Improving PrEP uptake and persistence by offering choice of interventions and tools best suited for specific populations

Science Generation Breakout Session 1

27 September 2023

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The task ahead

HPTN Regional Meeting

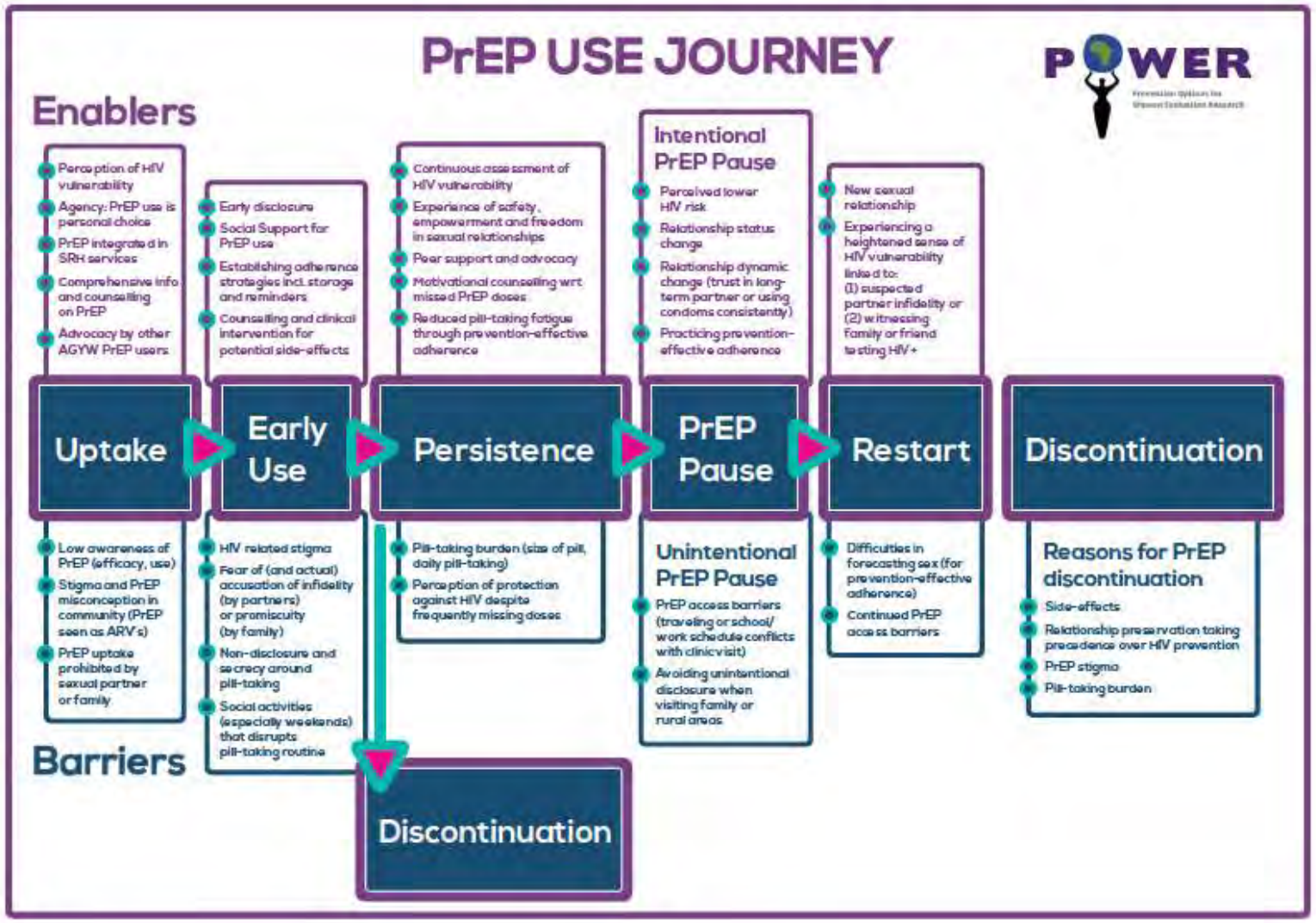
1. Review gaps in the research agenda,
2. Review the work that has already been done by the HPTN and in the larger HIV prevention field, and
3. Generate research proposals for leadership consideration and potential future protocol development.

2 hours today + 1 hour tomorrow

The 3 challenges in PrEP success!

