Success with PrEP:
Next Steps to Support Policy Decisions in Southern and East Africa

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HIV R4P Pre-Conference Discussion
Cape Town International Conference Centre
South Africa
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9h30 - 17h30

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Concept Note

BACKGROUND

PrEP (pre-exposure prophylaxis) is the use of antiretroviral medication to prevent HIV infection by people not infected with HIV, but who are at high risk of HIV exposure. We know from research on the efficacy of oral PrEP that it can prevent up to 90% of HIV infections in heterosexuals, men who have sex with men and people who inject drugs, but the level of effect is highly dependent on adherence with the daily drug taking required. PrEP is intended for integration in comprehensive HIV prevention programmes, combined with other proven strategies including the regular use of condoms with lubricant and safer sexual behaviour.

The challenge facing policy planners now is to use the current knowledge on PrEP to decide what place PrEP can have in national HIV prevention strategies, and to describe the framework required for its provision and how to facilitate this. Considerations such as identifying priority populations, defining the process for starting PrEP, providing appropriate testing, delivery and follow-up services, maximizing adherence and successfully funding these activities need to be addressed.

This meeting will bring together policy makers, investigators and members of research populations, with a focus on those groups actively working on PrEP in the eastern and southern Africa region. Through information sessions, sharing of experiences and discussion, participants can define a structured approach to considering the integration of PrEP in HIV prevention programmes in the region. In addition, the knowledge gaps that remain to be researched can be clearly identified.

PURPOSE

- To discuss emerging lessons from early implementation of oral PrEP.
- To identify how these results might feed into future policies and programs for HIV prevention, and the relevant procedures for this.
- To articulate key information gaps that need to be filled to facilitate decision-making.
- To outline specific, feasible next steps to address these gaps and measures to monitor progress in filling them.
- Focus on the experiences of ongoing demonstration projects and early implementers of PrEP.

PARTICIPANTS

- 55+ participants for action-oriented discussion, information sharing and strategic planning.
- PrEP demonstration project practitioners and implementers, advocates, civil society partners.
- Policy makers, especially in Southern and East Africa, considering possible PrEP activities.

Success with PrEP Meeting Report

I. Welcome, introductions and meeting outline

Rosalind Coleman, UNAIDS, and Mitchell Warren, AVAC

To discuss: What we know about PrEP, what we don't know and what we need to know.

To develop: Next steps for PrEP demonstration projects and roll out.

Participants: Policymakers involved in PrEP, policymakers not yet involved in PrEP, funders funding PrEP, other funders not yet funding PrEP, study researchers, designers and implementers, PrEP users and advocates.

Geographic Focus: Sharing global experiences to inform East and Southern Africa

II. Update on PrEP with particular focus on recent open---label extension results and national and international guidelines (e.g. WHO, US CDC)

Presented by Connie Celum, University of Washington (see Appendix for full presentation)

1. Oral PrEP: Evidence from Phase III randomized control trials (RCTs)

- Four studies showed efficacy (Partners, TDF2, Bangkok Tenofovir Study and iPrEx)

FOUR TRIALS DEMONSTRATE PREP EFFICACY IN DIVERSE GEOGRAPHIC AND RISK POPULATIONS
**Adapted from Connie Celum's presentation*

Study, population	PrEP agent	Number of HIV infections		PrEP efficacy (95% CI) Publication
		PrEP	Placebo	
Partners PrEP Study Heterosexual couples Kenya, Uganda (n=4758)	TDF/FTC	13	52	75% (55-87%)
	TDF	17		67% (44-81%) *Baeten et al. N Engl J Med 2012*
TDF2 Study Heterosexuals Botswana (n=1219)	TDF/FTC	10	26	62% (16-83%) *Thigpen et al. N Engl J Med 2012*
Bangkok Tenofovir Study (BTS) IDUs Thailand (n=2413)	TDF	17	33	49% (10-72%) *Choopanya et al. Lancet 2013*
iPrEx MSM Brazil, Ecuador, Peru, South Africa, Thailand, US (n=2499)	TDF/FTC	36	64	44% (15-63%) *Grant et al. N Engl J Med 2010*

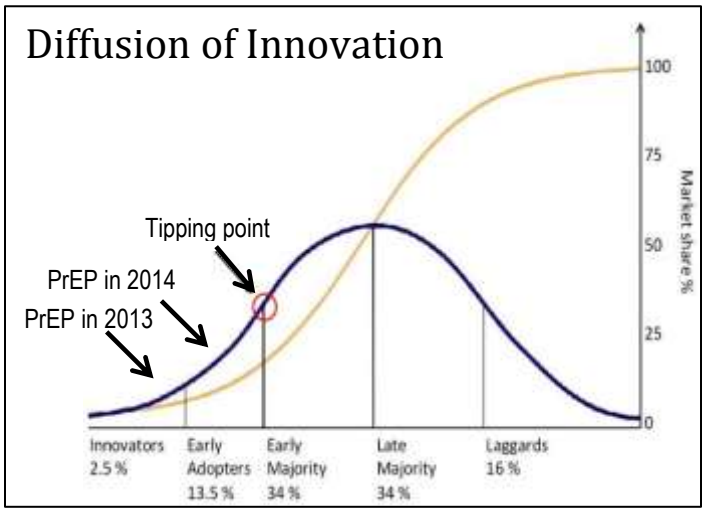
- *Partners PrEP findings:*
  - **Adherence:** Most who initiated prep maintained good adherence.
  - **Risk perception:** Main reason people stopped taking prep is that they were no longer in a serodiscordant couple and didn't perceive themselves at risk any longer.
  - **Risk compensation:** No evidence of risk compensation (i.e., would people stop using condoms because they felt safe on the drug). No change in unprotected sex
  - **Resistance:** A small number of people developed resistance who had undetected seronegative acute HIV infection at enrollment. Resistance was not an issue.
  - **PrEP efficacy:** Higher for those at higher risk (subgroup analysis for Partners PrEP.)
  - **HSV-2 acquisition:** Modest reduction with PrEP use shown. An additional benefit that should be considered.
  - **Safe and well tolerated:** Adverse events were small and typically resolved in the first month – i.e., GI, nausea. Bone mineral density issues were very minor.
  - **Oral TDF**: An alternative option for PrEP than TDF/FTC
    - No statistically different efficacy between TDF and TDF/FTC.
    - Oral TDF is lower cost, has less side effects and less resistance (low resistance in general with PrEP)
- *Two RCTs did not show PrEP efficacy: FEM-PrEP and VOICE:*
  - **Participant's age/location:** In FEM-PrEP and VOICE, the majority of participants were young women enrolled in South Africa. Very high HIV incidence in this population.
  - **Adherence:** Despite not showing efficacy, these trials show that when adherence to the drug was high, protection against HIV was high.
  - **What happened?** May not have pericevd themselves to be at risk; risk was dynamic; didn't have partner support; or, joined the research trial for other reasons (i.e., other health services; compensation).
  - **Real issue:** We do not have much to offer young women in terms of HIV prevention methods they can control; we should not assume that what happens in a clinical trial will happen in the context of delivery.

"… when adherence to the drug was high, protection against HIV was high." Connie Celum on FEM-PrEP and VOICE findings

- *What's next after an efficacy finding?*
  - Approvals and guidelines: FDA approval followed by guidelines by CDC and WHO with a focus on PrEP for MSM.
  - Prescribing PrEP: Risk assessment; eligibility; follow-up; discontinuing PrEP is expected.
  - **<u>However, guidelines don't replace experience. So…</u>**

- *The next phase in evidence: Open label extensions and demo projects*
    - **Need to know more:** We need more than just clinical trial data to move the field forward—we need to know how to deliver it, how to support adherence, do we have demand, do we have the capacity to deliver PrEP.
    - **Diffusion of innovations theory:** People who will adopt quickly and then the late adopters.

Demonstration Project Questions **Adapted from Connie Celum*	
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 behaviour	Is PrEP use associated with *risk compensation*?
Impact	*HIV incidence*? *Resistance*? *Incremental cost effectiveness?*



- *PrEP evidence in MSM*
    - **iPrEx OLE:** iPrEx trial participants offered open label truvada. High uptake in 76% of iPrEx participants. There was a higher level of uptake among men reporting condomless receptive anal sex (81%), which is the high-risk group that needs to be targeted.
        - **Adherence:** higher adherence among older & more educated men and during periods of risk.
        - **Incidence:** 49% lower HIV incidence in PrEP users vs. non-PrEP users.

    High adherence during periods of high risk.
    iPrEx OLE

    1. **Demo projects in the US in MSM:** Some preliminary data from demo projects is available.
        - **Interest is high**: At San Francisco, DC and Miami SF, over 50% of men eligible were initiated. In Chicago, there is very high uptake among young MSM of color.
        - **Adherence is high:** 77% had levels detected consistent with dosing 4 times/week.
    2. **PROUD Pilot study in the UK:** 500 MSM randomized to immediate use of TDF/FTC.
        - **Demonstrated efficacy** in 500 men, 40% had used PEP

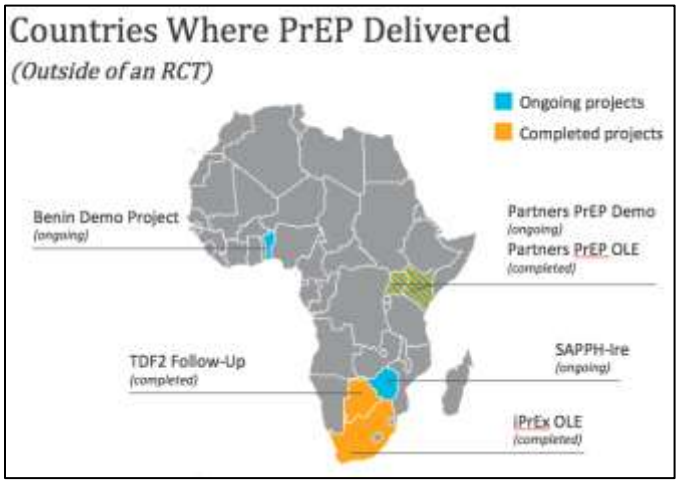
        - **PEP use:** 40% had used PEP

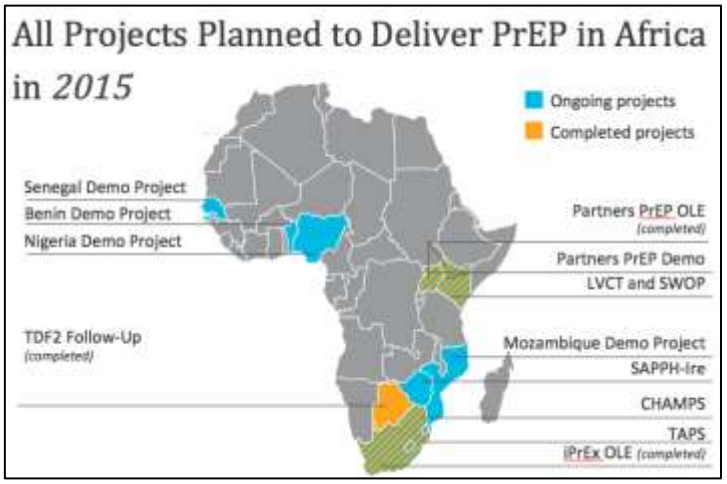
    3. **What PrEP offers:** Social benefits: decreased anxiety; increased communication/disclosure; increased intimacy/trust; sense of community; increased self-efficacy; increased sexual pleasure & intimacy (sex is not a clinical event).

- *PrEP as part of combo prevention for serodiscordant couples* –
    - **Both PrEP and ART:** ART is clearly the priority for HIV+ partners with lower CD4 counts; PrEP as a time limited bridge to ART for negative partners until positive partner is on treatment.
    - **Partners PrEP Demo Project:** New, high risk HIV-1 serodiscordant couples (Kenya, Uganda).
        - **Status:** Finished enrollment in 2014; complete in 2016.
        - **Follow-up:** Moved from monthly to quarterly visits; scaled back on more intensive adherence counseling provided in the trial.
        - **High uptake** of prep–over 90% of negative partners chose to initiate prep.
        - **Adherence support:** Project suggests people will take PrEP and can deliver it without as much adherence support as in trial.
- *Next steps:*
    - **Not for the general population:** initial focus on key populations (i.e., MSM in US; HIV serodiscordant couples; FSWs; young women; injection drug users).
        - MSM in higher risk periods (young men; men with STIs; men practicing unprotected sex).
        - HIV serodiscordant couples trying to conceive and before HIV positive partner is on ART.
        - FSWs, PWID, young women.
    - **Understanding PrEP users:** Who are the early adopters; who are the late adopters; who uses it and how do they use it. It is necessary to understand the barriers, motivators and how to increase motivation.
    - **Understanding how to deliver PrEP:** Bundling with other services (FP); risk screening for targeting (risk scores); community delivery to reduce burden (move outside clinic); less frequent visits (3 months visits now, at some point less); self testing to identify early infection with fewer visits (high acceptability so far in partners sub-study); adherence monitoring; delivery costs and costs per infection delivered.

III. **Linking what has been learnt to current concerns:** A synthesis presentation based on pre---meeting interviews and summaries to outline broad areas of lessons being learned with a view to identifying common themes, approaches or needs.

- *Summary of PrEP Demonstration Projects, Deirdre Grant, AVAC (see Appendix for full presentation)*





- *Summary of issues to consider: AVAC and UNAIDS completed qualitative interviews with 12 PrEP demonstration project investigators. The below summarizes key findings from the interviews.*
    - **Resources:** For PrEP but also healthcare infrastructure
        - **Site issues:** Sites include research sites, STD clinics, population-specific health clinics
            - Research-naïve vs. new sites; mix and challenges in getting newer sites on board; also issue of geographic diversity (or lack thereof) of sites within a country when only a few sites may end up informing a policy that's country-wide.
    - **Recruitment:** Most self-referral or referred after screening visit (and met risk criteria) in healthcare setting.
        - At one of the US sites, most of the referrals came from HCT counselors, referrals from PEP and STI clinics—not primary care

        - How to access those who aren't accessing health care necessarily, like recruitment of transgender women low across the projects that enrolled them—need CBOs
        - Need to monitor how sites using facilities that certain pops already use for more comprehensive care and are established as a go-to space
    - **Testing:** Almost all quarterly testing at visits; one looking at home testing as a sub-study (Rapid tests, RNA, pooled RNA).
        - **Are there other tests that can be done?** Is it necessary to "stick a needle in your arm" to continue on PrEP rather than routine blood tests? [Peter Godfrey-Faussett]
    - **Pregnancy:** Sub-study in Partners and majority are treated on case-by-case basis with women having option to continue PrEP while pregnant.
    - **Equity:** "Designer" drug or reach all in need
    - **Logistics:** Impact on existing patient flow and burden of follow-up (for all staff)
    - **Risk compensation:** Worry of condomless sex; hasn't happened
    - Long-term access: Will Gilead create a Medication Assistance Program outside of US?
    - **Delays with ethics boards and/or regulatory bodies:** May not be relevant when using PrEP in a program
    - **Next Steps:** Several projects noted that national leaders have said seemed amenable to possibility of PrEP rollout, but need evidence that it's "deliverable" first; classic quandary—"can't pay for treatment so how do we pay for PrEP?"; WHO guidance on PrEP – what can we expect in 2015?

IV. **Delivering PrEP in Demonstration Projects:** Brief presentation from those projects already delivering oral PrEP in East and Southern Africa–SAPPH-Ire (Zimbabwe), Partners Demo Project (Kenya and Uganda), Desmond Tutu HIV Foundation (South Africa). Moderated discussion amongst all Moderated by Kevin O'Reilly, consultant to WHO.

- *SAPPH-Ire, Frances Cowan, Zimbabwe (see Appendix for full presentation)*
    - **PrEP Demo Project nested** within the cluster RCT (behaviour change program).
    - **Sites:** 14 outreach sites that offer services to sex workers one day a week, in usual service sites through the Sisters with a Voice program. The health education, testing and counseling was enhanced in 7 sites. Women who are HIV negative are encouraged to test regularly every 6 months; women who are HIV positive are getting access to point of care CD4 and on site delivery.
    - **Status:** Intervention rolled out in early-July 2014. 800 – 1,000 women eligible to access PrEP overall. 79 women currently taking PrEP (2-3 times this number have been screened).

- **Adherence:** Sisters program—a buddy program with women taking ART and PrEP where they select an adherence "sister" and attend a monthly training group with their sister. Only sister knows whether they are on ART or PrEP.
- **Testing:** Creatinine every 6 months. Monthly HIV tests that will reduce to every 3 months over time.

- *Partners PrEP demonstration project, Connie Celum (see Appendix for full presentation)*
  - **Enrollment:** Evaluate the ability to do targeted enrollment of higher-risk HIV-1 serodiscordant couples into a longitudinal HIV-1 prevention study. Research naïve couples.
    - Risk score: Using a risk score to define couples at highest HIV risk (i.e., younger couples; no children; no VMMC; unprotected sex; higher viral load).
    - **Gender breakdown:** 1/3rd of infected partners are female.
    - **Uptake:** 90% uptake at screening; finding very high adherence (starts to drop by month 6). 86% had detectable tenofovir. Now that Ugandan and Kenyan guidelines have changed for serodiscordant couples, there might be changes moving forward.
  - **Aim:** Initiation and adherence to PrEP and ART.
  - **Testing:** 6 month creatinne screening
  - **Adherence:** Pill counts, MEMS caps and tenovofir testing in plasma in a random sample of 15% of participants.
  - **Pregnancy incidence:** Substantial pregnancy incidence. Fertility intentions are high and many couples are viewing PrEP as a way to achieve desires safely. Women in project can chose to continue PrEP during pregnancy.
  - **Outside partners:** In HPTN 052 and Partners PrEP, many infections came from outside partners.
  - **Age and relationships:** Importance of how to target young women. When most young people found out they were in discordant relationships, they ended the relationship and the younger they were the higher chances of them ending the relationship (more relationship instability).
  - **VL data:** Partners is using the VL data to make PrEP discontinuation decisions.

- *Desmond Tutu Foundation – iPrEx OLE (Brian Kanyemba)*
  - **Age matters:** Younger participants had problems adhering to study medication.
  - **Adherence "next step" counseling:** How to remember to take PrEP—i.e., write PrEP or truvada on a towel and every time you take a shower you see it, or on your toothbrush. Need to look at the best ways to provide this strong adherence system for younger men.

- **Need for PrEP:** One participant seroconverted in between the trial end and OLE start date. MSM in Africa need PrEP.

