trials Network (MTN)
 - VOICE, VOICE-C and VOICE-D protocol teams
 - ASPIRE protocol team
 - MTN-017: R. Cranston, I. Balan, A. Carballo-Diéiguez and Team
- K. Rivet Amico, ADAPT trial
- Collaborators
- Sponsors
 - NIH/NIAID/NIMH; DAIDS

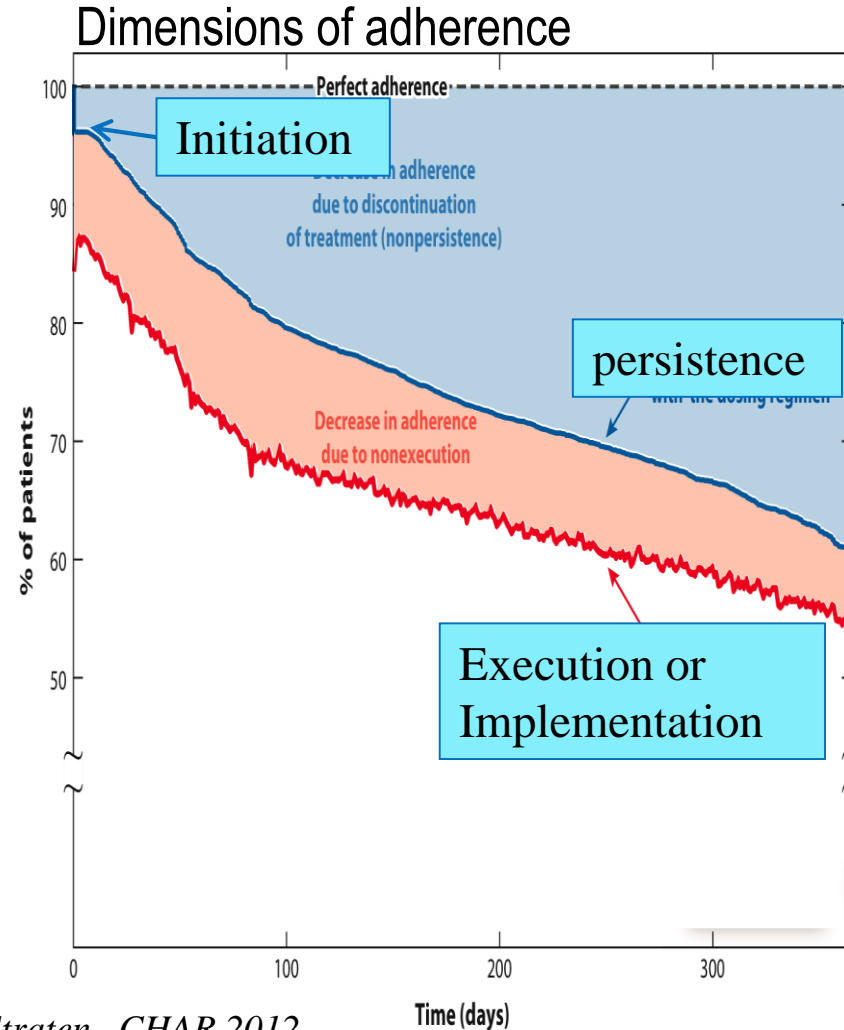
Thank you!