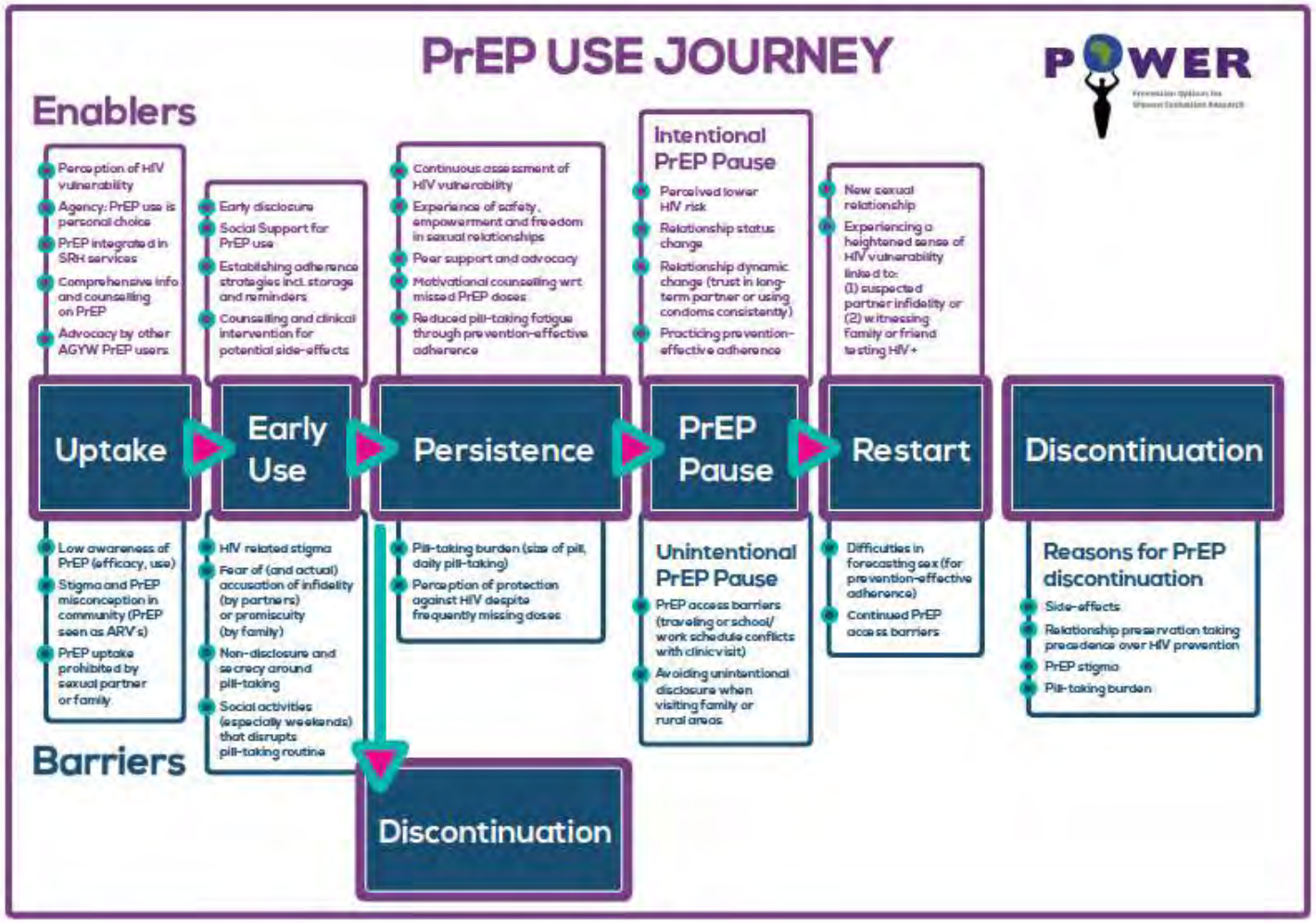
- Uptake
  - appropriate use
- Effective use
  - drug levels at time of exposure
- Persistence
  - sticking with prevention

For the PrEP user:



Rousseau E, et al. Adolescent girls and young women's PrEP-user journey during an implementation science study in South Africa and Kenya. PLoS One. 2021 Oct

And even then – it isn't feasible for everyone



...I have hidden them [PrEP pills], so no one knows about them, so if I forget to take them, there won't be anyone to remind me…

(TGW, 28 years, inconsistently adherent).

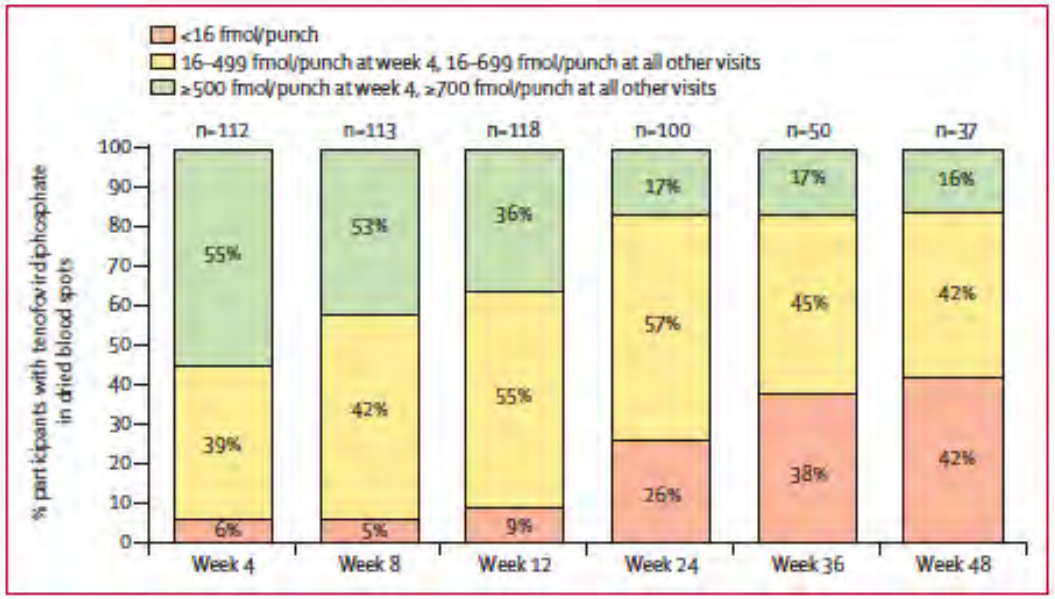
Kimani et al., 2021, Plos One

Challenges with effective use – *everywhere, but especially amongst the young*.