- *Conclusion:* Moving from the concept of PrEP to demonstrating efficacy was a huge undertaking, but the next step of how to implement is equally huge. The way we are currently doing demonstration projects is full of "bells and whistles" we won't get to implement in the real world," but, we don't know what they are. (*Kevin O'Reilly, WHO*)

- *New/about to start demonstration projects:*

    - **Mozambique Demo Project (Tom Ellman):** People in remote settings actively coming forward to request PrEP—i.e., sex workers came forward and requested PrEP from the government in Mozambique, referring to HPTN 052.
        - **Sites:** Beira Corridor (500 sex worker cohort; 3.5% seroconversion after 3 weeks testing); Malawi (program in 2 central prisons; 40% risk among cohort; condom use denied in this setting); Kwazulu Natal (2.9% incidence among 19-29 year olds.
        - **Goal:** Identify motivated high-risk people, most outside of relationships, and offer and initiate them on treatment. Inform national rollout.

    - **LVCT (Michael Kiragu):** Study looking at young women and PrEP use.
        - **Willingness is high:** Over 85% are willing to take PrEP; those who have had a lot of STIs in the past are more motivated
        - **Policy makers concerns:** Resistance and risk compensation are big concerns for policy makers.
        - **Regulatory:** No pharmacy board in Kenya so there were should be no major regulatory hurdles to give PrEP to the first participant.
        - **PrEP in Kenya Roadmap:** PrEP is included in the Kenya HIV Prevention Revolution Road Map. There is support for PrEP policy.
        - **The new director** of the National AIDS Commission is the PI of the PrEP demo project.
        - **Benefited from** the Partners Demo project, who provided advice on how to get started.

    - **RHI Sex Worker Demo Project (Robyn Eakle):** Study enrolling 400 sex workers on PrEP and 300 on treatment in South Africa.
        - Clinic based demonstration project aiming to make a "real world" scenario.
        - **Stakeholder engagement:** Just formed a new CAB.
        - **Impact:** Costing study and a modeling study will look at the impact the project.

- **Senegal Demonstration Project (Pierre Ndiaye):** Demonstration project for sex workers.
    - **Two Phase Study:** Designed with two phases, a feasibility and focus group phase and a demonstration project phase.
    - **Enrollment:** 1,500 HIV negative, aged 18 and older female sex workers enrolled in five health centers with a three month accrual period, followed for one year. Follow-up study visits at months one, three, six and 12. HIV tests and STI screening every three months.

- **Discussion:**

    - **Creatinine tests:** Even when creatinine tests are in the guidelines, they are not being done. With 500,000 patients on HIV treatment in Mozambique, there are lessons to be learned when we make PrEP national policy.

    - **Seroconversion:** Once there is a seroconverter, what will they be offered? What is the level of resistance to tenofovir? Do enough people need to be recruited to show there wasn't a high level of resistance?

PrEP is not an emergency decision. *Connie Celum*

"Across studies, the data shows that resistance is not an issue. However, as we move from monthly to quarterly testing we'll see that it might increase a little—that said, it's still probably not an issue." *Connie Celum*

"We need a practical approach—we should do RNA or antigen testing to try to identify resistance and screen for acute HIV if there is recent high-risk exposure. PrEP is not an emergency decision." *Connie Celum*

"How do we detect the people who are resistant so that we don't put people who are already infected onto monotherapy? There is mounting resistance on second and third line ARVs. It's a big issue in our minds." *Owen Mugurungi, Ministry of Health and Child Care, Zimbabwe*

"Resistance is an issue that is always on our minds. The more data we get the easier it is for policy makers to make the decision to move towards implementation. There is no way to move towards zero new infections unless we have PrEP as part of the interventions package." *Owen Mugurungi, Ministry of Health and Child Care, Zimbabwe*

    - **Cost-effectiveness evidence:** One of the main concerns in Mozambique is sustainability—how do we guarantee financial

resources or support for people on PrEP when we don't have the resources to guarantee all who need treatment have it. [*Noela Chicuecue, Ministry of Health, Mozambique*]

- **Not a resource question:** The question is whether or not this is an effective intervention and if we can demonstrate delivery. The resource question will always be there, but if we don't provide effective prevention options, we have to provide treatment for life.
- **Young women:** In South Africa, the issue of being able to identify and find the people most at risk—young women—and being able to motivate young women to take PrEP.

V. Users' perspectives· Members of research populations to describe their experiences, concerns, attitude of their communities, etc. with using PrEP

Moderated by Rosalind Coleman, consultant to UNAIDS

Summary of Issues Discussed:
- Long clinic visits
- Side effects
- "Power" of controlling prevention method
- Dosage strategy
- Other risk behaviours (i.e., drinking, drugs)
- Reaching most at-risk

- **Langton Sanyanga,** Desmond Tutu HIV Foundation, South Africa, iPrEx participant
  - *I first heard about [the project] through a friend and decided to join. At first, it wasn't very easy—at the time I drank a lot and had many [sexual] episodes a week. I had a reminder next to my toothbrush. I was very careful with my sexual behaviours because they explained that you might be taking truvada or a placebo.*
  - *With the behaviour change counselling I reduced episodes per week and am still carrying on with safer sex behaviour. I am practicing safe sex now. I know that you won't get results if you don't take it [truvada] every day.*
  - *I think it [truvada] must be made available as soon as possible in South Africa.*

- **Marco Charles,** Desmond Tutu HIV Foundation, South Africa, iPrEx participant
  - *I have less anxiety when I take it [truvada]. I tried to take it every day.*
  - *Some of my friends weren't keen on the idea. They didn't know about the drug and heard about the side effects and got scared even though it's only 10 percent of people.*
  - Do you have a concern if seen with the pill (i.e., stigma)? *Some of my friends don't even know it is HIV medication.*

- **Phillis Mushati,** Centre for Sexual Health & HIV/AIDS Research, Zimbabwe, research coordinator

- 79 women were initiated on PrEP in 36 sex worker clinic sites around Zimbabwe. However, very few young women are coming to the program. Some parents are discouraging their daughters from going because of the sites and some young people are "too shy" to be seen in public going to a sex worker clinic.
- More workshops are needed to get to women who aren't coming in (slow uptake).
- Looking at how the use of drugs and alcohol by sex workers affects adherence and outcome. So far, haven't seen anyone saying they can't take PrEP because of alcohol.

- **Bathabile Nyathi**, Centre for Sexual Health & HIV/AIDS Research, Zimbabwe, demonstration project participant
  - We need PrEP because… *condoms burst or we have violent clients, we don't have the power to have a discussion with the client. We don't have any control over condom use. We are abused by clients and the police. I'm very happy for truvada.*
  - *I did have side effects; I vomited for two weeks and was dizzy. But the side effects went away.*
  - *I am enjoying truvada and I am happy. [PrEP has shown me] that women can be protected and we are going to see an end to AIDS.*
  - *There is a need to decriminalize sex work in Zimbabwe and a need to partner with law enforcement. One sex worker had her ARVs taken away from her. The policy against sex workers is very violent, if you are found with a condom you get arrested, if you are found without a condom you get arrested. If you have a bottle of pills you get arrested if you don't have a prescription.*
  - Prevention option: Injectables would be ideal for a highly mobile population.
  - Adherence strategy: SMS messages for adherence.
  - Location: Would rather go to a specific sex worker clinic, not a public clinic, because they will know she is a sex worker.

- **Noluthando Maholwana,** Desmond Tutu HIV Foundation, South Africa, trial participant
  - *I attended a talk at Desmond Tutu Foundation about truvada and the protection [against HIV] it provides. I wanted to join because if you're going to give me prophylaxis then I'll take it. The Hep B vaccine was also being offered and there was no financial loss. There was compensation for transportation and full blood work was also provided.*
  - *However, I didn't want to join in some ways because I was HIV*

I like the fact that protection conferred power. *Noluthando Maholwana*

negative and I thought what would happen when I do get it, will tenofovir work for me?

- *No one in the community knew I joined. I told my mother and boyfriend. My mother thought I was hiding something, so I had to tell her. My partner understood.*
- *After each sex act you have to take truvada, but this can be a problem because it's not the first thing on your mind after sex.*
- *I didn't like the long clinic visits, blood work or the side effects. When I first joined I had nausea. However, I liked the power, that I had some protection on my part. I like the fact that protection conferred power.*
- *I would have preferred capsules to the big and bulky tablets.*

VI. Moderated discussion including Q&A with policy makers and program planners to explore where PrEP might fit and what are the outstanding questions/issues. *Moderated by Carlos Caceres, NEMUS*

How will PrEP fit into national HIV/AIDS programming?

1. What kind of information will demonstration projects give us and what won't they tell us?
2. Do we need demonstration projects in every country?
3. Licensing for truvada for prevention–is it needed everywhere or only in some places?
4. What is going to happen about the cost? Can we get to economies of scale?
5. Delivery questions—the dichotomy between personalized prescriptions and scaled up delivery?
6. How people who might be good candidates for PrEP might self-identify?

Key Discussion Points:

1. Government buy in:
   - Funding: Need cost-effectiveness studies to ensure buy-in (value for money)
   - Adherence issues
   - Real world implementation
   - ART vs. PrEP spend
2. Health systems capability to handle providing PrEP
3. Demonstration projects should mimic normal clinical settings
4. Cost per infection averted
5. Who wants and needs it
6. The impact of stigma and PrEP

- **Nevilene Slingers, South African National AIDS Council (SANAC):** Focuses on developing a national strategy, and how PrEP will fit in. Developing an implementation plan—setting targets and costing. The major issue is funding—how to find and allocate funding for PrEP implementation.
  - Useful if all pilot or demonstration projects include an element of cost.

- **Noela Chicuecue, Ministry of Health, National HIV/STI Program Mozambique:** Funding the funding for this intervention and the need for cost-effectiveness studies of PrEP to provide evidence that it is cost-effective. The first-line regimen in Mozambique is currently tenofovir + 3TC. There are concerns around approval for implementation of truvada for prevention because of adherence issues and the need to consider how to provide a strong adherence strategy.
- **Uganda Ministry of Health:** Before considering adding PrEP to national guidelines, the need to understand more about it—there isn't much literature on PrEP in the

general population. The Ministry of Health is not yet convinced to implement a PrEP policy and are questioning if they invest in PrEP, what the outcome will be (i.e., will it be "value for money"). While the evidence is that PrEP works, most of the clinical trials and studies implement PrEP in an ideal environment—the situation needs to be more "real world."

- **Nduku Kilonzo, National AIDS Control Council, Kenya:** The cost of ART vs. PrEP debate: the key issue is making sure PrEP is not discussed as if it is a standalone intervention. PrEP is both a health intervention and a public health intervention. "We have the data, we have the technical information and we need to start to speak with policy makers."
    - PrEP is always going to be a contested issue. Regulators should sit on advisory teams when demonstration projects are started.
    - There is an additional cost and an additional benefit of PrEP. It is not delivered as a standalone. The whole intervention must be costed. *Every year there are 88,000 new infections added to the number of people that require treatment in the future and we need to make a strong case for why, if we don't invest in prevention, we won't get very far.* A cost analysis is needed.
    - Health systems capability to provide additional interventions.
    - Key populations and the language of rights

- **Owen Mugurungi, Ministry of Health and Child Care, Zimbabwe:** *We already have prevention methods that are working and now we have an extra method. Enough evidence needs to be presented that if we implement PrEP we are going to achieve impact. When male circumcision was introduced in Zimbabwe, we began to see results—incidence and prevalence came down. We need to say: If we continue on the current trend we will get to X number of new infections by 20XX; if we add PrEP we will get to Y number of new infections by 20XX.*
    - **Human resource to provide PrEP:** The demonstration sites have physicians, counsellors etc. How do to deliver the program outside of these settings.

- **John Idoko, National Agency for the Control of AIDS, Nigeria:** Various clinical trials and demonstration studies convinced us very it is important to implement PrEP. How do we use the science that we have to convince the policy people?
    - **The base of PrEP is combination prevention**: How do we use prep with ART to ensure that we can drastically reduce new infections?
    - **Key populations:** How does stigma affect implementation?

VII. Breakout sessions to outline key gaps and possible next steps. Can include discussions about adherence support, service links and requirements, population specific strategies, engaging stakeholders, funding.

Small groups to be facilitated by:

- Nduku Kilonzo, National AIDS Control Council, Kenya
- Frances Cowan, Centre for Sexual Health & HIV/AIDS Research, Zimbabwe
- Alasdair Reid, UNAIDS/South Africa
- Robyn Eakle, Wits Reproductive Health and HIV Institute, South Africa

- Christine Ondoa, Ugandan AIDS Commission, Uganda

VIII. Feedback from breakout sessions to focus on information gaps and policy considerations: Facilitated summary session to articulate what is still missing. What is needed to advance decision-making? What could come from demonstration projects? What other areas need work (e.g. regulatory environment; information packages for relevant populations and/or practitioners; tools for risk assessment or prioritization; design of services appropriate for different key populations; international and national guidelines, etc.) *Moderated by Papa Salif Sow, Bill & Melinda Gates Foundation*

What is success and where should we be by the end of 2015?

- We know PrEP works: Why is PrEP not reaching those who need it and what is needed to get PrEP to people who do need it?

Knowledge Gaps/Reasons for Slow Implementation:
1. **Costs** • Cost-effectiveness • Cost of scaling up national programs • Opportunity costs • Impact: Cost per case averted, improved modeling, potential national global impact
2. **Selecting target populations**/those that will benefit most/most feasible approach (short risk period of vulnerability vs. lifelong period) • Link between costs and target population: In places where the incidence of HIV is high enough, PrEP becomes cost saving. Need to address the framework for how costs and target populations are tied together.
3. **Demand creation** • Dissemination of information, engagement of leaders, community mobilization • Advocacy package to convince policymakers • Knowledge of likely demand in different settings
4. **Identifying the optimal package** of interventions around PrEP • e.g. young women and girls – SRH, social (conditional) grants, STI screening and treatment
5. **Competing priorities** for HIV policy makers- reasons for slow implementation–new ART guidelines; PMTCT guideline changes – trying to struggle with treatment/prevention etc.

Priorities for Implementers
1. Create information hub to share data between implementation studies to strengthen evidence/experience base for implementers
2. Advocacy package for policymakers • Compilation of evidence, experience and cost/benefit analysis • Prioritisation of investment • Normalizing PrEP, not exceptionalising • Package in context of combination prevention • Share evidence re: side effects
3. Global PrEP clinical guidelines strengthened
4. Defining combination package –develop HIV prevention cascade and lifecycle approach • Packaging: Package PrEP in the context of combination prevention.
5. Develop national impact model, policy, and strategy for PrEP implementation in the context of combination HIV prevention plan; develop plan that's costed to make the investment case, with key milestones. Move from demonstration project forward with buy-in from a range of key stakeholders to minimize delay from research to rollout;

• Indicators of success; what are they and what are the milestones?
6. Engage funders to hold people accountable, support civil society and supportive of national strategy to bring programming to scale
7. Political commitment to prevention – OGAC/90*90*90
8. Risk, motivation and access to services – prioritize group with most impact and identify where we can demonstrate success (e.g., Kenyan context and road map)
9. Budgeting and costing–where do we get the resources? • Costing: Instead of looking at cost-effectiveness, how do we answer the question of "where am I going to get the money."
10. Consider focus on groups that appeal to policy maker
11. Consider politics • Framing: Rather than focus on key populations, may get political traction if we focus on serodiscordant couples and young women and girls.
12. Involve policy makers in technical working groups, regional meetings and campaigns
13. Consider the context of government research agenda; involve government and potential lead in demonstration projects and pilots where possible; weigh against how government may act towards key populations who need to access PrEP
14. Just deliver it. How can we promote in other countries per US experience of rollout alongside demonstration and pilot projects; feasible in what countries without registration? • Questions of how best to deliver PrEP: Where are we going to have the low hanging fruit in terms of service delivery, (i.e., task shifting and integrating services). • Registration: PrEP is not registered everywhere. However, nevirapine has international guidance to support its use for prevention and is not registered everywhere. There are also PEP guidelines and it is not registered everywhere. Misoprostol is also widely used for abortion and it is not registered but is used all the time off label.
15. Strengthen stakeholder engagement and specifically engage end-users
16. Learn from experience of VMMC • From the first evidence of VMMC in 2005 to 2010, research was too slowly translating to rollout. A renewed understanding and emphasis on demand creation is also necessary. For VMMC, a target was set by the US of 4.7 million circumcisions and money was put towards this target and people were held accountable. After this target was set, there were more VMMCs performed in 18 months than in the first four years after the efficacy results.
17. PrEP for safer conception "PrEP-ception"
18. **Articulate roles and responsibilities of above**

APPENDIX

Meeting Agenda	
Topic	Time
Welcome, introductions and meeting outline *Rosalind Coleman, UNAIDS, and Mitchell Warren, AVAC*	09.30 – 09.45 15 minutes *Coffee/Tea from 09.00*
Update on PrEP with particular focus on recent open-label extension results and national and international guidelines (e.g. WHO, US CDC) *Presented by Connie Celum, University of Washington*	09.45-10.15 30 minutes
Linking what has been learnt to current concerns • A synthesis presentation based on pre-meeting interviews and summaries to outline broad areas of lessons being learned with a view to identifying common themes, approaches or needs • Brief presentation from those projects already delivering oral PrEP in East and Southern Africa – *SAPPR-Ire (Zimbabwe), Partners Demo Project (Kenya and Uganda), Desmond Tutu HIV Foundation (South Africa)* • Moderated discussion amongst all *Moderated by Kevin O'Reilly, consultant to WHO*	10.15 – 11.00 45 minutes
Break	11.00 – 11.20 20 Minutes
Users' perspectives • Members of research populations to describe their experiences, concerns, attitude of their communities, etc. with using PrEP *Moderated by Rosalind Coleman, consultant to UNAIDS*	11.20– 11.50 30 minutes
Moderated discussion including Q&A with the project implementers and PrEP users to focus on what we are learning in real time *Moderated by Francois Venter, Wits Reproductive Health and HIV Institute*	11.50 – 12.30 40 minutes
Lunch	12.30-13.30 60 minutes
Programme planners/policy maker perspectives • Programme planners to provide perspectives with their thoughts and concerns when considering PrEP in national programmes, including structural and procedural issues	13.30-14.15 45 minutes
Moderated discussion including Q&A with policy makers and program planners to explore where PrEP might fit and what are the outstanding questions/issues. *Moderated by Carlos Caceres, NEMUS*	14.15 – 14.45 30 minutes