ariane@rti.org

Extra slides

Definition and adherence components

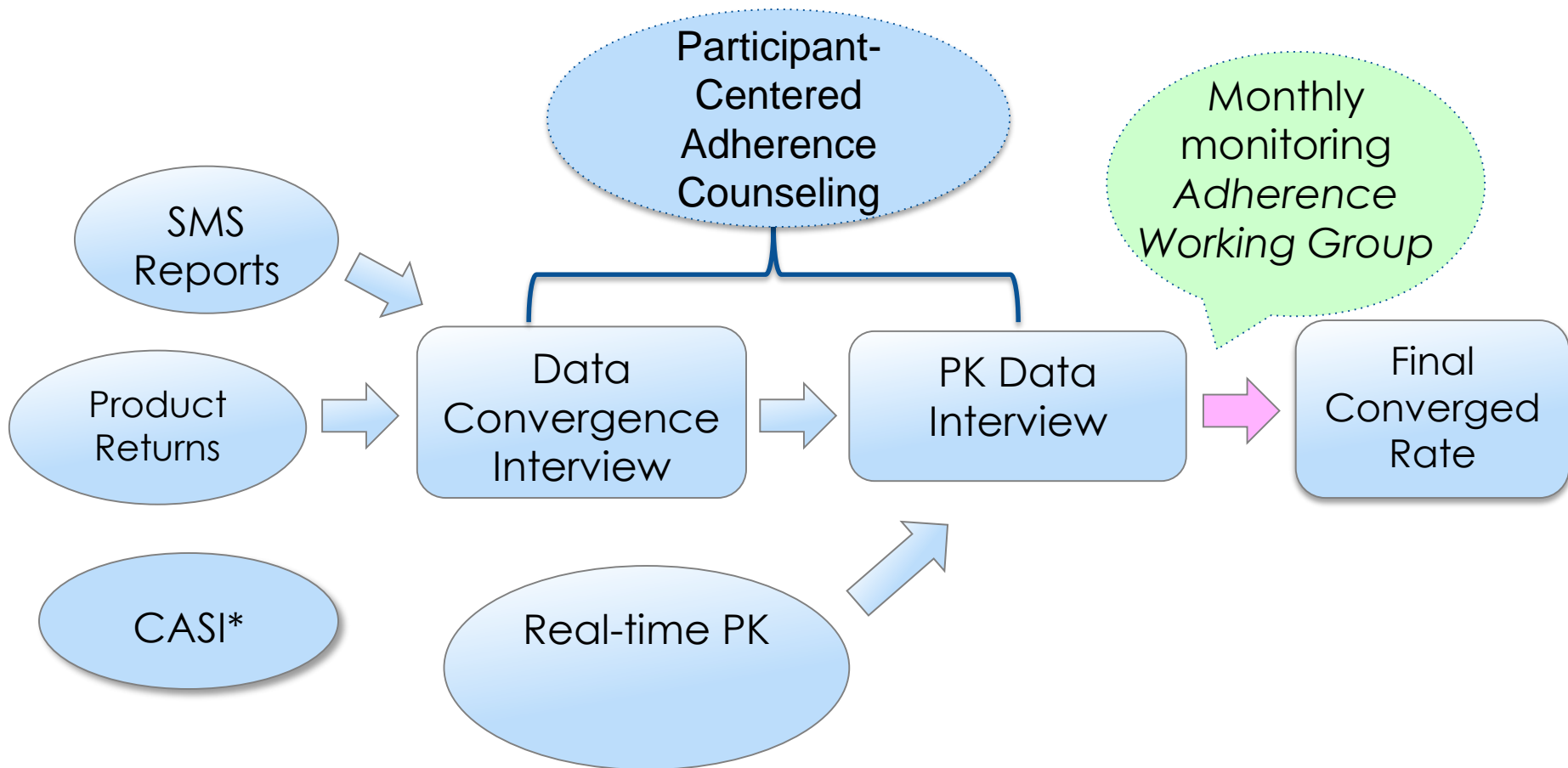
- **Adherence** (in trials) = *participant's use of study product as instructed*
- **Dimensions of adherence:**
 - *Initiation* = time point of first dose
 - *Discontinuation* = time point of last dose
 - *Implementation/quality of execution*
 - *Persistence*: time period between initiation and discontinuation



MTN-017 Phase II open label oral & rectal gel trial

- N= 195 MSM and TGW (US, SA, LA, Thailand)
 - Real-time feedback from individual-level PK data
 - Embedded qualitative component
 - Product adherence reconciliation interviews
- **Primary results**
- High intensity study, high staff/analyst burden

Triangulation of Adherence Data



*CASI data reviewed at end of study

Adapted from Pool et al. (2010) *PLoS One*

DCI & PKCI: Conclusions

- Feasible in a brief interaction (~2-3 min.)
- No strong negative reactions
 - If introduced in collaborative manner, did not elicit defensiveness
- Other adherence measures contextualized PK results
 - SMS and Calendar highlighted patterns of use vis-a-vis PK results
 - Process could be automated
 - By triangulating the data, almost 50% of undetectable PK results could be explained
- Being “confronted” with PK results does not by itself appear to deter non-adherence
 - Undetectable PKs did not vary greatly by study period