148 adolescents (15-19 years) in 2 RSA cities

- Monthly visits until week 12 and then quarterly visits until week 48
- As visit frequency decreased, so did adherence

55% had FTV-DP levels consistent with >4 pills/week in week 4 – dropping to 16% in week 48



Gill K, et al Lancet child adol 2020

POPULATION	ADHERENCE
Young MSM (12-22 yrs), US *Hosek et al., 2017, JAIDS*	FTV-DP levels consistent with >4 pills/week • Wk 4: 56% • Wk 48: 34%
TGW & MSM, Sub-Saharan Africa *Kimani et al., 2021, Plos One*	Any FTV-DP detected at 24 wks (6 months) • TGW: 62.5% (5/8) • MSM: 14.7% (5/34)
Population assessment in rural Uganda & Kenya (SEARCH Study) *Koss et al., 2020*	• 1/3 had drug concentrations consistent with poor adherence • Young people & women showed lower odds of [PrEP] consistent with daily dosing
HPTN 083 – TGW & MSM (subset of participants – 372) *Landovitz RJ et al. AIDS 2020, #OAXLB01*	Overall: 76.1% showed TFV-DP levels consistent with > 4 doses/week Plasma TFV levels • 87% >10 ng/ml • 75% >40 ng/ml

Parallel Universes/Journeys

Multiple decisions for a client before selecting which option best suits them today

Providers & Health Systems

- Who is at risk?
- Where do I find them?
- When I can test them?
- What do I tell them?
- Where can I provide px info and products to them?
- What px options can I provide them?
- Oral, ring, injectable, condoms, DPP?

Users

- What do I want?
- Who do I want to talk with about sex and relationships?
- Do I want an HIV test?
- Where do I want to get an HIV test?
- Do I need and want HIV prevention?
- What kind of HIV px do I want?
- Oral, ring, injectable, condoms, DPP? — Choice
- Where and from whom do I want it? — Choice

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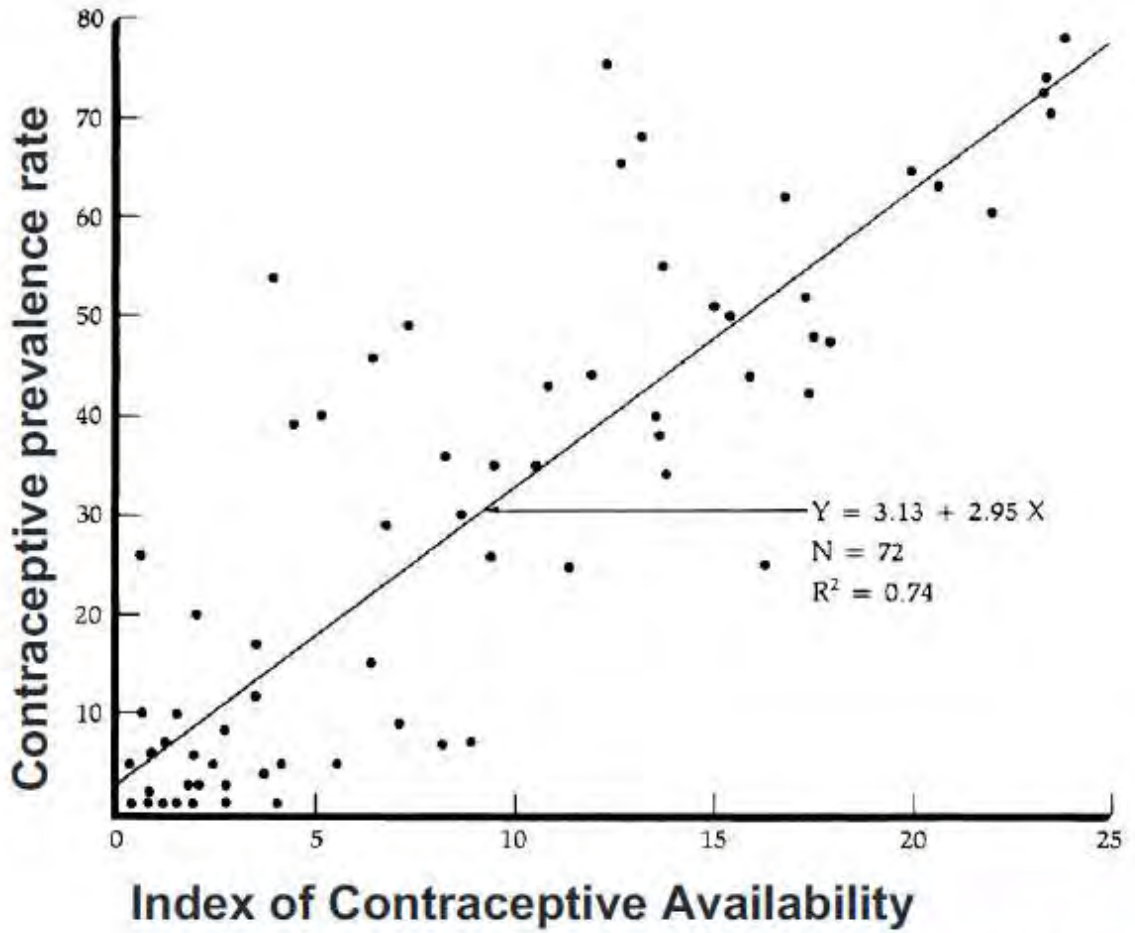
Choice Matters

- WHO systematic review (231 articles) showed increased choice associated with:
  - **Increased persistence** on chosen method
  - **Better health outcomes**
  - **12% increase in contraceptive prevalence for each additional method**
- Similar to contraceptive needs: different people have different HIV prevention needs at different times



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OFFERING *CHOICE*

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Having PrEP options *available* isn't the same as making a *choice*

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- Decision making process varies
- Special considerations for adolescents and pregnant people result in more intense process for offering PrEP

Awareness

Tailored communication strategy for exchange of info (format, provider, messaging)

PLATFORM?
WHO?
WHERE?
DEMAND CREATION?