Meeting Agenda	
Topic	Time
Breakout sessions to outline key gaps and possible next steps. Can include discussions about adherence support, service links and requirements, population specific strategies, engaging stakeholders, funding. *Small groups to be facilitated by* • *Nduku Kilonzo, National AIDS Control Council, Kenya* • *Frances Cowan, Centre for Sexual Health & HIV/AIDS Research, Zimbabwe* • *Alasdair Reid, UNAIDS/South Africa* • *Robyn Eakle, Wits Reproductive Health and HIV Institute, South Africa* • *Christine Ondoa, Ugandan AIDS Commission, Uganda*	14.45 – 15.45 60 minutes *Including coffee break*
Feedback from breakout sessions to focus on 'information gaps' and 'policy considerations' • Facilitated summary session to articulate what is still missing. What is needed to advance decision-making? What could come from demonstration projects? What other areas need work (e.g. regulatory environment; information packages for relevant populations and/or practitioners; tools for risk assessment or prioritization; design of services appropriate for different key populations; international and national guidelines, etc.) *Moderated by Papa Salif Sow, Bill & Melinda Gates Foundation*	15.45-16.30 45 minutes
What is success and where should we be by the end of 2015? • Based on what we have learned to date (in the first couple of hours) and what policy makers need to make decisions (in the previous sessions), ***a moderated discussion to articulate specific milestones that can be feasibly reached in the next 14 months and how these fit within existing country planning deadlines and opportunities****.* *Moderated by Rosalind Coleman, UNAIDS, and Mitchell Warren, AVAC*	16.30-17h00 30 minutes
Wrap-up and next steps	17h00-17h15 15 minutes

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PRESENTATIONS

1. Oral PrEP: Efficacy & demonstration projects to inform policy, Connie Celum, MD, MPH University of Washington

2. Summary of PrEP Demonstration Projects, Deirdre Grant, AVAC

3. SAPPH-Ire Demonstration Project, Frances Cowan

4. High initiation and adherence among high risk African HIV-1 serodiscordant couples in a demonstration project of PrEP and ART for HIV-1 prevention

Oral PrEP: Efficacy & demonstration projects to inform policy

Connie Celum, MD, MPH
University of Washington

Success with PrEP: Next Steps to Support Policy Decisions in Southern and East Africa meeting

Cape Town, October 2014

Outline

- Oral PrEP: Evidence from phase III RCTs
- The next phase in evidence: Open label extensions & demonstration projects
  - iPrEX OLE
  - Partners Demonstration Project
- Goals of new demonstration projects

Four trials demonstrate PrEP efficacy in diverse geographic and risk populations

Study, population	PrEP agent	# of HIV infections		PrEP efficacy (95% CI) publication
		PrEP	placebo	
Partners PrEP Study Heterosexual couples Kenya, Uganda (n=4758)	TDF/FTC	13	52	**75%** **(55-87%)**
	TDF	17		**67%** **(44-81%)** Baeten et al. N Engl J Med 2012
TDF2 Study Heterosexuals Botswana (n=1219)	TDF/FTC	10	26	**62%** **(16-83%)** Thigpen et al. N Engl J Med 2012
Bangkok Tenofovir Study (BTS) IDUs Thailand (n=2413)	TDF	17	33	**49%** **(10-72%)** Choopanya et al. Lancet 2013
iPrEx MSM Brazil, Ecuador, Peru, South Africa, Thailand, US (n=2499)	TDF/FTC	36	64	**44%** **(15-63%)** Grant et al. N Engl J Med 2010

Partners PrEP:
Both TDF & FTC/TDF are highly efficacious

- Comparable efficacy: 75% FTC/TDF compared to 67% TDF (p=0.16)
- 85% estimated efficacy of TDF & 93% of FTC/TDF, based on tenofovir detection in plasma
- Oral TDF is an alternative option of for 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

Baeten et al Lancet ID 2014

Adherence and HIV protection: oral PrEP

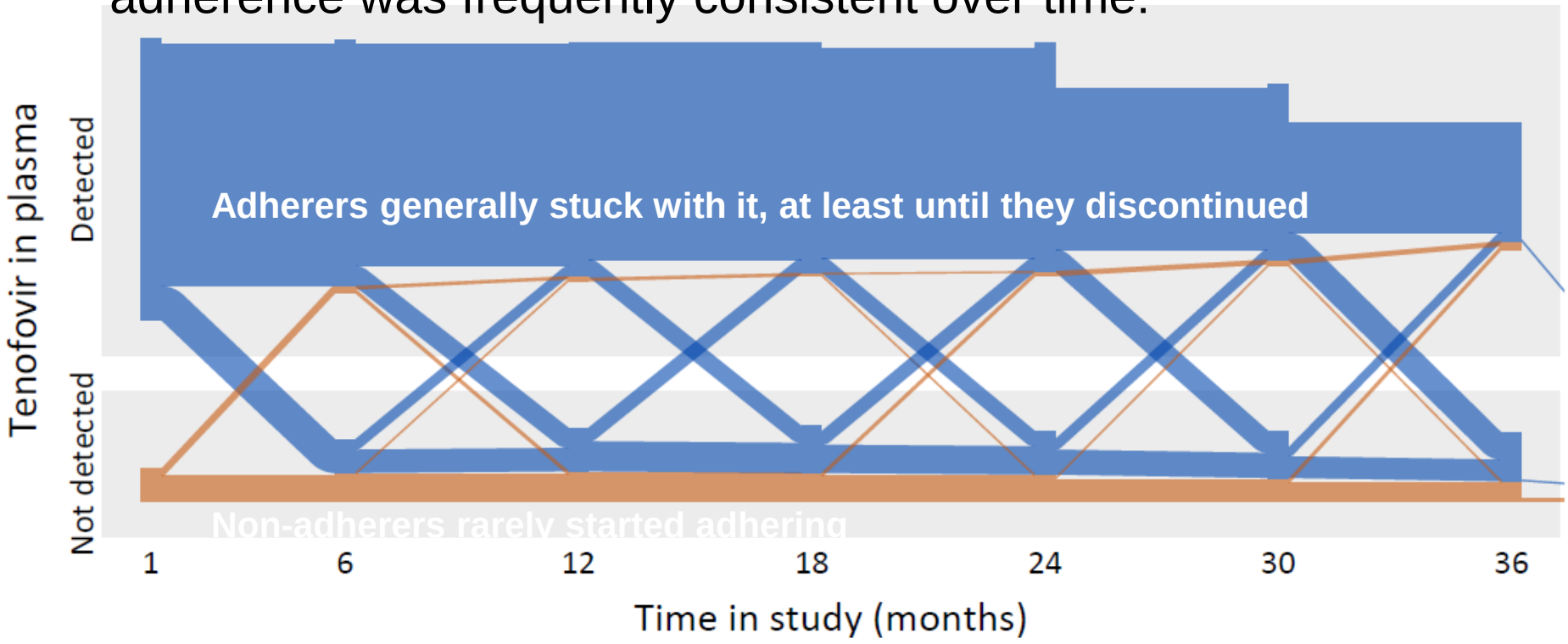
	% of blood samples with tenofovir detected	HIV protection efficacy in randomized comparison	HIV protection estimate with high adherence
Partners PrEP **TDF/FTC arm**	81%	75%	90% (tenofovir in blood)
TDF2	79%	62%	78% (prescription refill)
BTS	67%	49%	70% - 84% (tenofovir in blood / pill count)
iPrEx	51%	44%	92% (tenofovir in blood)
FEM-PrEP & VOICE	<30%	No HIV protection	N/A

When adherence was high, HIV protection is consistent and high.

Baeten et al N Engl J Med 2012; Thigpen et al N Engl J Med 2012; Choopanya et al Lancet 2013; Grant et al N Engl J Med 2010; Van Damme et al N Engl J Med 2012; Marrazzo et al CROI 2013

Most who initiated PrEP maintained good adherence

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



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

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
    - *Reporting sex without condoms*
    - *With an STI*
    - *With an HIV+ partner who has a high plasma HIV viral load*
    - *Women <30 years of age*
  - MSM (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 higher than for the trial population as a whole, because adherence was often greater for persons taking greater risks

Rare antiretroviral resistance

Resistance from PrEP was very rare, with only a small number who had acute infection at the time they were started on PrEP.

	# of HIV seroconverters assigned PrEP with HIV resistance	
	HIV infected after enrollment	**Seronegative acute HIV infection at enrollment**
Partners PrEP	0 / 48	2 / 10
iPrEx	0 / 36	2 / 2
TDF2	0 / 10	1 / 1

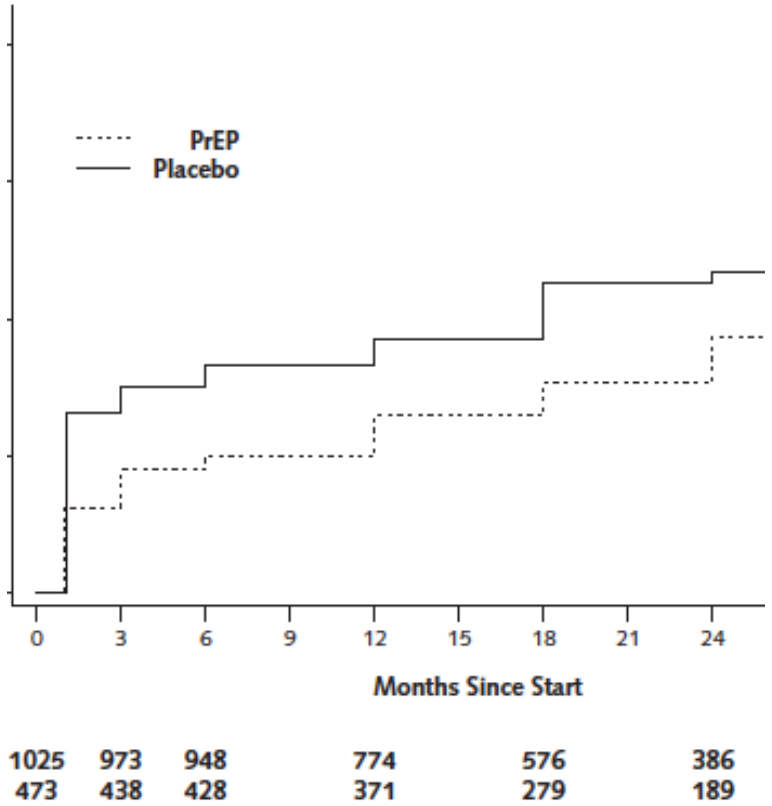
Resistance = K65R (TDF) or M184V/I (FTC) mutations

30% reduction in HSV-2 acquisition with PrEP in Partners PrEP Study

- 1522 HSV-2 seronegative persons at enrollment
  - HSV-2 seroincidence: 7.7 in placebo arm & 5.6 per 100 p-yrs in PrEP arms
  - HR 0.7 (95% CI 0.49-0.99, p=0.046)

- Consistent with CAPRISA 004 (tenofovir gel) & in vitro data about tenofovir & HSV-2

- Valuable added prevention benefit of PrEP, given that HSV-2 is a risk factor for HIV & limited HSV-2 prevention interventions



Celum et al, Ann Intern Med 2014

PrEP safety

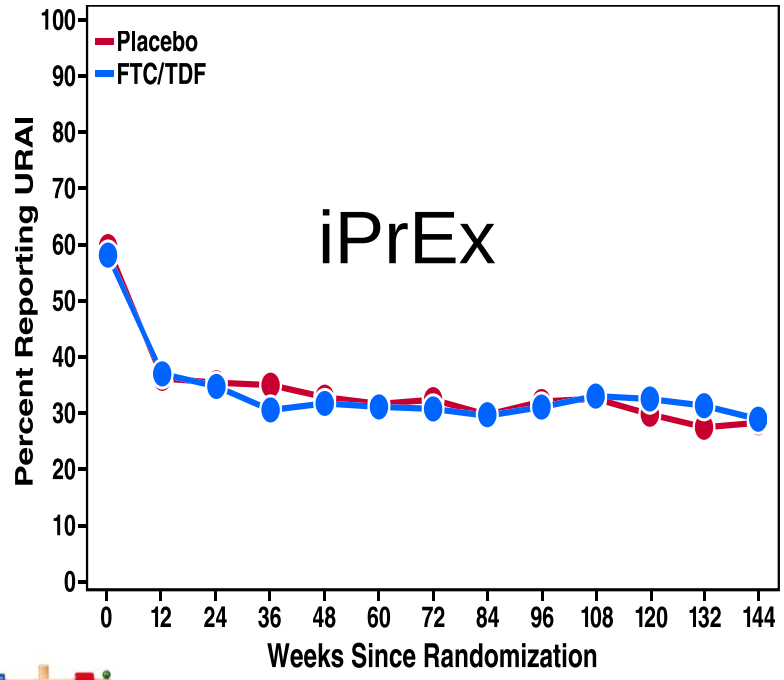
- Rates of death, serious adverse events, and laboratory abnormalities (including renal dysfunction) were low and not significantly different between those taking PrEP and those taking placebo

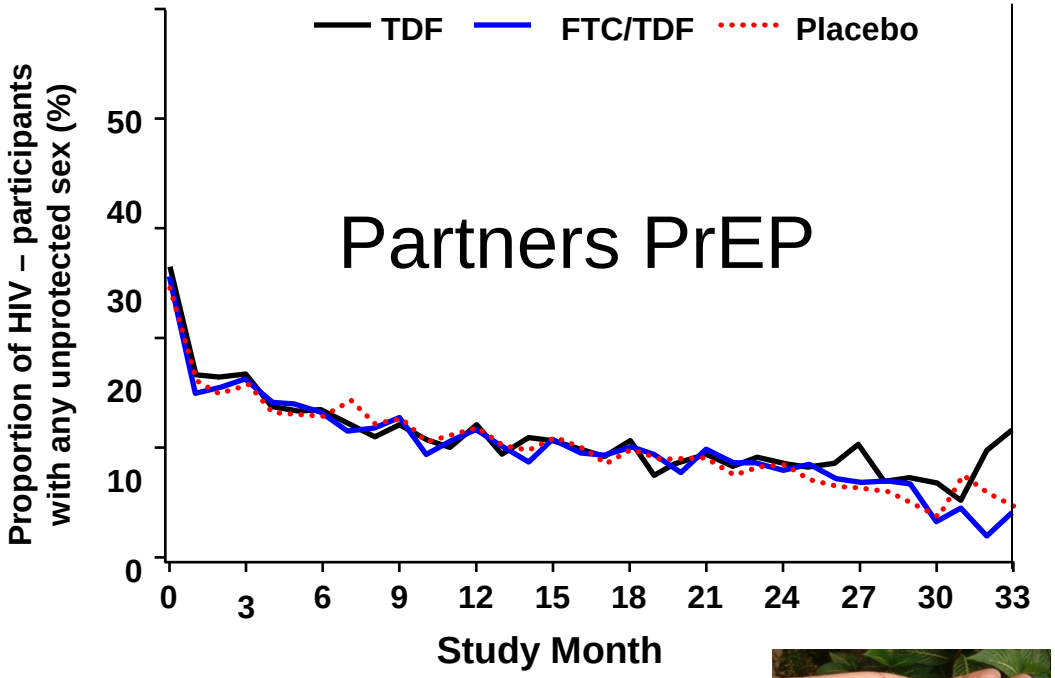
- PrEP was well tolerated
  - Adverse effects occurred in minority of subjects
  - GI adverse effects (e.g., nausea) more common in those receiving PrEP than placebo
    - Occurred in < 10% and primarily during the first month only (PrEP “start up” symptoms)

- PrEP associated with a small change (~ 1%) in bone mineral density but without increased risk of fracture

No evidence of risk compensation in PrEP clinical trials

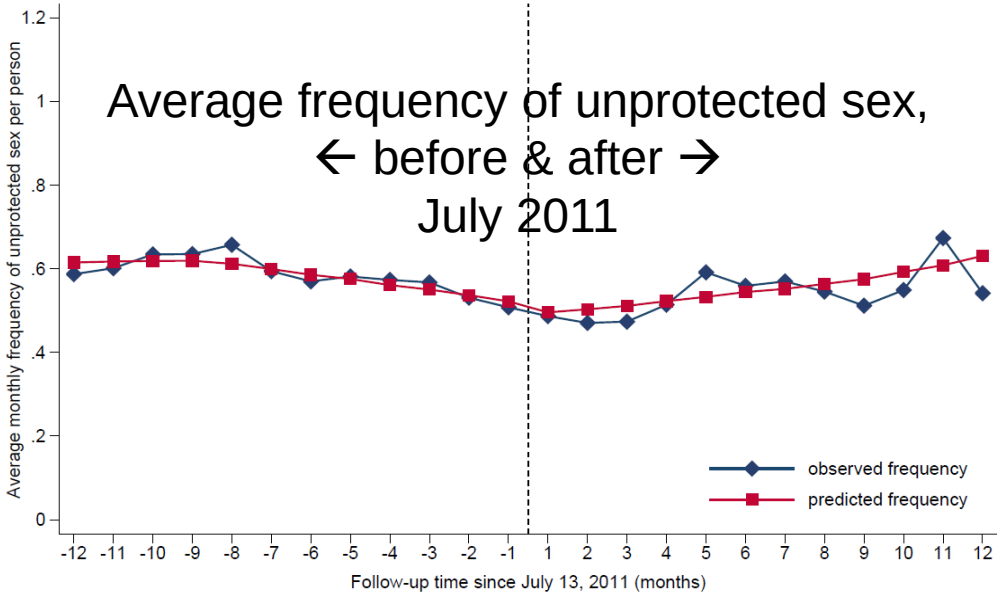
In both iPrEx and Partners PrEP, unprotected sex and STIs were less common over time – suggesting synergy of ongoing risk-reduction counseling along with PrEP.





Lack of risk compensation in those receiving 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

Understanding lack of oral PrEP efficacy in young African women

- HIV incidence was 6% in context of monthly visits & other HIV prevention services
- Hypotheses for low daily gel & oral PrEP uptake & adherence in young women in FemPrEP & VOICE:
  - Women may not have been motivated because risk is dynamic? Perceived risk is low? Perceived benefits are low?
  - Importance of partner engagement & support?
  - Women joined trial for other reasons? (van der Stratten, R4P)
- However, now that efficacy is known, uptake & adherence may be different outside a clinical trial

FDA approval of FTC/TDF PrEP for HIV prevention

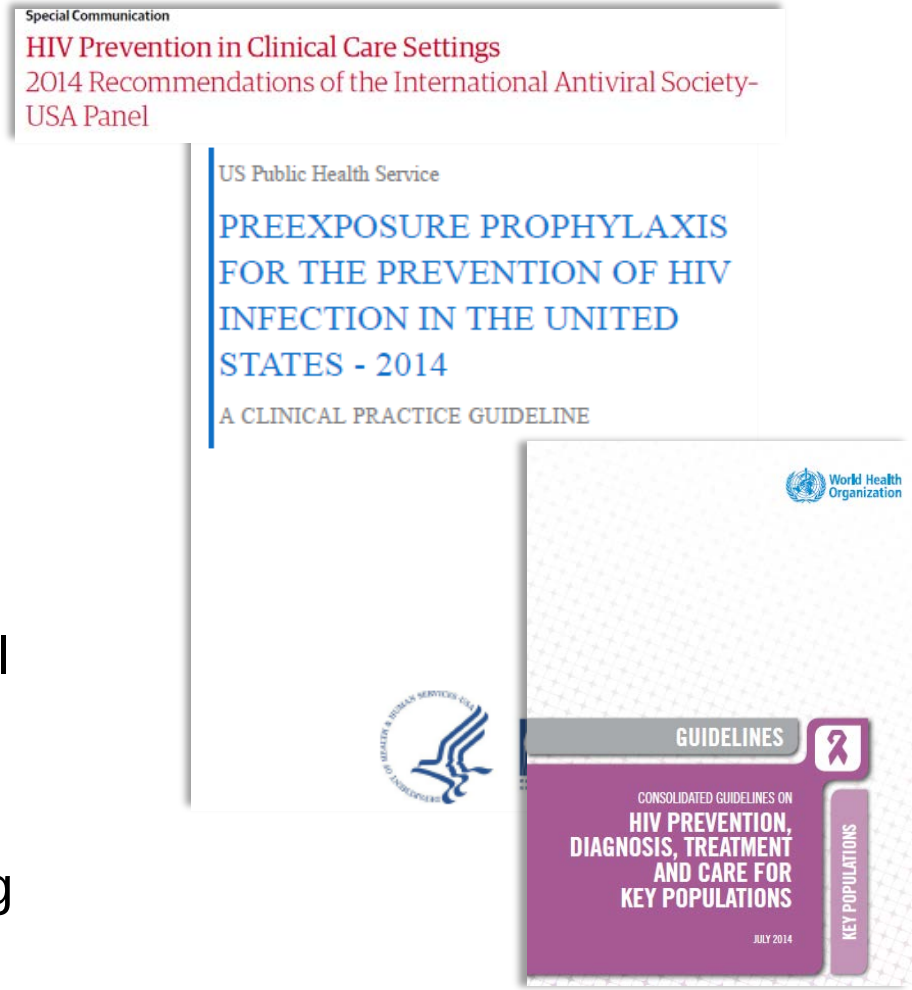
FDA Approves First Medication to Reduce HIV Risk

"It is still better to prevent HIV than to treat a life-long infection of HIV."

Deborah Birnkrant, director of the Division of Antiviral Products, US FDA, 16 July 2012

Prescribing PrEP

- **Risk assessment**
  - PrEP is indicated for those at high HIV risk
- **Eligibility**
  - HIV negative, adequate renal function, HBV testing
- **Follow-up**
  - Prescribe for daily use, periodic HIV testing (3-monthly), counsel about risk-reduction
- **Discontinuing PrEP is expected**
  - PrEP is not meant to be life-long = for periods of highest risk

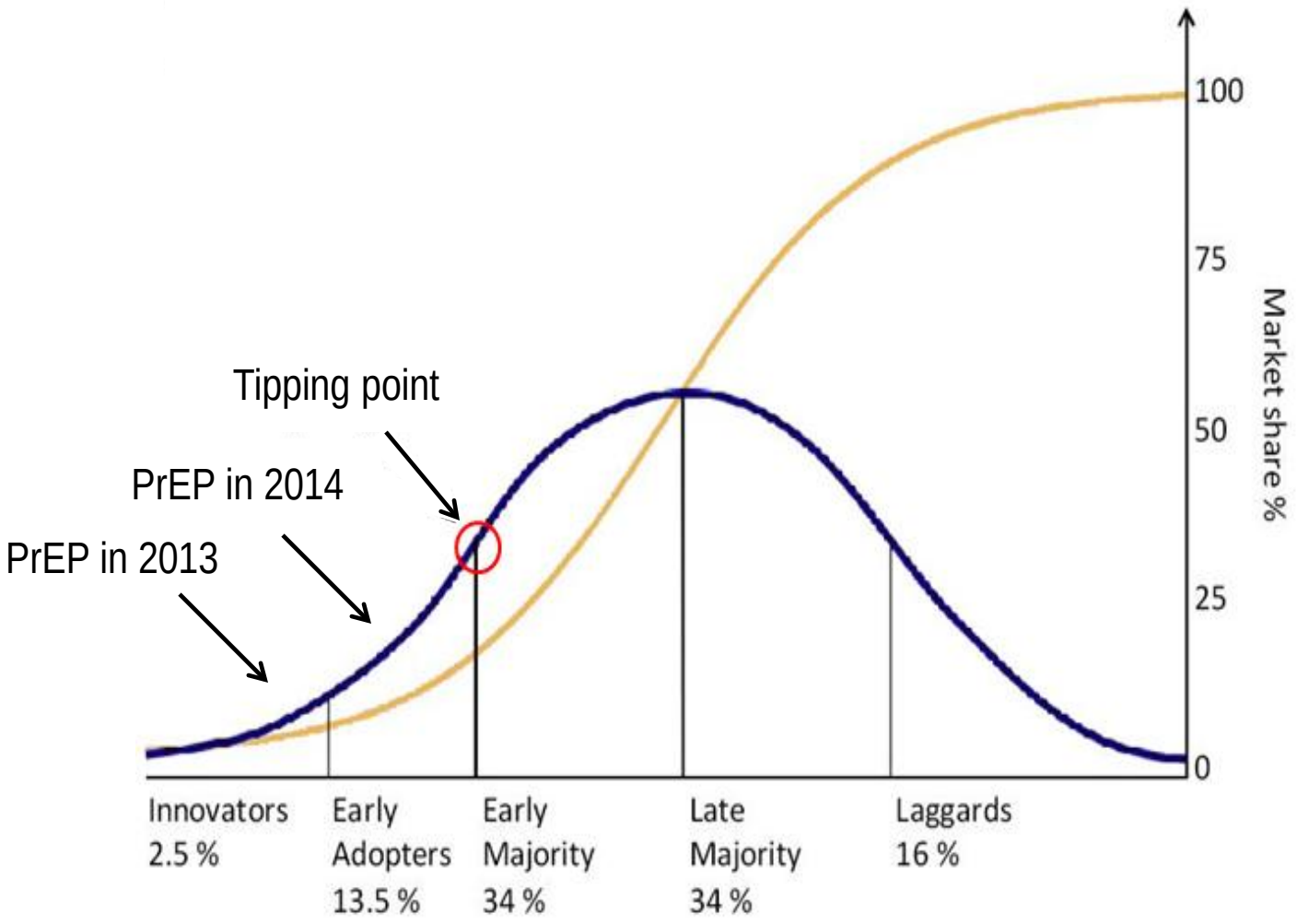


Moving from efficacy to implementation
-Proof of deliverability & impact-

Moving PrEP from evidence to implementation requires…

- **Time** for diffusion of new innovations (eg PrEP)
- **Experience**: how to deliver, motivate use, & support adherence
  - Demonstration projects of PrEP for populations with high HIV incidence
  - Define who wants PrEP, how long they use it, when & how to discontinue PrEP
- **Effective PrEP formulations,** including long acting, less user-dependent PrEP strategies
  - While evaluating long-acting PrEP products, can learn important lessons from delivery of oral PrEP
- **Political will & support**

Diffusion of Innovations theory



PrEP demonstration project questions

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?*

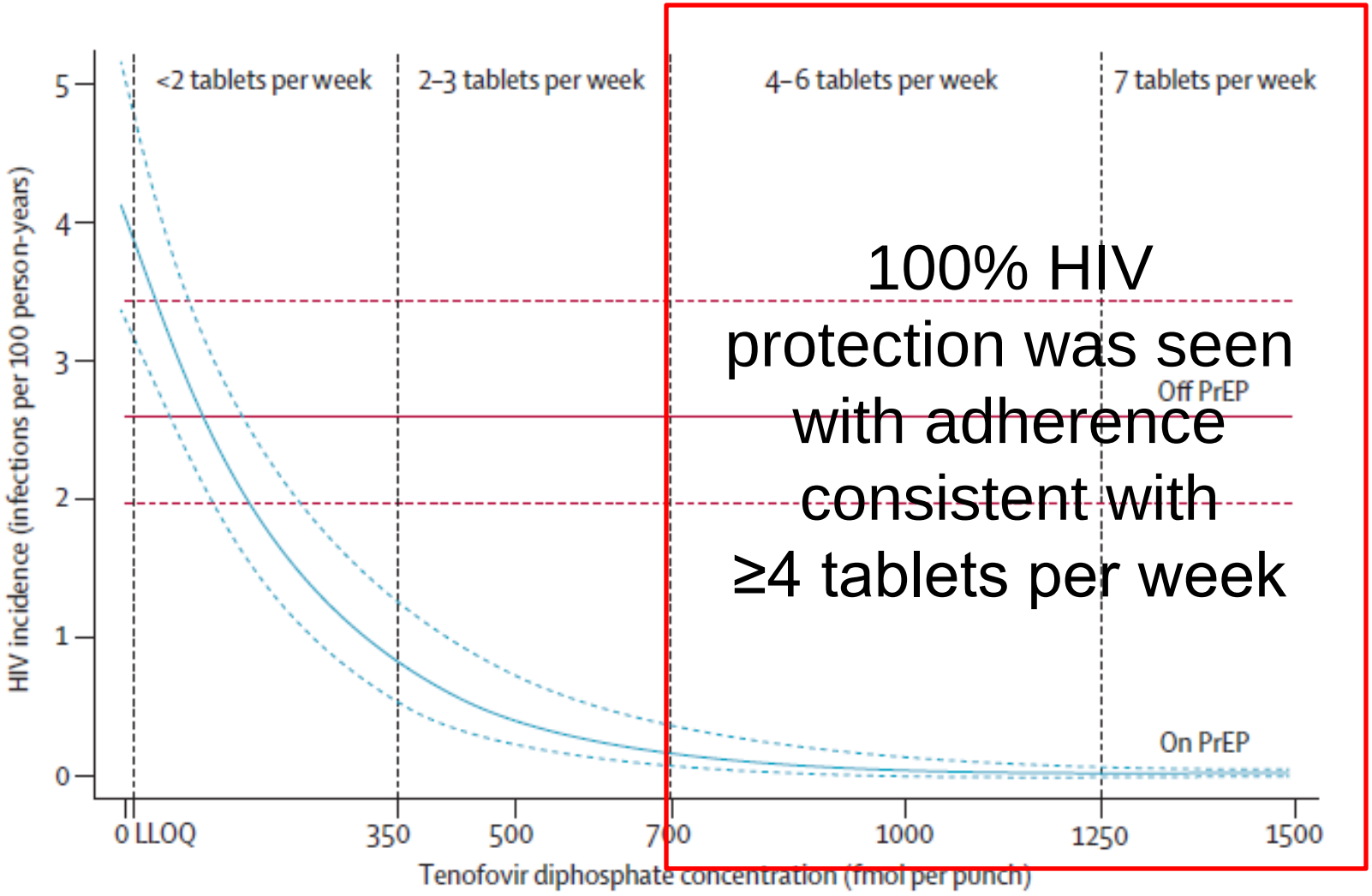
PrEP as part of combination HIV prevention for men who have sex with men (MSM)

iPrEX OLE

- High uptake: 76% of 1603 iPrEX ppts
  - Higher uptake among men reporting condomless receptive anal sex (81%)
- Higher adherence among older & more educated men & during periods of risk
- 49% lower HIV incidence in PrEP users vs those who did not take PrEP
- Modeling: High efficacy among those taking >4 pills/week

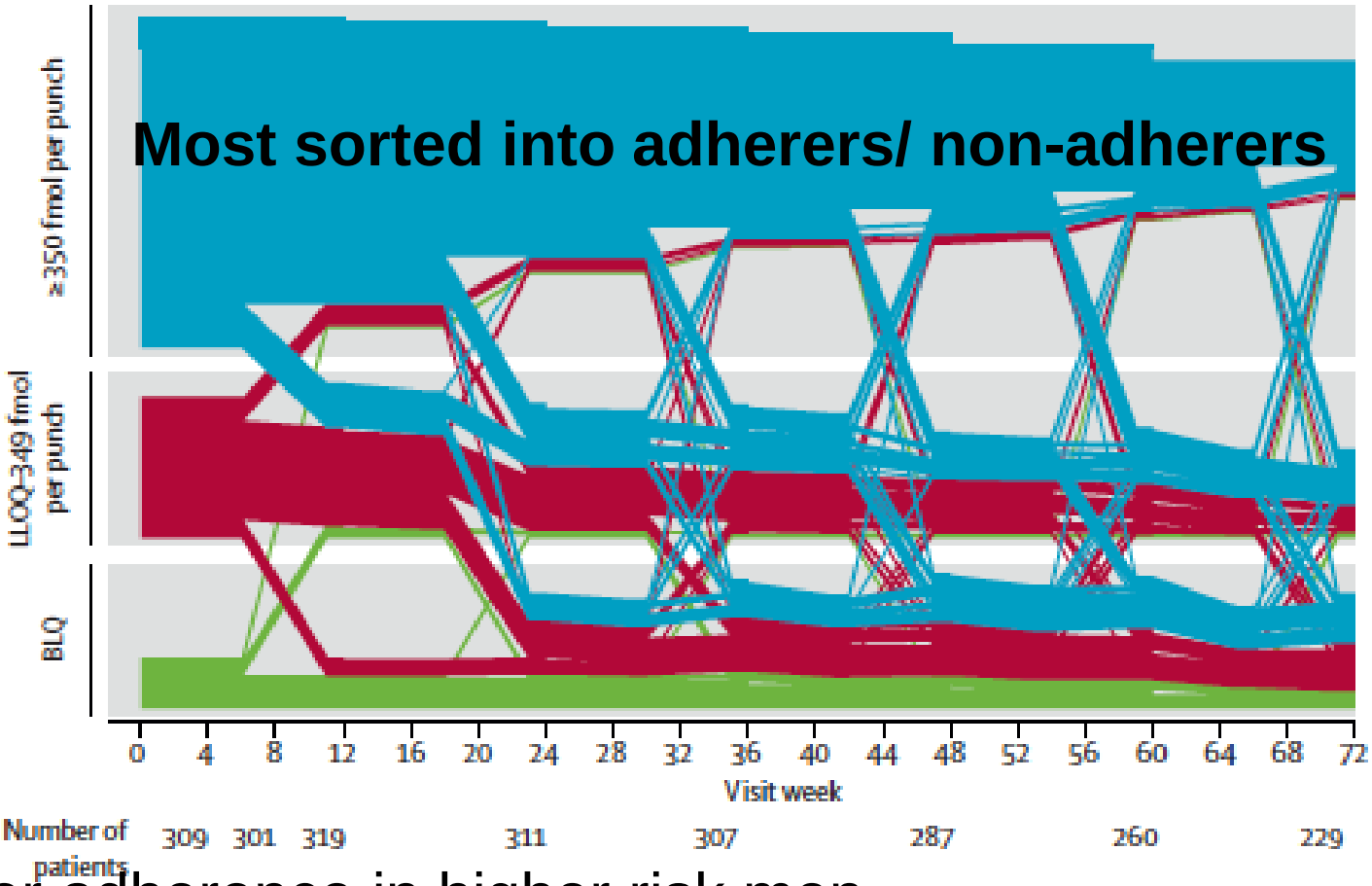
Grant et al Lancet ID 2014

Enough is not necessarily perfection: iPrEx OLE



Grant et al. Lancet ID 2014

iPrEX OLE; Lessons about adherence



- Higher adherence in higher risk men
- Adherence declined over time; need ways to identify those at risk who need adherence support

Grant et al Lancet ID 2014

MTN microbicide trials network

PrEP Demo Projects in the US

Study	Population (N)	Sites	Timeline
Demo Project	600 MSM/trans women	San Francisco Miami Washington DC	Enrollment started Sept 2012, results 2015
CCTG 595	700 MSM/trans women	San Diego Long Beach, LA Torrance	Enrollment Q2 2013, results 2016
PATH-PrEP	375 MSM/trans women	Los Angeles	Enrollment April 2013, results 2017
CRUSH	150 young MSM of color, high risk women	Oakland	Enrollment Q1 2013
ATN 110 and 113	300 young MSM age 15-22	14 sites in US	Enrollment Dec 2012, results Q4 2014
HPTN 073	225 Black MSM	Washington DC, LA, Chapel Hill	Enrollment June 2013, results 2017
SPARK	~300 MSM and trans women	New York	Enrollment Q4 2013

MTN
microbicide trials network

Preliminary results from US PrEP demo projects for MSM

- Interest is high
  - >50% of MSM eligible for PrEP demo project in SF, Wash DC and Miami initiated PrEP
  - High uptake among young MSM of color in Chicago
- Adherence is high
  - 98% had any tenofovir detected & 77% had levels detected consistent with dosing ≥ 4 times/week
- However, low awareness of PrEP & provider barriers in internet survey of MSM