PrEP Offer

Once full comprehension of HIV prevention, contraception, and different PrEP options

CLIENT READY?
ENABLING ENVIRONMENT?
PROVIDER BARRIERS?

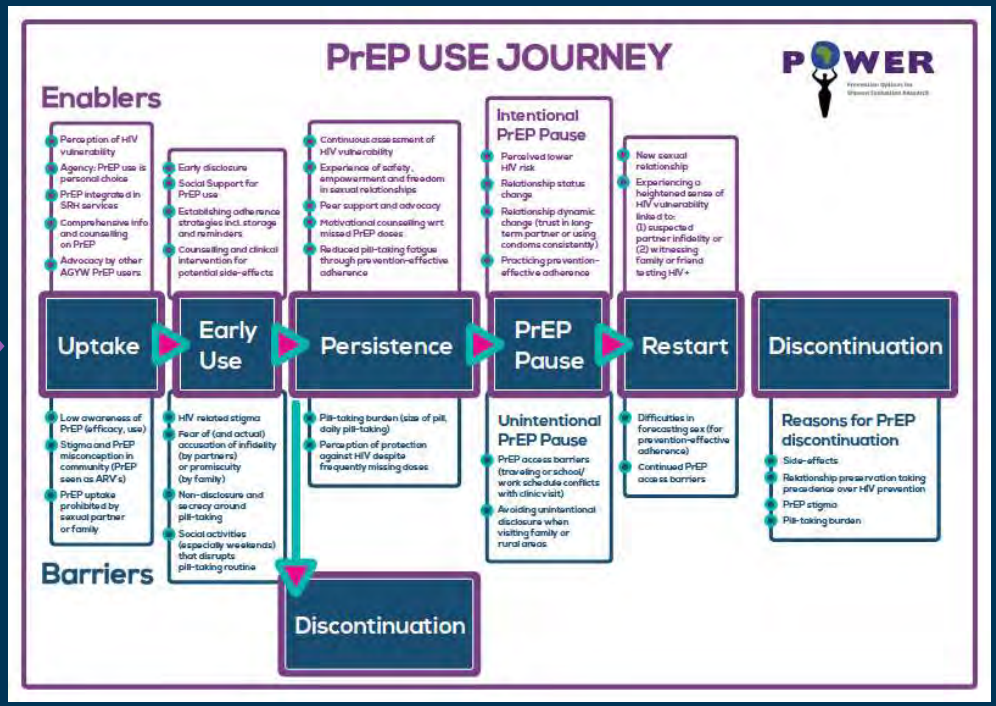
Contemplation

Influenced by peers, parent/guardian, child's father.

WHO?
HOW TO SUPPORT?

Decision

Relatively less info about safety may lead to uncertainty. Influenced by provider



WHEN AND HOW TO REVISIT CHOICE?

Gaps in the prevention field

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- Can PrEP be integrated in family planning and youth centers and be delivered along with reproductive health, GBV, STI prevention and treatment, mental health, and couples-based interventions for AGYW?
- Behavioral interventions provided to increase uptake and adherence to PrEP among AGYW.
- Targeting HCPs and providers of PrEP as component of or standalone studies (person-centered support, joint decision making/choice, value clarification/stigma, effective service delivery).
- Understanding “seasons of risk” and short-term regimens consistent with changing sexual behavior, and particularly exploring measurement issues around season-driven (women) or event-driven (men) PrEP and assessing preventive-effective adherence.
- Offering and supporting informed choice to pregnant and/or lactating persons.
- Approaches to de-medicalized prevention (including self-care) and differentiated delivery.
- Understanding impact of choice on uptake and adherence, product switching.

What has the HPTN already done?

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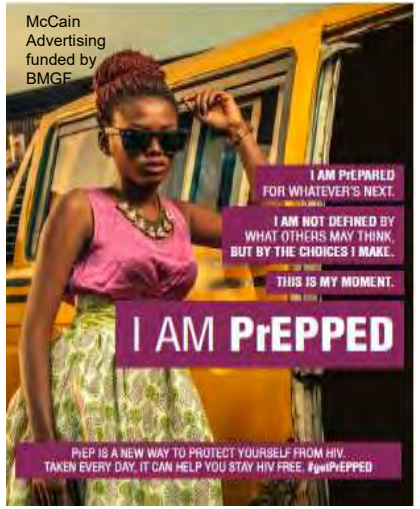
- HPTN 094 is testing whether mobile service delivery of an integrated prevention and treatment package of interventions (incl PrEP) can increase uptake and adherence among PWID.
- HPTN 107/DMID 19-0004 is evaluating the Bexsero meningococcal vaccine for prevention of gonococcal infection in collaboration with IDCRC (US and possibly Malawi).
- HPTN 112 is providing a systems-navigator delivered integrated prevention package in heterosexual men at STI clinics.
- HPTN 113 will evaluate PrEP and DoxyPEP uptake in young Latino SMM facilitated by a number of apps.