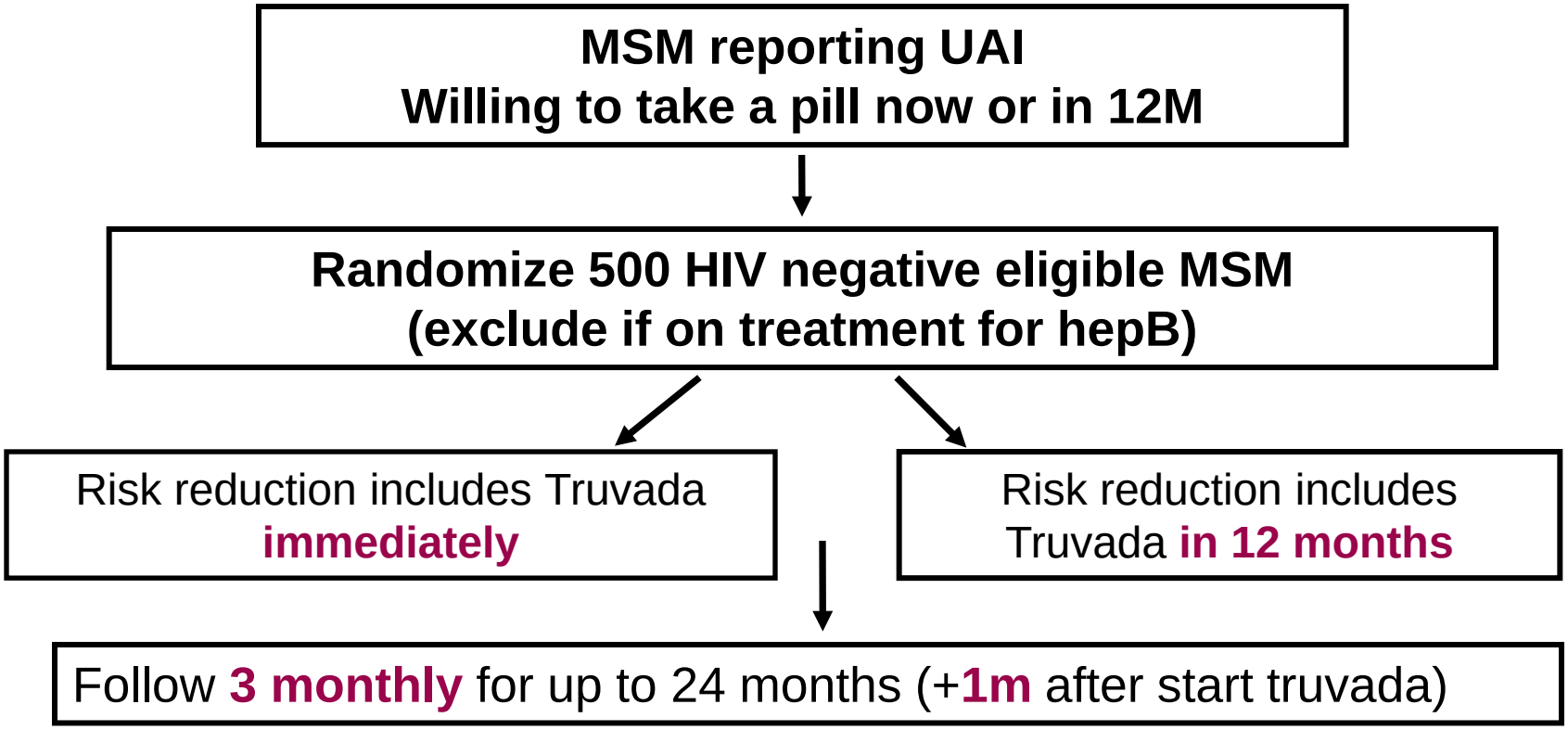
Cohen S, CROI 2014 abst 954
Hosek S, CROI 2014 abst 951
Mayer K, CROI 2014 abst 952

What PrEP offers

- Social benefits
  - Decreased anxiety
  - Increased communication/disclosure
  - Increased intimacy/trust
  - Increased sense of community
  - Increased self-efficacy
  - Increased sexual pleasure & intimacy (and a reminder to us that sex is not a clinical event)

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)

PROUD Pilot, United Kingdom



Outcome: HIV incidence in immediate vs deferred arm

Based on pilot, plan to enroll 500 men

What PrEP looks like in real world delivery: PROUD Study (Oct 2014)

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

PROUD study interim analysis finds pre-exposure prophylaxis (PrEP) is highly protective against HIV for gay men and other men who have sex with men in the UK

- Among MSM in the UK, delivery of PrEP (compared to randomization to deferred access to PrEP) *was so effective in preventing HIV* that the deferred arm was discontinued early.
  - Effect was sufficiently powerful in a sample of just ~500 men, only 10% of what was expected for the full study population.
  - At baseline, the 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

PrEP as part of combination HIV prevention for HIV serodiscordant couples

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

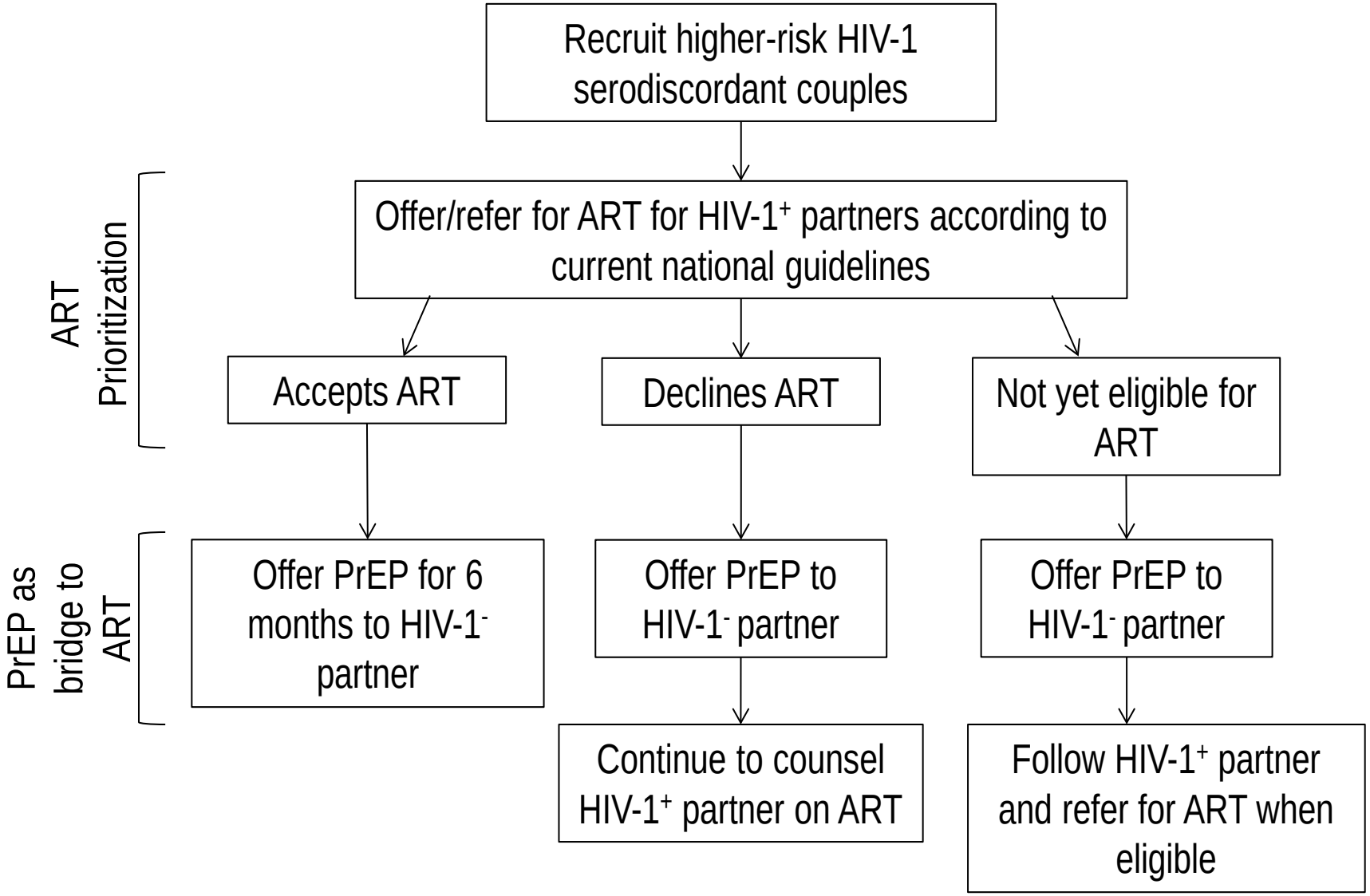
  (Hallett et al. PLoS Med 2011; Mitchell et al. STI World Congress 2013)

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.

Demonstration project approach – PrEP as a bridge to ART and viral suppression



Partners Demonstration Project: milestones and timeline

Partners Demo Project Methods

- Enrollment of high-risk HIV serodiscordant couples from November 2012 to August 2014
  - Risk score derived & validated in 3 cohort studies of HIV serodiscordant couples to identify couples with ≥5% HIV incidence (Kahle JAIDS 2013)
- 4 sites: Thika & Kisumu, Kenya; Kampala & Kabwohe, Uganda
- Quarterly study visits for up to 2 years
  - HIV prevention services, including couples-based prevention counseling
- ART offered according to national guidelines
  - Changed from CD4<350 to 500 and for all HIV serodiscordant couples

Participant Characteristics

- Enrollment of 1012 high risk couples completed August 2014
- 67% of couples have HIV-1 uninfected male partners
- 47% of couples have a risk score ≥7
- Higher risk characteristics than Partners PrEP
  - Median age = 30 (Partners PrEP = 33)
  - 56% of couples have no children (Partners PrEP = 22%)
  - Median monthly coital frequency = 4-6 acts (Partners PrEP = 4)
  - 64% of participants reported unprotected sex with study partner in the month preceding enrollment (Partners PrEP = 26%)
  - HIV-1 infected partners have median viral load of 4.6 (3.9-5.0) $\log_{10}$ copies/mL (Partners PrEP = 3.9)

Partners Demo Project Status

- High uptake of PrEP at enrollment: >90% of participants
- High adherence to PrEP based on MEMS and plasma tenofovir levels
- ART willingness is high among ART eligible participants at enrollment: 62% accept a referral or on-site ART
- 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

Heffron R. CROI 2014
Heffron R 2014 R4P (Thursday)

What PrEP looks like in real world delivery: Partners Demonstration Project

- The Partners Demonstration Project has enrolled 1013 high-risk HIV serodiscordant couples in Kenya and Uganda into a demonstration project providing PrEP and ART for prevention.

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%

- Notably, the Demonstration Project population is at considerably higher behavioral risk than the clinical trial population was

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

PrEP demo projects: Next steps

- Initial focus on key populations
  - MSM in US
  - HIV serodiscordant couples in Nigeria
  - FSWs in Kenya, Senegal, South Africa, Zimbabwe
  - Young women in South Africa
  - Injection drug users
- Understanding who is at risk, who is motivated to use PrEP & how they use it

Who to target for PrEP?
Time-limited PrEP for key populations:
During 'seasons' of vulnerability

- MSM in higher-risk periods
  - Young men
  - Men with STIs
  - Men practicing unprotected sex
- HIV serodiscordant couples trying to conceive & before HIV+ partner is on ART
- FSWs, PWID, young women
- Other risk factors: intimate partner violence, relationship transitions, depression, alcohol & drug use
- *And, we should expect PrEP use to map to periods of high risk (and perhaps this means stopping, starting)*

Key priorities for PrEP demo projects

- Learn from early (& later) adopters with PrEP delivery
  - Who uses PrEP, patterns of use, & discontinuation of PrEP
  - Understand barriers, motivators & how to increase motivation
- Identify efficient delivery systems, utility of risk scores & tools, & adherence monitoring strategies
- Lessons will be relevant to future prevention products
  - Longer acting, less user dependent formulations
  - Multi-prevention technologies (contraceptive & ARV)

How to deliver PrEP?

- Bundling with other services (e.g., FP for women)
- Risk screening for targeting (e.g. condomless anal receptive sex for MSM, risk score for serodiscordant couples)
- Community delivery to reduce burden?
- Less frequent visits
- Self-testing to identify early infection with fewer visits
- Adherence monitoring?
- Costs & cost per infection delivered

Thanks

- Jared Baeten
- BMGF for funding Partners PrEP Study
- BMGF, USAID, NIH for funding Partners Demonstration project
- AVAC, WHO, UNAIDS for organizing the meeting

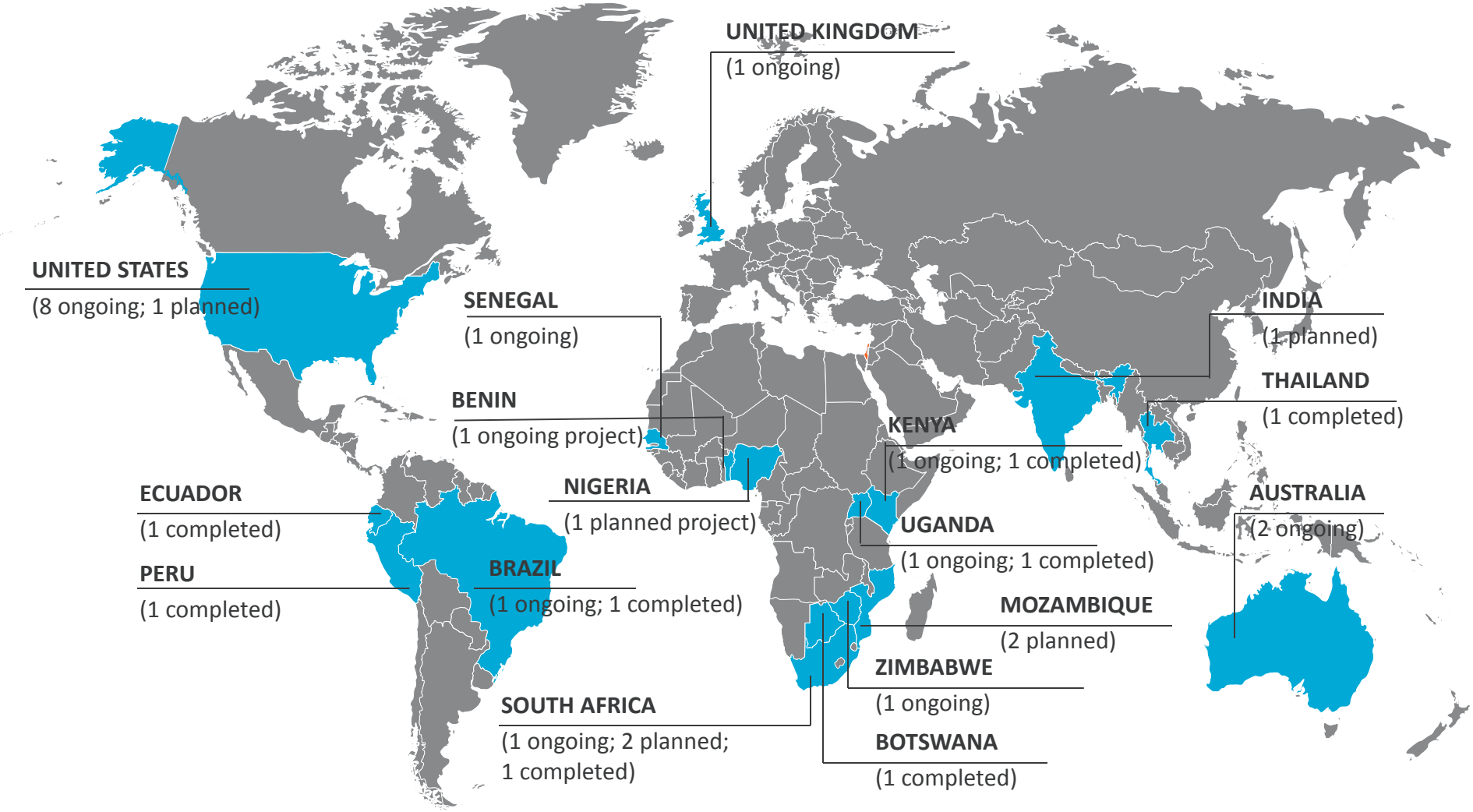
Summary of PrEP Demonstration Projects

Success With PrEP

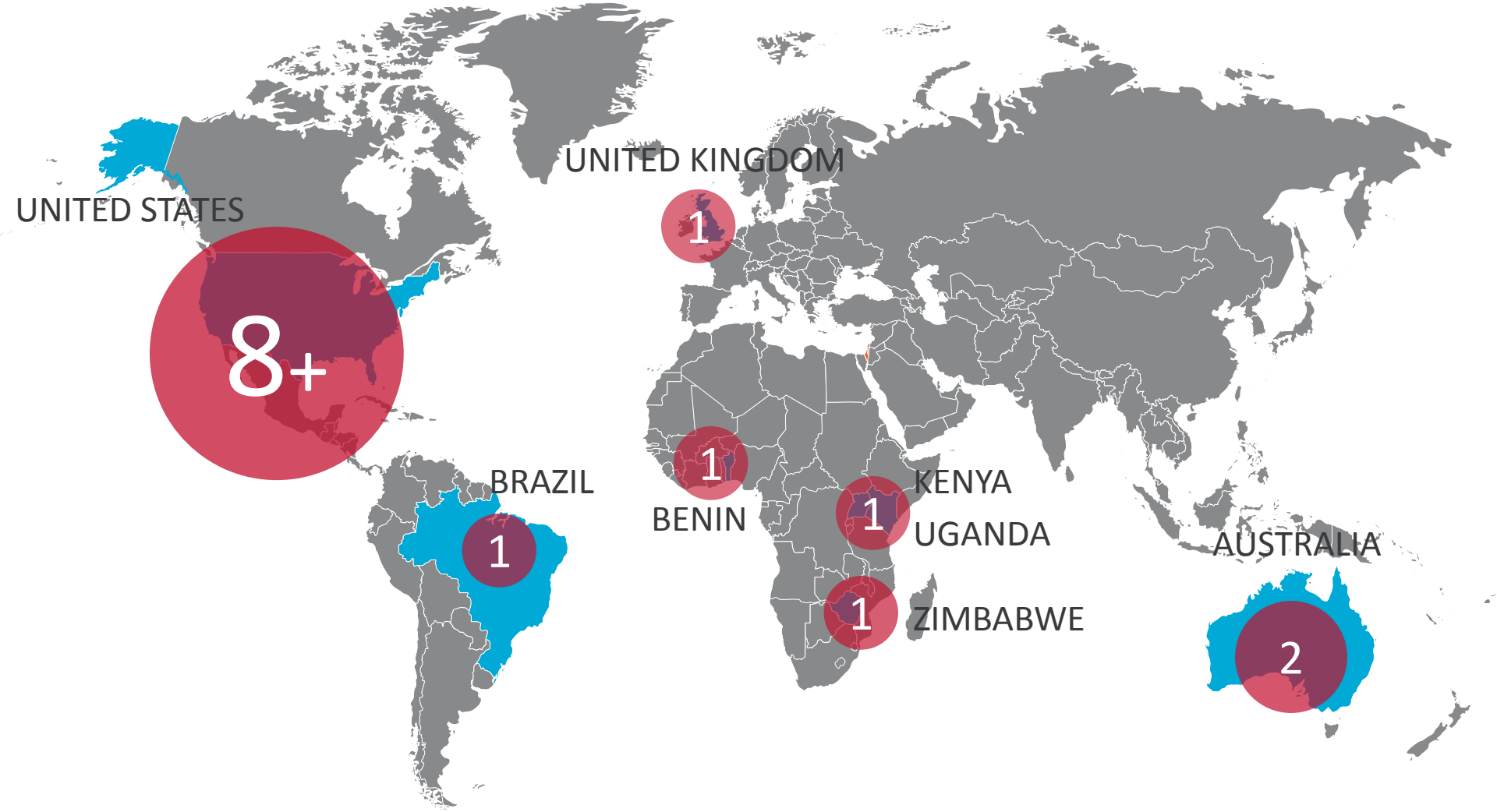
Sunday, October 26, 2014

AVAC, WHO/UNAIDS

PrEP Demonstration Projects: Planned, ongoing and completed project locations



Projects currently delivering PrEP



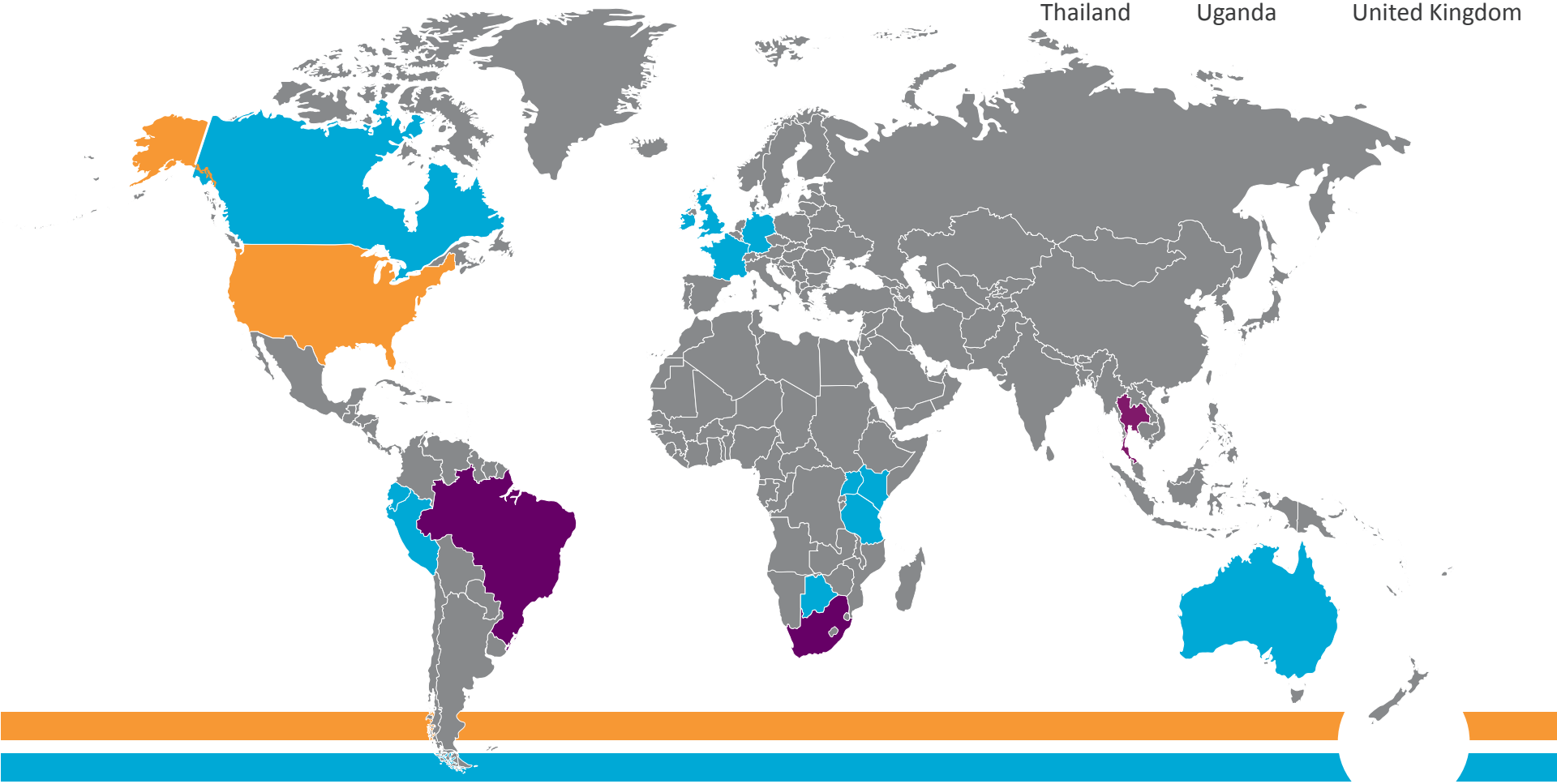
Status of Regulatory Approval for Daily TDF/FTC for Prevention in Host Countries

TDF/FTC approved for prevention
United States

Regulatory application filed for a prevention indication for TDF/FTC
Brazil
South Africa
Thailand

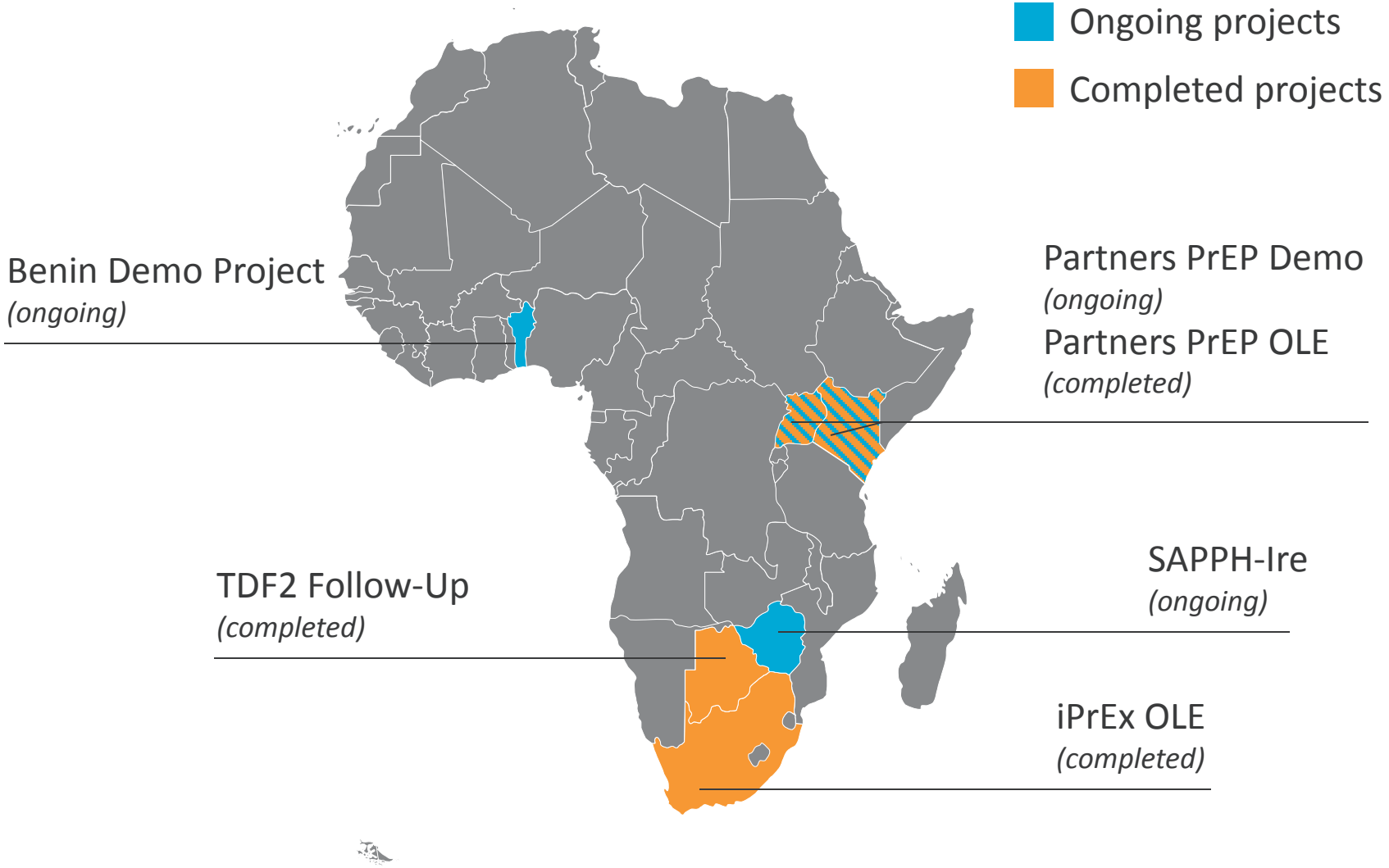
Host countries with no regulatory application filed for prevention

Australia	Botswana	Canada
Ecuador	France	Germany
Kenya	Peru	Tanzania
Thailand	Uganda	United Kingdom



Countries Where PrEP Delivered

(Outside of an RCT)



All Projects Planned to Deliver PrEP in Africa in *2015*

Ongoing projects

Completed projects

Senegal Demo Project

Benin Demo Project

Nigeria Demo Project

TDF2 Follow-Up *(completed)*

Partners PrEP OLE *(completed)*

Partners PrEP Demo

LVCT and SWOP

Mozambique Demo Project

SAPPH-Ire

CHAMPS

TAPS

iPrEx OLE *(completed)*

Population Data: Project population data available by completion of current ongoing and planned projects in Africa

Population	*Number of Projects*
Female sex workers (FSW)	5
Men who have sex with men (MSM)	2
Transgender women	1
Injecting drug users (IDUs)	0
Serodiscordant couples	2
Heterosexual women	3
Heterosexual men	1
Adolescents	1

Summary Issues to Consider

- Resources: For PrEP but also healthcare infrastructure
- Equity: “Designer” drug or reach all in need
- Logistics: Impact on existing patient flow and burden of follow-up (for all staff)
- Risk compensation: Worry of condomless sex; hasn’t happened
- Long-term access: Will Gilead create a Medication Assistance Program outside of US?
- Delays with ethics boards and/or regulatory bodies: May not be relevant when using PrEP in a program

Site Issues

- Sites include research sites, STD clinics, population-specific health clinics
- Research-naïve vs. new sites; mix and challenges in getting newer sites on board; also issue of geographic diversity (or lack thereof) of sites within a country when only a few sites may end up informing a policy that's country-wide

Recruitment

- Most self-referral or referred after screening visit (and met risk criteria) in healthcare setting
- At one of the US sites, most of the referrals came from HCT counselors, referrals from PEP and STI clinics—not primary care
- How to access those who aren't accessing health care necessarily, like recruitment of transgender women low across the projects that enrolled them—need CBOs
- Need to monitor how sites using facilities that certain pops already use for more comprehensive care and are established as a go-to space

Adherence

- Not much data on actual adherence as many of the studies haven't initiated pill taking yet
- Projects vary on level of counseling to support adherence and include things like next-step counseling, client-centered, "enhanced adherence support" with counselors walking through with participants how they might be able to adhere—making a specific plan while in the office and not just giving them the tools to make a plan on their own at home
- Adherence measures include pill count, DBS, self-report, MEMS – few projects use adherence data in real-time with counseling as not reflective of what's possible in real world.
- Some projects lack resources to do PK analysis.

Testing

- Almost all quarterly testing at visits; one looking at home testing as a sub-study
- Rapid tests, RNA, pooled RNA

Pregnancy & PrEP

- Sub-study in Partners and majority are treated on case-by-case basis with women having option to continue PrEP while pregnant

Next Steps

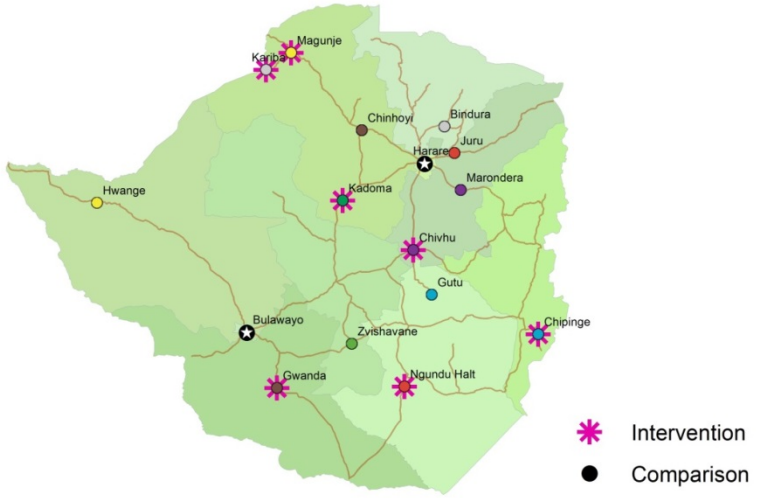
- Several projects noted that national leaders have said seemed amenable to possibility of PrEP rollout, but need evidence that it's "deliverable" first
- Classic quandary—"can't pay for treatment so how do we pay for PrEP?"
- WHO guidance on PrEP – what can we expect in 2015?

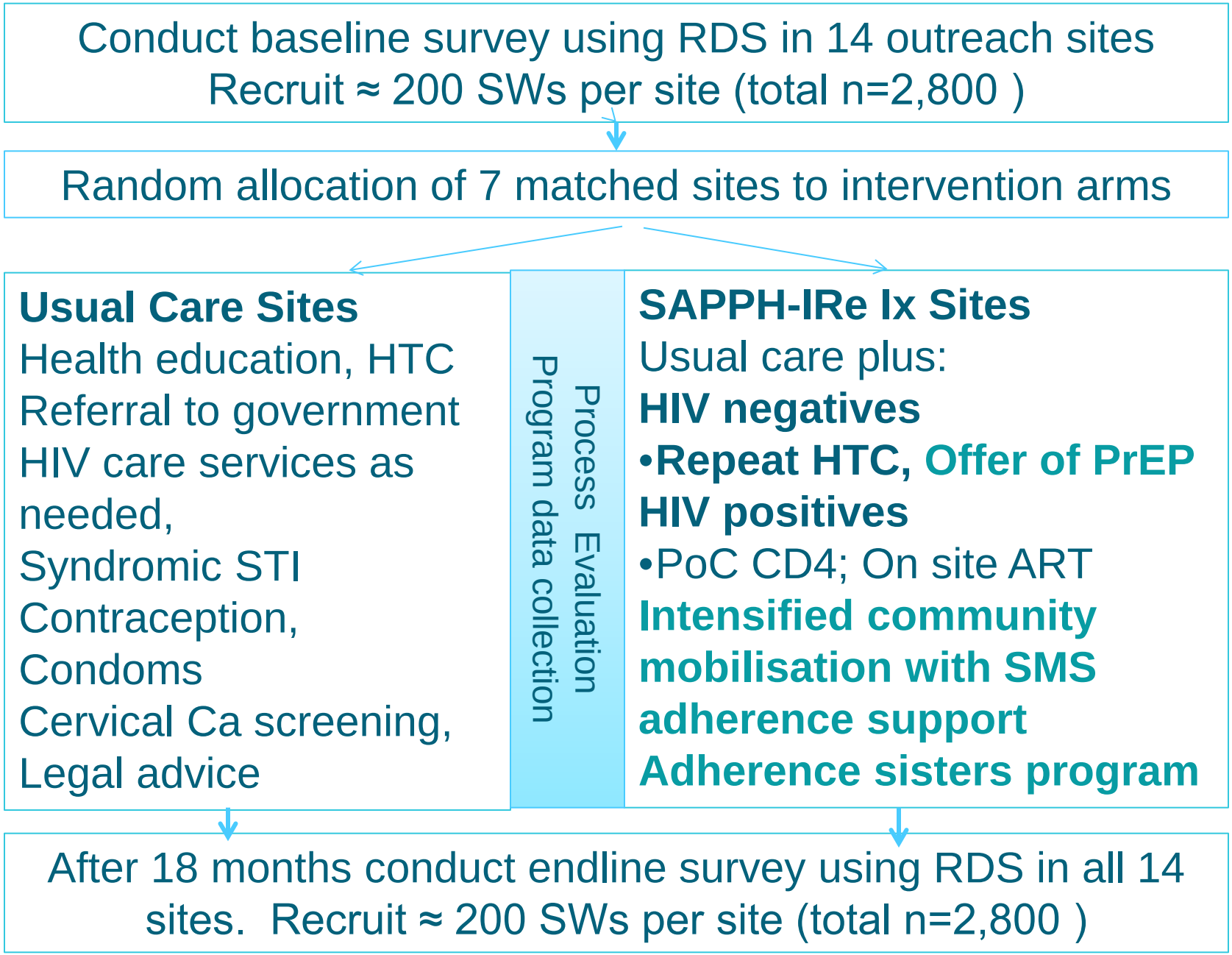
SAPPH-IRe

Sisters Antiretroviral therapy Programme for Prevention of HIV

an Integrated Response

Goal: to reduce the % of SWs living in communities with viral load > 1000 copies/ml




Conduct baseline survey using RDS in 14 outreach sites
Recruit ≈ 200 SWs per site (total n=2,800)
Random allocation of 7 matched sites to intervention arms
Usual Care Sites
Health education, HTC
Referral to government HIV care services as needed,
Syndromic STI
Contraception,
Condoms
Cervical Ca screening,
Legal advice
Process Evaluation
Program data collection
SAPPH-IRe Ix Sites
Usual care plus:
HIV negatives
•Repeat HTC, Offer of PrEP
HIV positives
•PoC CD4; On site ART
Intensified community mobilisation with SMS adherence support
Adherence sisters program
After 18 months conduct endline survey using RDS in all 14 sites. Recruit ≈ 200 SWs per site (total n=2,800)

Support for PrEP uptake and adherence - SAPPH-IRe sites

General support

- Enhanced community mobilisation
- Specific CM sessions
  - testing
  - linking to care
  - PrEP
  - Adherence
- SMS reminders
- Active follow up

Adherence Sisters Programme

- ART and PrEP users together
- Women nominate their Sister
- Monthly training as a group with their Sister – non-disclosing
  - What Is being an adherence sister all about?
  - Your Thoughts, Feelings and Behaviour
  - Choosing Your Thoughts
  - Supporting your Sister

High initiation and adherence among high risk African HIV-1 serodiscordant couples in a demonstration project of PrEP and ART for HIV-1 prevention

Early results from the Partners Demonstration Project

Renee Heffron, Connie Celum, Nelly Mugo, Elly Katabira, Elizabeth Bukusi, Stephen Asiimwe, Kenneth Ngure, Nulu Bulya, Josephine Odoyo, Edna Tindimwebwa, Deborah Donnell, Jessica E. Haberer, Lara Kidoguchi, Jennifer Morton and Jared M. Baeten

PARTNERS DEMONSTRATION PROJECT

USAID FROM THE AMERICAN PEOPLE
PEPFAR
UNIVERSITY OF WASHINGTON INTERNATIONAL CLINICAL RESEARCH CENTER
BILL & MELINDA GATES foundation
NATIONAL INSTITUTES OF HEALTH

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.