PrEP trials – how did they do?

Intervention name	Implementation outcome	Findings
HPTN 082[27 36]	Adoption	95% initiation rate
	Sustainability	20.9% continuity rate at 6 months (overall); I—20.1%; C—21.7%; adjusted OR 0.92, 95% CI 0.55 to 1.34, p=0.76
POWER Cohort study[37 38]	Adoption	94% initiation rate
	Sustainability*	20% continuity rate at 6 months. 14% restarted PrEP
	Feasibility	Private youth-friendly clinics were a better fit than family planning clinics for PrEP
	Penetration	Adoption by non-study staff was low because PrEP was perceived to be outside their work
DREAMS[39 40]	Adoption	PrEP initiation; I—28.1%; C—0.6%; Adjusted OR 63.82, 95% CI 19.78 to 205.90; p<0.001
DREAMS[41]	Adoption	0% initiation rate. PrEP awareness increased from 2% in 2017 to 9% in 2018.
MPYA Trial[42 43]	Sustainability*	26.8% adherence rate at 24 months (overall); with SMS reminders—27.0%; without SMS reminders—26.7%; adjusted IR 1.16, 95% CI 0.93 to 1.45, p=0.19
3Ps for Prevention Study[44 45]	Adoption	56.4% were 'definitely interested' in taking PrEP after watching the PrEP social marketing campaign video
	Sustainability*	56% in incentive group and 41% in control group had TFV-DP levels≥700 fmol/punch at month 3; RR 1.35;95% CI 0.98 to 0.067, p=0.067

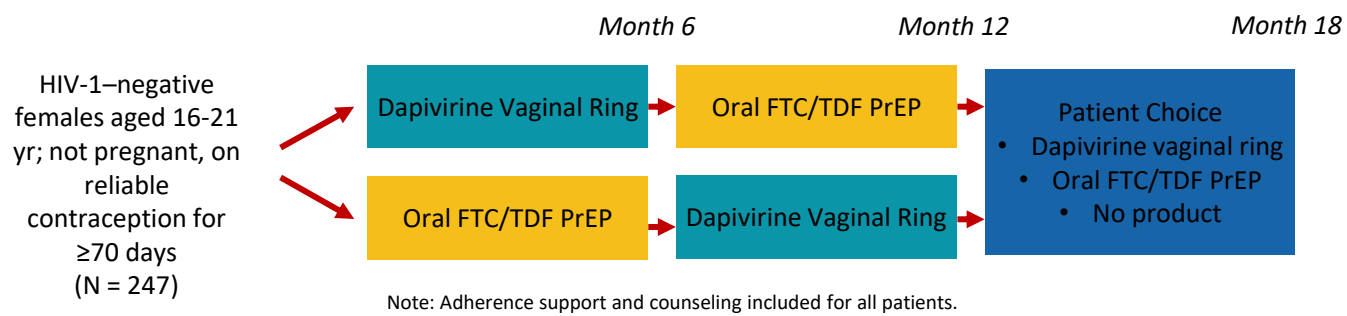
*Sustainability was defined as continuation or commitment to PrEP use whether measured objectively (eg, detectable Tenofovir-Diphosphate TFV-DP levels >700 fmol/punch) or via a proxy (eg, retention in care or refill after 1 month).
C, control; DREAM, Determined, Resilient, Empowered, AIDS-free, Mentored and Safe; HPTN, HIV Prevention Trials Network; I, Intervention; IR, Incidence Ratio; MPYA, Monitoring Pre-Exposure Prophylaxis for Young Adult Women (MPYA); OR, Odds Ratio; POWER, The Prevention Options for Women Evaluation Research; RR, relative risk.

Ekwunife et al., 2022, BMJ Global Health



(MTN 034) REACH

Randomized, open-label, phase IIa crossover study



Note: Adherence support and counseling included for all patients.

- Endpoints: safety (AEs ≥ grade 2), adherence, acceptability, preference

Adherence	DPV (Rate Based on No. Returned Rings)	FTC/TDF (Measured via Dried Blood Spots)
High	≥0.1071 mg/day	≥4 doses/wk (>500 fmol/punch at Wk 4, >700 fmol/punch at Wk 8)
Medium	0.0321- <0.1071 mg/day	~1-3 doses/wk (16.6-499 fmol/punch at Wk 4, 16.6-699 fmol/punch at Wk 8)
Low	≤0.0321 mg/day	No drug detected (<16.6 fmol/punch)

Nair. IAS 2021. Abstr OALC01LB01.

Acceptability of longer-acting, alternative methods

ADOLESCENTS & YOUTH

Gill et al., 2020

UChoose: acceptability and preference of adolescents (n=180, 15-19 yrs) in Cape Town for proxy HIV prevention methods using contraceptive – oral, ring, and injection (*open-label, cross over design)*

- Order of preference: injection, ring, the pill
- Injection was found by 96.3% to be the most convenient
- More ring users request to change to other option – but those who stayed on the ring had higher adherence than the pill (p<0.0001).

PREGNANCY & POST-PARTUM

Wara et al., 2023

Survey (2021-2022) amongst pregnant and post-partum women in SA and Kenya on PrEP attitudes and preferences.

- 75% current oral PrEP use – 49% reported negative attributes (side effects + pill burden).
- 75% preference for injectable over oral (long term efficacy + discretion).
- Predictors of preference: injectable contraceptive use, disliking one attribute of oral PrEP, or preference for infrequent PrEP use.

MEN (Incl. MSM)

Montgomery et al., 2021

DCE to assess preferences for long-acting PrEP amongst young men (18-24 yrs) in Cape Town – incl. 47% MSM.

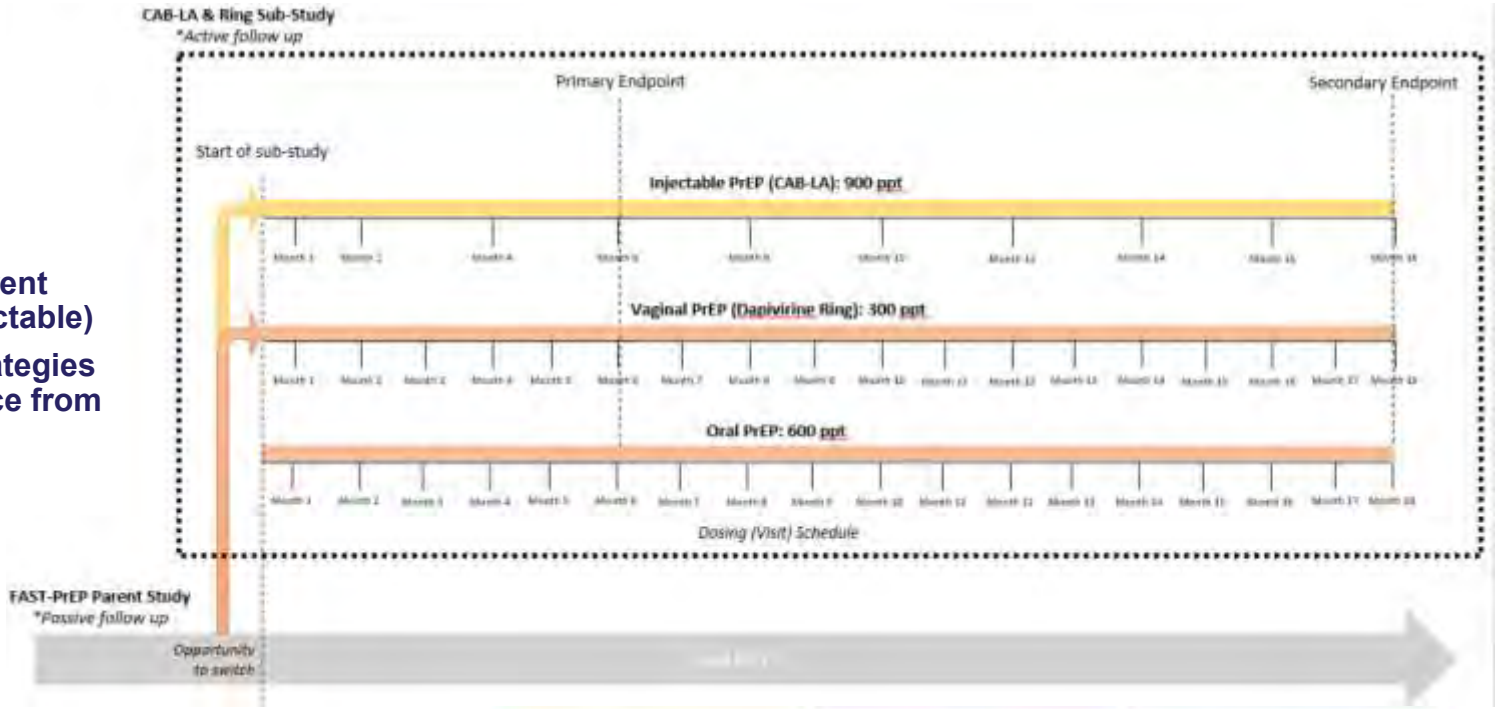
- Duration was the most important attribute – preference for something longer like an implant over an injection
- MSM more likely to prefer injection

Importance of product choice!

PrEPared to Choose study: an example of a choice experiment

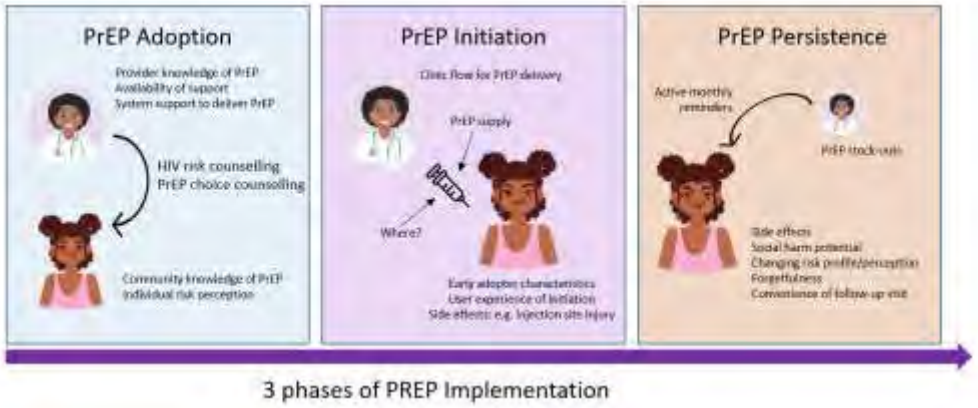
Substudy objective:

1. **PrEP persistence patterns across different PrEP modalities (vaginal, oral, and injectable)**
2. **identify successful implementation strategies that will aid the provision of PrEP choice from multiple delivery platforms.**



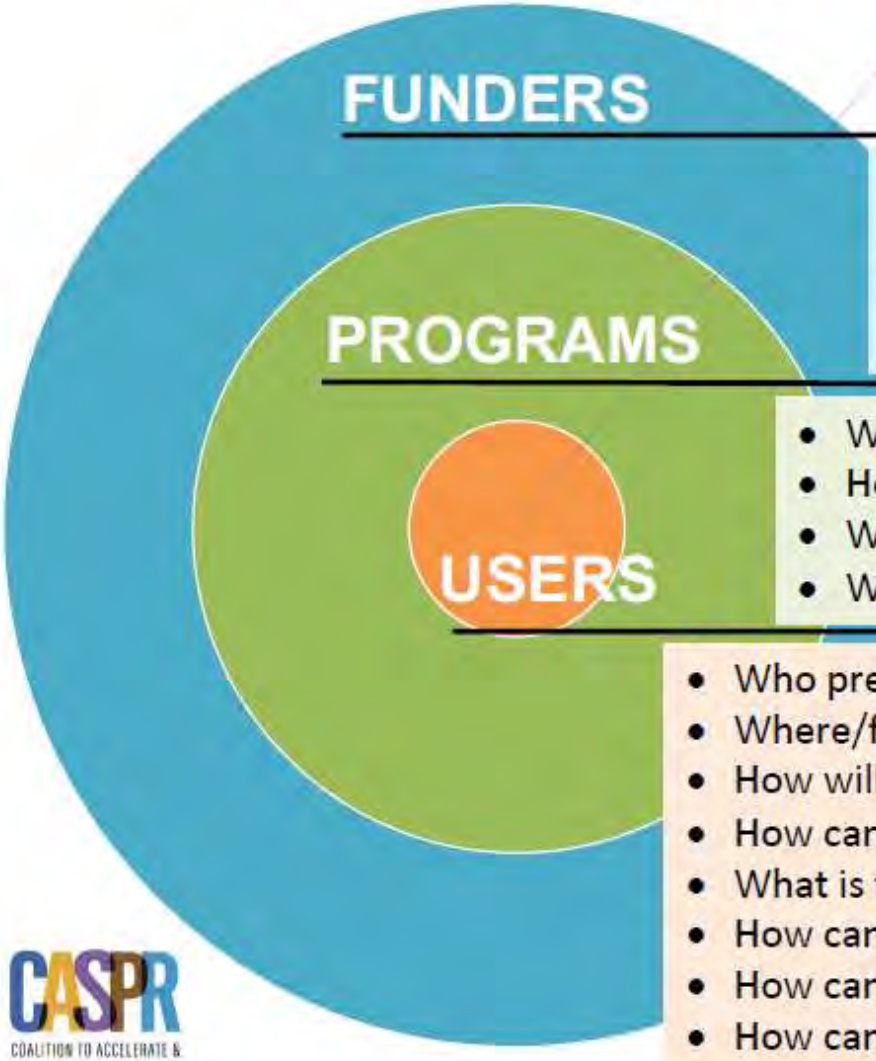
Participants:

- 1200 adolescent girls and young women *(15-29 years)*
- 300 young key populations (MSM, sex workers) *(15-29 years)*
- 300 intimate male partners *(any age)*



Accelerating Introduction of New Prevention

Those who Use; Those who Choose; Those who Pay the Dues



What we need to know – and fast

FUNDERS

- What is the cost for procurement AND for programming?
- What is the cost-effectiveness?
- What is the market size, generally and relative to other PrEP products?
- How will introduction affect the current market share and size of other PrEP?

PROGRAMS

- What policies need to change to plan for & introduce new option?
- How to overcome siloes in procurement & service delivery?
- What type of training & support do providers need?
- What are optimal service delivery platforms and communication channels?

USERS

- Who prefers which option, and what are their motivators and barriers?
- Where/from whom do potential users desire to hear about and access product?
- How will product use/preference change over time?
- How can we increase & support adherence?
- What is the end user's path to initiation and continued, effective use?
- How can peer groups/influencers be leveraged to support uptake & adherence?
- How can providers be supported to have more knowledge and empathy?
- How can the product be packaged to better support uptake/ adherence?

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SCHEMA (1 OR 2)

- Title
- Purpose
- Design
- Population
- Region/Location
- Regimen/intervention
- Study duration
- Primary objectives (1 or 2)
- Endpoints

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Strategies for prioritization

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- Clearly define your primary objectives, endpoints and measurable data.
- Consider proposals that are inclusive of multiple sites.
- Ensure alignment with HPTN specific aims:
  - Long-acting antiretroviral (ARV) agents and novel delivery systems for pre-exposure prophylaxis (PrEP)
  - Multipurpose prevention technologies (MPTs) that concurrently prevent HIV and pregnancy, sexually transmitted infections (STIs) or opioid dependence
  - Broadly neutralizing antibodies (bnAbs), alone and in combination, for PrEP
  - Integrated strategies for HIV prevention
- Consider ideas consistent with the epidemiology of HIV and gaps in knowledge regarding HIV transmission.
- Consider ideas that advance research that would have impact on the HIV epidemic.
- Consider ideas that build on vanguard studies already conducted or ongoing by the HPTN.
- Consider large, multi-site studies or smaller pilot studies that lead to larger studies