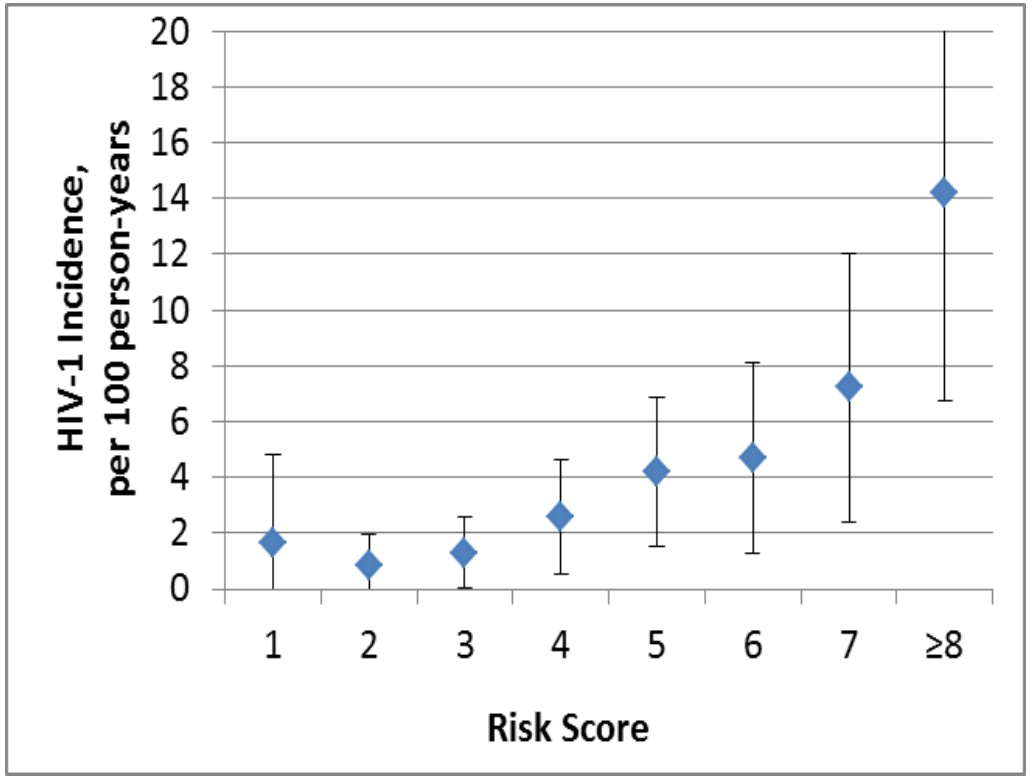
5. Assess **factors influencing preferences, uptake and adherence** for antiretroviral-based HIV-1 prevention.

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

PARTNERS PrEP STUDY

Kahle et al JAIDS 2013

Methods

- At enrollment, HIV-1 uninfected partners have adequate renal function, are not infected with Hepatitis B, are not pregnant or breast feeding, and are not using PrEP
  - Follow up visits include HIV-1 testing, screening for acute HIV-1 symptoms, PrEP refills, and 6-monthly creatinine screening
  - PrEP adherence assessed by clinic pill counts, MEMS caps, and tenofovir testing in plasma in a random 15% sample of participants
- At enrollment, HIV-1 infected partners are not using ART
  - 6-monthly CD4 and viral load monitoring
  - ART initiation is encouraged based on national guidelines

Lab Testing

- Serum creatinine- screening, month 1, 6 & 18
- HIV serology- quarterly
- HBV surface antigen – screening
- Urine pregnancy – screening
- Substudy of monthly HIV self-testing

Methods

- The study is ongoing; enrollment is complete
- Total couples enrolled = 1013
- Total follow up time accrued = 440 person years (22% of total time expected)

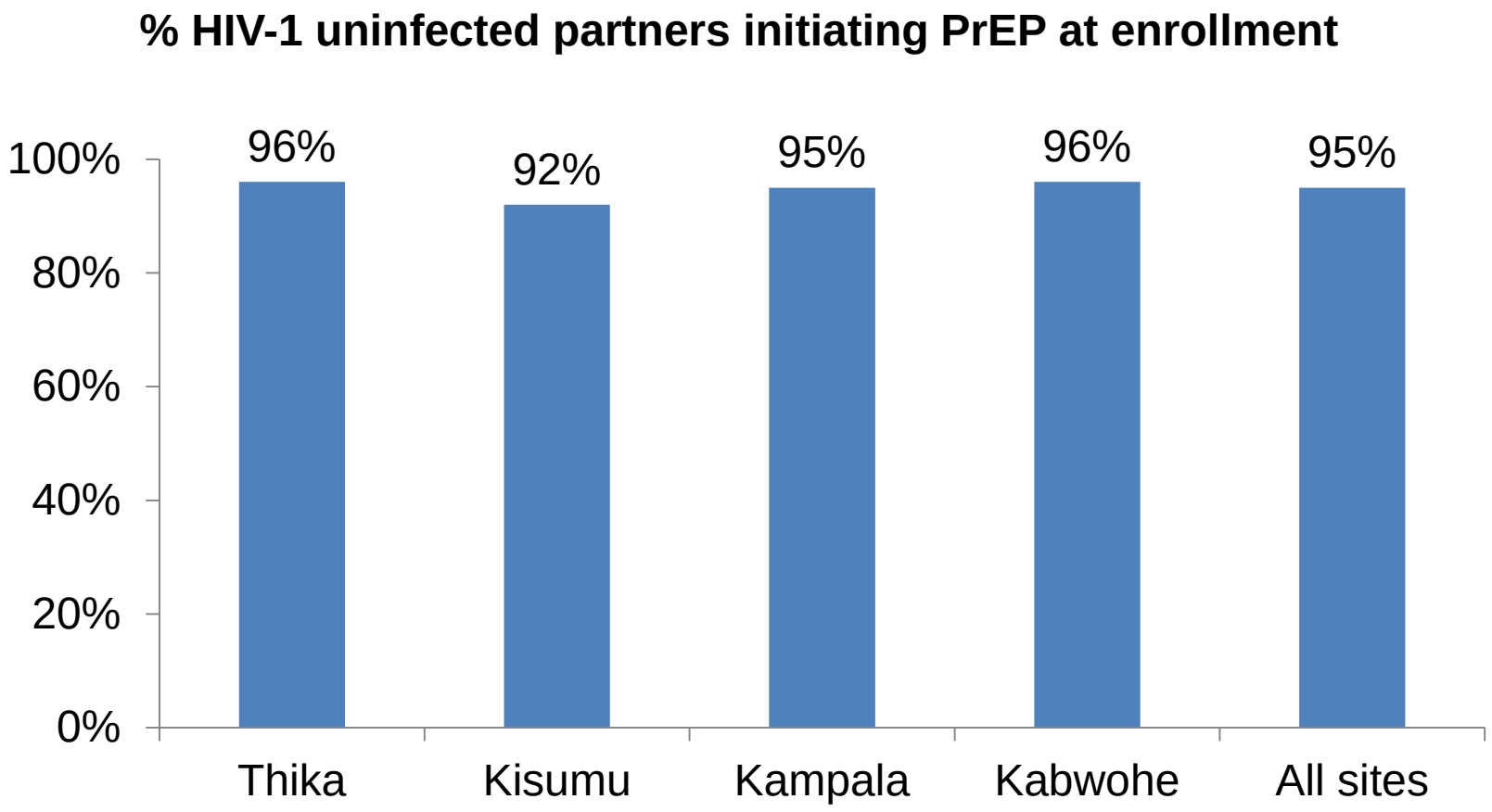
Participant characteristics

N=1013 HIV-1 serodiscordant couples	
HIV-1 infected partner is female (% of couples)	67%
Age of HIV-1 uninfected partners (Median, IQR)	30 (26-36)
Age of HIV-1 infected partners (Median, IQR)	28 (23-35)
Children within the couple (Median, IQR)	0 (0-1)
Years living together (Median, IQR)	2.5 (1-7)
Years aware of HIV-1 serodiscordant status (Median, IQR)	0.1 (0.1-0.3)
Any unprotected sex between study partners, month prior to enrollment (% of participants)	65%
Viral load of HIV-1 infected partner (Median, IQR)	4.6 (3.8-5.0)

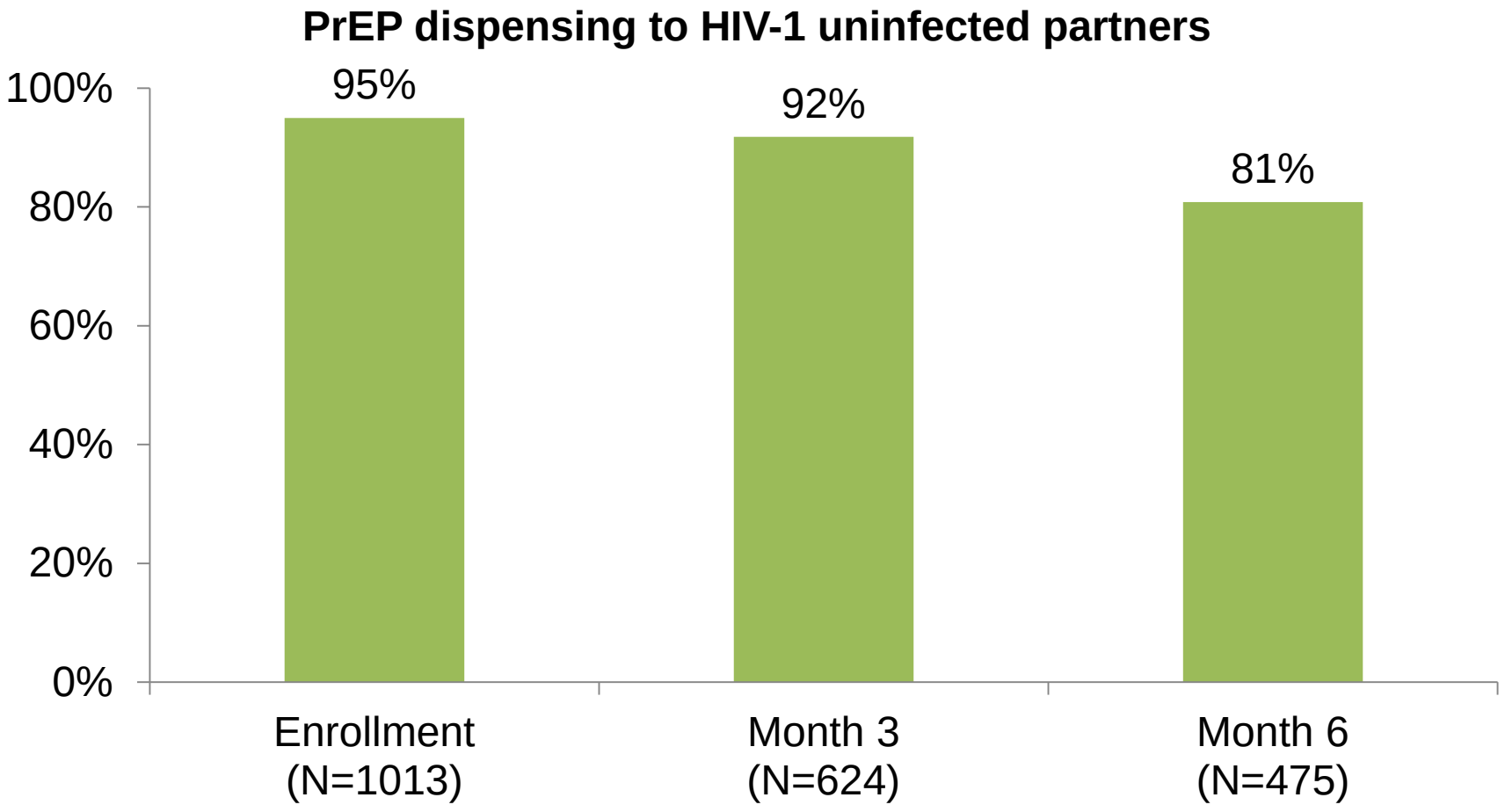
Partners Demonstration Project: High demand among high risk couples

- 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

PrEP initiation



PrEP adherence – pill dispensing



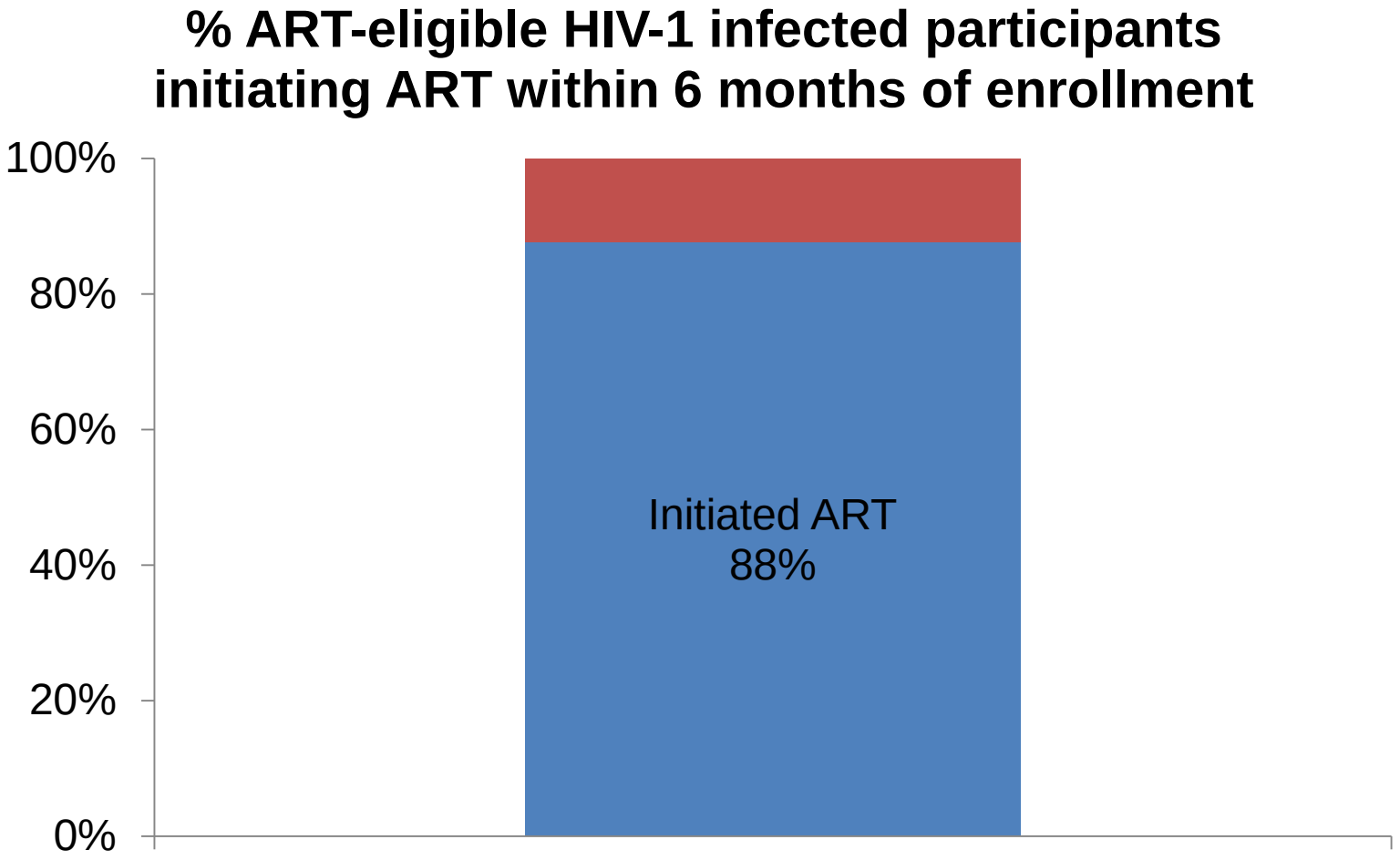
PrEP adherence

% HIV-1 uninfected participants taking ≥80% of expected PrEP doses		
	MEMS cap	Clinic pill counts
Enrollment to Month 3	75%	87%
Month 3 to Month 6	74%	88%

PrEP adherence – tenofovir detection

Results from tenofovir testing among HIV-1 uninfected participants dispensed PrEP		
Samples tested	Detectable tenofovir	Undetectable tenofovir
168 (from 74 participants)	86%	14%