Way of doing this……

- Collaborative brainstorm
  - Everyone raises at least one possible idea- rapid brainstorm
  - See what ideas and rank in order of most feasible/preferred
  - Flesh out details in smaller groups
  - bring it all back asap

Thank you

@HIVptn

HPTN Regional Meeting

Adolescents at Risk SC – Audrey Pettifor, Linda-Gail Bekker (Sinead Delany-Moretlwe)

HPTN HIV Prevention Trials Network

- CHOICE: interventions and tools to help AGYW and providers choose the best method for them with the goal of improving PrEP persistence
- MEASUREMENT: how to better measurePrEP covered events for AGYW. Sex can be sporadic- how to measure use aligned with sexual activity better.
- IMPLEMENTATION: how to getPrEP out of clinics for healthy, uncomplicated cases- delivery out of clinic could improve persistence
- PLUS: combination prevention is not just putting PrEP in family planning clinics or STI clinics. Requires combining PrEp with interventions that address structural and behavioral barriers to HIV prevention (e.g. interventions focusing on GBV, poverty, adherence, etc.)

Acknowledgments

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- The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Research Agenda

HPTN Regional Meeting

1	LA ARV agents and delivery systems	*Long-acting systemic ARV agents will facilitate adherence with PrEP, a major limitation to PrEP effectiveness.*
2	MPTs (pregnancy, STIs, dependence)	*HIV prevention products are likely to achieve greater and more durable coverage with more significant health impact if they have a broader prevention profile for specific populations*
3	bNAbs alone and in combination	*A combination of bnAbs, if proven to be safe, effective and scalable, would be an additional option to ARV-based PrEP*

AIMS 1-3 TEST NEW PrEP OPTIONS

THESE OPTIONS FEED INTO AIM 4 TO TEST DELIVERY APPROACHES (HOW, WHO, WHERE, WHEN, WITH WHAT ELSE)

4	Integrated Strategies	*Effective HIV prevention requires an integrated package of interventions tailored to the needs of populations at risk*

Specific Aims of the HPTN

HPTN Regional Meeting

1. To design and conduct studies of long-acting antiretroviral (ARV) agents and delivery systems for pre-exposure prophylaxis (PrEP)

Rationale: Long-acting systemic ARV agents will facilitate adherence with PrEP, a major limitation to PrEP effectiveness.

1a. To design and conduct Phase 1 and 2 studies to evaluate the safety, acceptability and pharmacokinetic/pharmacodynamic (PK/PD) characteristics of long-acting ARV agents and novel delivery methods.

1b. To design and conduct Phase 3 studies to evaluate the safety and efficacy of novel long-acting ARV agents for HIV prevention. These may be delivered orally, by injection or infusion, or via devices such as implants or microneedle patches.

1c. To design and conduct bridging studies to evaluate the safety and acceptability of long-acting ARV agents among specific populations such as adolescents and pregnant women.

2. To design and conduct studies to evaluate multipurpose prevention technologies (MPTs) that concurrently prevent HIV and pregnancy, sexually transmitted infections (STIs) or opioid dependence.

Rationale: HIV prevention products are likely to achieve greater and more durable coverage with more significant health impact if they have a broader prevention profile for specific populations.

2a. To design and conduct Phase 1 and 2 studies to evaluate the PK/PD, drug interactions and safety of MPT candidates (e.g., injectable, implants, patches, rings) for HIV and contraception, STIs or opioid dependence.

2b. To design and conduct Phase 3 studies to evaluate the safety and efficacy of an MPT for prevention of HIV and pregnancy which may be delivered by an injection, implant, microneedle patch or intravaginal ring.

2c. To design and conduct studies to determine the acceptability and adherence with a co-formulated TDF/FTC-contraceptive oral agent; as an attractive option for women seeking contraception and HIV prevention. A Phase 3 study may not be required as efficacy of each component is known.

Specific Aims of the HPTN

HPTN Regional Meeting

3. To design and conduct studies in collaboration with the HIV Vaccine Trials Network to evaluate broadly neutralizing antibodies (bnAbs), alone and in combination, for PrEP

Rationale: A combination of bnAbs, if proven to be safe, effective and scalable, would be an additional option to ARV-based PrEP.

3a. To design and conduct Phase 1 and Phase 2 studies to evaluate PK/PD, safety and the *ex vivo* viral neutralization activity of bnAbs with different specificities and binding sites.

3b. To design and conduct Phase 3 studies of a multi-target bnAb or combinations of bnAbs to evaluate their efficacy and safety for PrEP.

4. To design and conduct integrated strategies for HIV prevention

Rationale: Effective HIV prevention requires an integrated package of interventions tailored to the needs of populations at risk

4a. To design and conduct integrated strategies studies consisting of biomedical, socio-behavioral and structural interventions appropriate for priority populations at risk for HIV.

4b. To use diverse designs for integrated strategies studies including cluster randomization, factorial, and step-wedge to evaluate the effectiveness of package and individual components for HIV prevention.

4c. To identify geographic “hotspots” and clusters of HIV transmission using HIV recency testing, HIV molecular phylogeny and phylogeography, enabling focused HIV prevention interventions.

4d. To include robust process measures to determine reasons for success or failure of integrated HIV prevention strategies.

4e. To utilize mathematical modeling of data from integrated strategy studies to estimate impact at a population level