ART initiation



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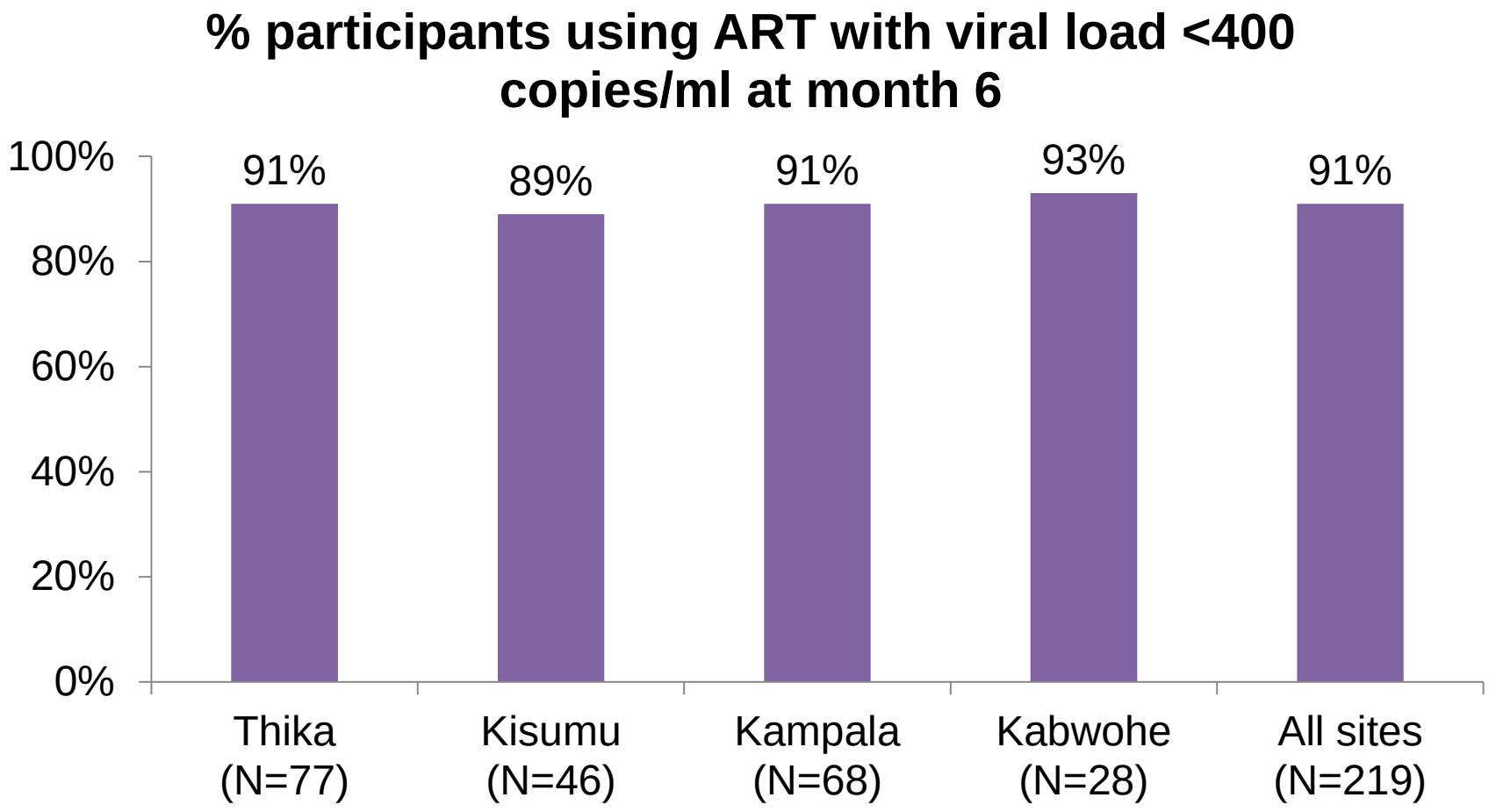
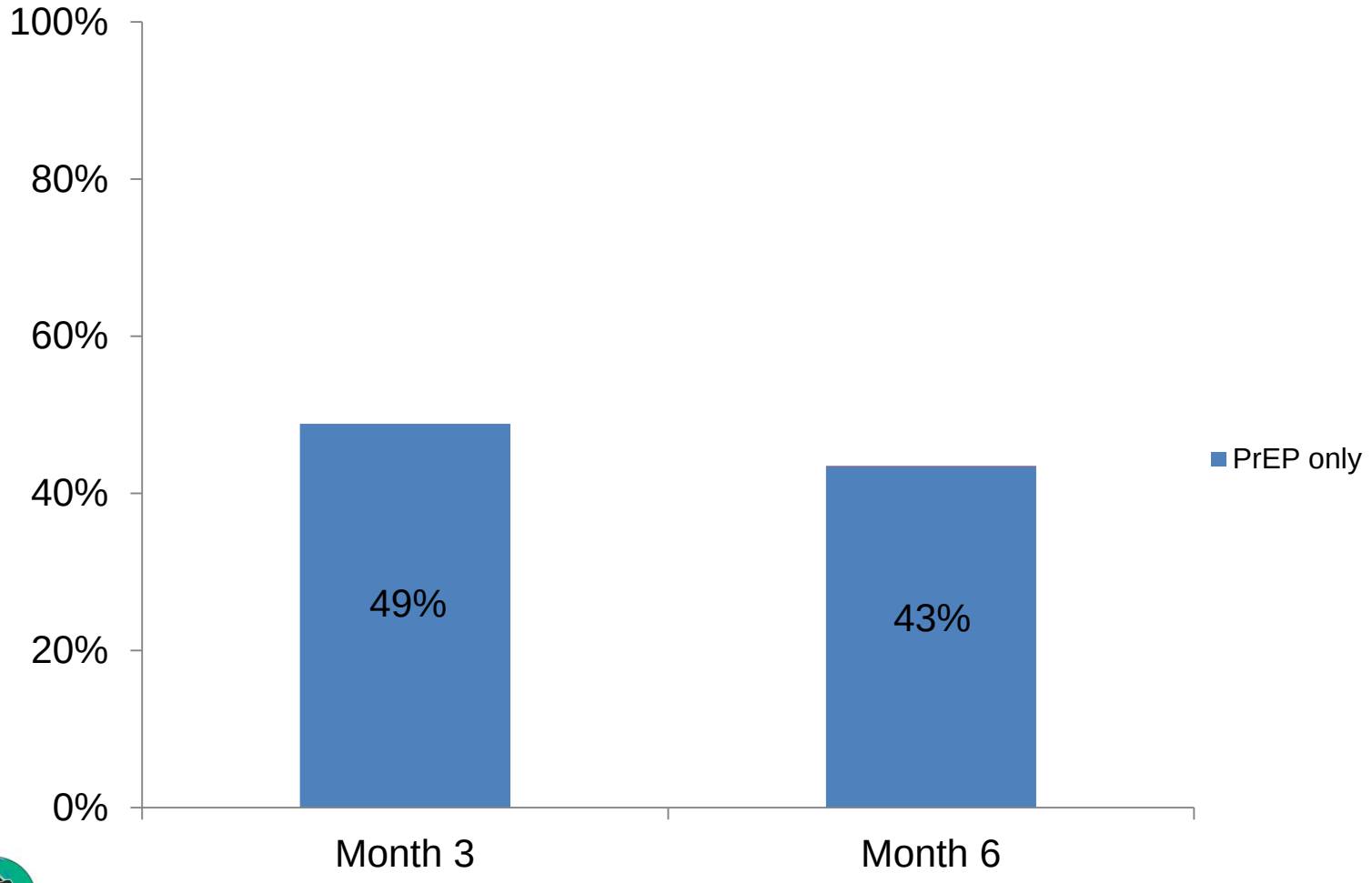
ART adherence



Couple-level PrEP and ART use



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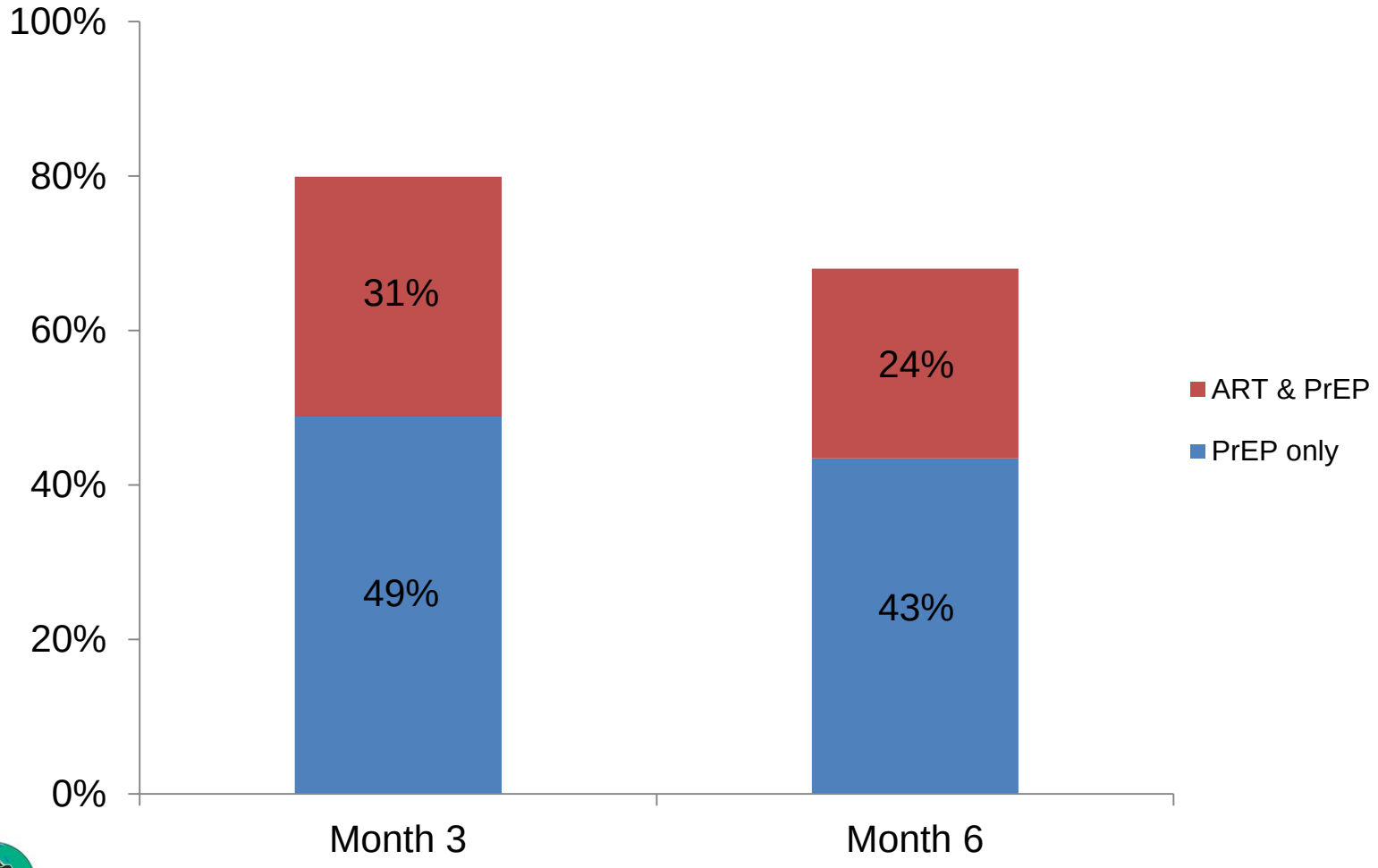
Couple-level PrEP and ART use



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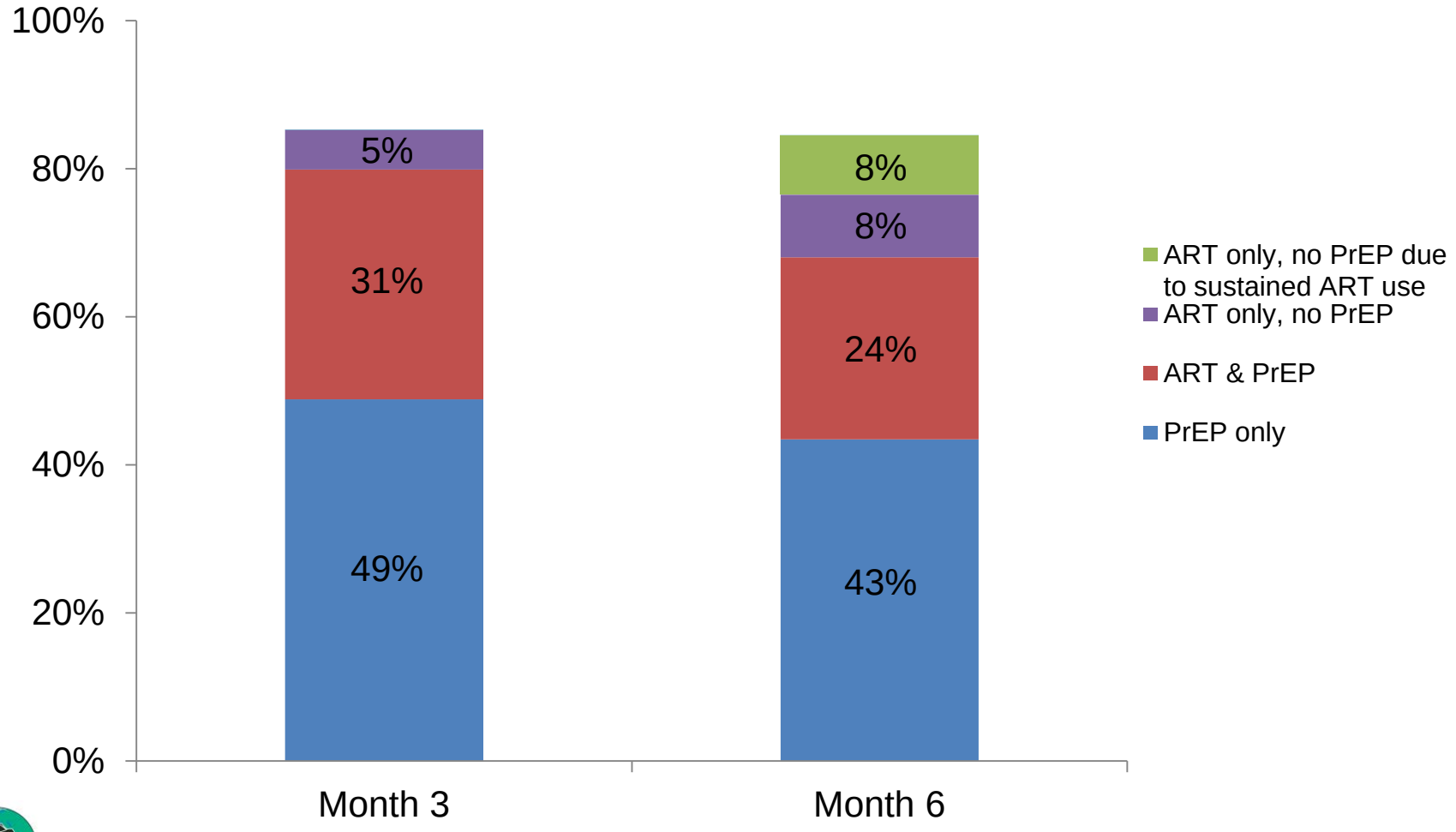
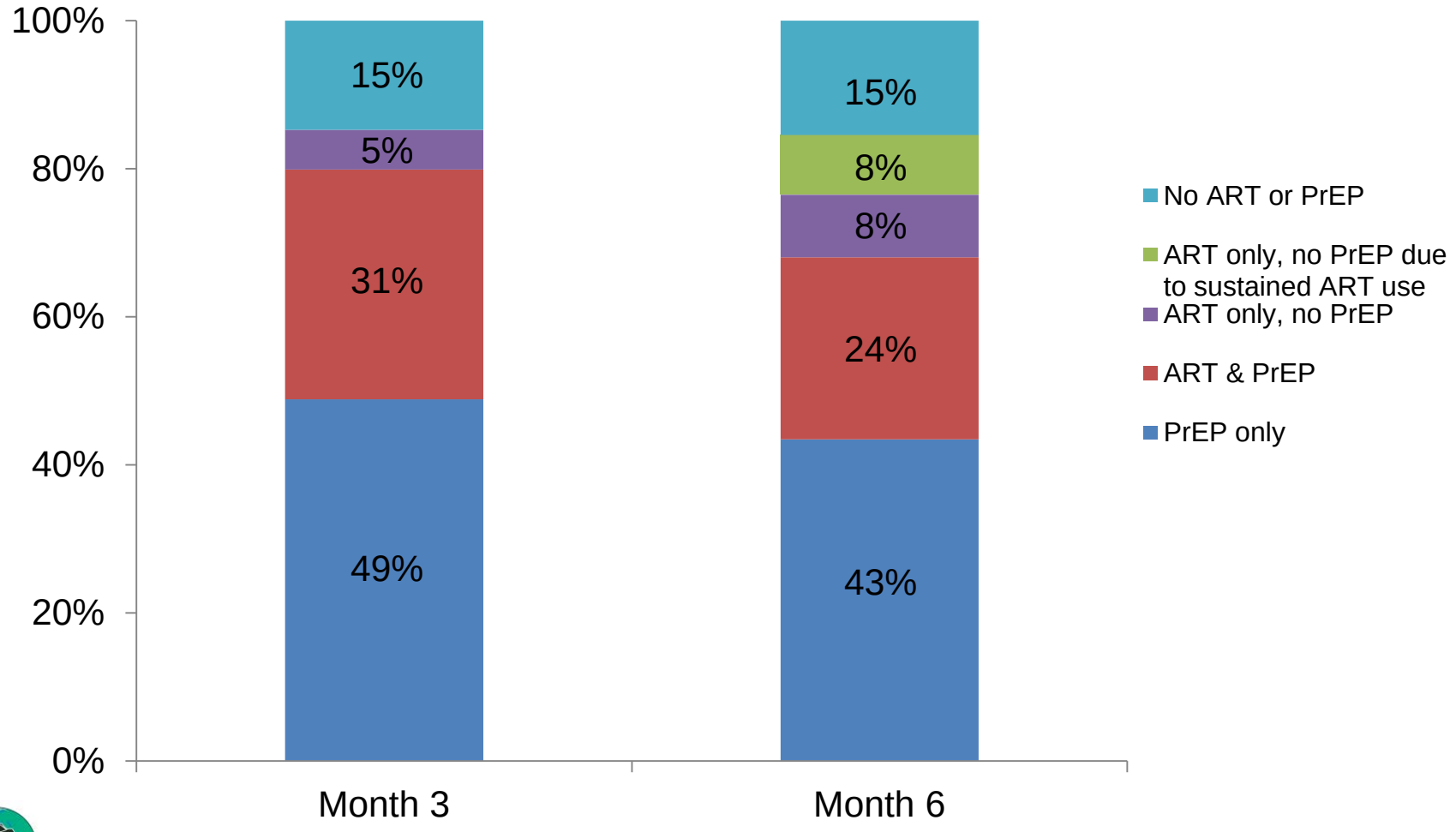
Couple-level PrEP and ART use



Couple-level PrEP and ART use



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Summary

- Initial PrEP uptake is high and PrEP use appears to be sustained among people who start and have ongoing HIV-1 risk
- ART initiation is high among people with clinical indications; ART adherence is high among those who start
- After 6 months in the study, most couples are protected by PrEP and/or ART
- Further follow up will provide greater understanding of couple choices around PrEP and ART use

Partners Demonstration Project Team

Thank you to the research participants

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, ICRC Operations, Data and Administration teams
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- 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)

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

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