South Africa Stakeholder Consultation Summary and Key Comments

D2D Pillar 3
19 October 2022

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MATRIX
Advancing R&D of Innovative
HIV Prevention Products for Women

South Africa Stakeholders Consultation

- Was the first of three in-country consultations
- Took place in Johannesburg 5-6 October 2022
- Of 45 meeting participants, 27 were external stakeholders, including:
  - Representatives of the National Department of Health (NDoH)
  - CEO of South African Health Products Regulatory Authority (SAHPRA)
  - WHO representative
  - An ethicist
  - Young women advocates, including a member of the MOSAIC NextGen Squad
  - Former trial participants and PrEP users
  - Civil Society and seasoned advocates

Other attendees included 5 USAID representatives – 3 from the US and 2 based in South Africa, plus D2D Pillar 3 representatives and MATRIX investigators, accounting for an additional 10

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Meeting Objectives

1. Introduce MATRIX and describe its rationale and approach for accelerating early research and development of innovative HIV prevention products for women.
2. Sensitize stakeholders regarding the notion of early phase trials, including first-in-human studies, being conducted in Eastern and sub-Saharan Africa and discuss ways to mitigate potential community concerns.
3. Seek stakeholders' feedback on the MATRIX product pipeline generally with more in-depth discussions focused on those products closest to being evaluated in placebo-based acceptability studies (i.e., the 30-day dapivirine vaginal film and the non-antiretroviral/non-hormonal MPT vaginal ring), or in Phase I safety, PK/PD and acceptability studies (i.e., TAF/EVG fast-dissolving insert).
4. Establish a foundation for ongoing, bi-directional engagement through the lifecycle of the project and the product development lifecycle.

Agenda: Interactive Sessions and Deep Dives

- The agenda began with overviews of the current HIV prevention landscape, MATRIX, the research and development process and what's involved in conducting early phase studies, followed by interactive sessions and deep dives
- Interactive sessions made using of polling software (Audience Response System – ARS) to seek views regarding:
  - The need for additional HIV prevention options (besides oral PrEP, dapivirine ring and CAB-LA)
  - Different product classes (e.g., on-demand, MPTs)
  - The overall MATRIX pipeline
  - The notion of conducting early phase studies in SSA
- Deeper dives into:
  - TAF-EVG fast-dissolving insert and MATRIX-001
  - Monthly dapivirine vaginal film and MATRIX-002
  - MPT vaginal ring (LAMP-IVR)

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Is there a place for new methods and product formulations?

ARS results and sentiments expressed during the meeting

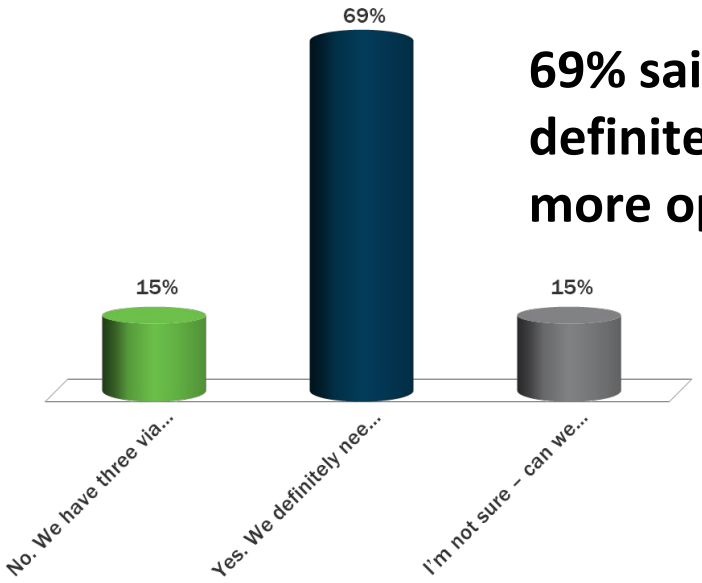
Are other options needed?

Daily oral PrEP, the monthly dapivirine vaginal ring and long-acting injectable cabotegravir are biomedical HIV prevention methods that have been approved and/or are under regulatory review in several countries. **Are other options needed?**

A. No. We have three viable options, and we should be focusing our efforts on seeing that they are made more widely available and ensuring counseling programs are in place to support their effective use

B. Yes. We definitely need more options. Women have different needs and preferences at different times in their lives.

C. I'm not sure – can we talk about this some more?



69% said Yes. We definitely need more options.

"*Little did we know that using oral prep for the long term would have effects on the kidneys and the liver, especially when you are also taking alcohol… I'm no longer using oral PrEP and I'm at risk of getting HIV. I do not have any options that suit my lifestyle.*" (Young woman and former PrEP user)

"Can we have more products that people, we can get over the counter and not have to go to the facility?"

(NDoH representative)

"A woman should not have to adapt her lifestyle to a product, the product should fit in her lifestyle."

(Clinical trial site community educator)

What about on-demand products?

Two of the products in the MATRIX pipeline are the kind of products that are sometimes referred to as “on-demand” because they are to be used at or around the time of sex. Both are fast-dissolving inserts that when placed inside the vagina release the active agent as it slowly dissolves. Women would insert these themselves. **What are your views regarding on-demand products for HIV prevention?**

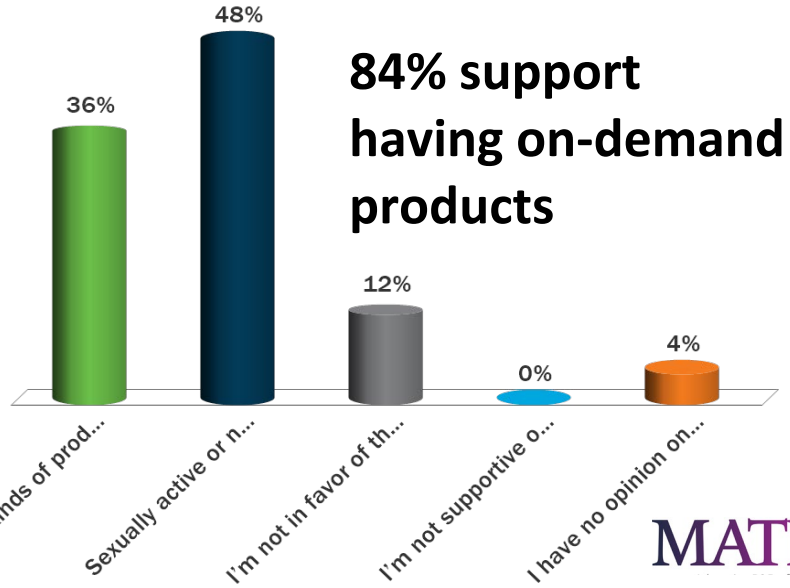
A. These kinds of products would be good for women who are only having sex occasionally and are likely to be preferred over a method needing to be used daily or that is long-acting.

B. Sexually active or not, there will be women who prefer not to use a systemic method, so an on-demand product might be an appealing option.

C. I’m not in favor of these so-called on-demand products because everyone should have protection all the time.

D. I’m not supportive of on-demand products for other reasons.

E. I have no opinion one way or another.



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"Sometimes we do not even have a choice to have sex, we need access to products that help us take charge of our own protection"

(Young woman advocate)

How long should on an-demand product provide protection against HIV?

A. 2 - 4 hours

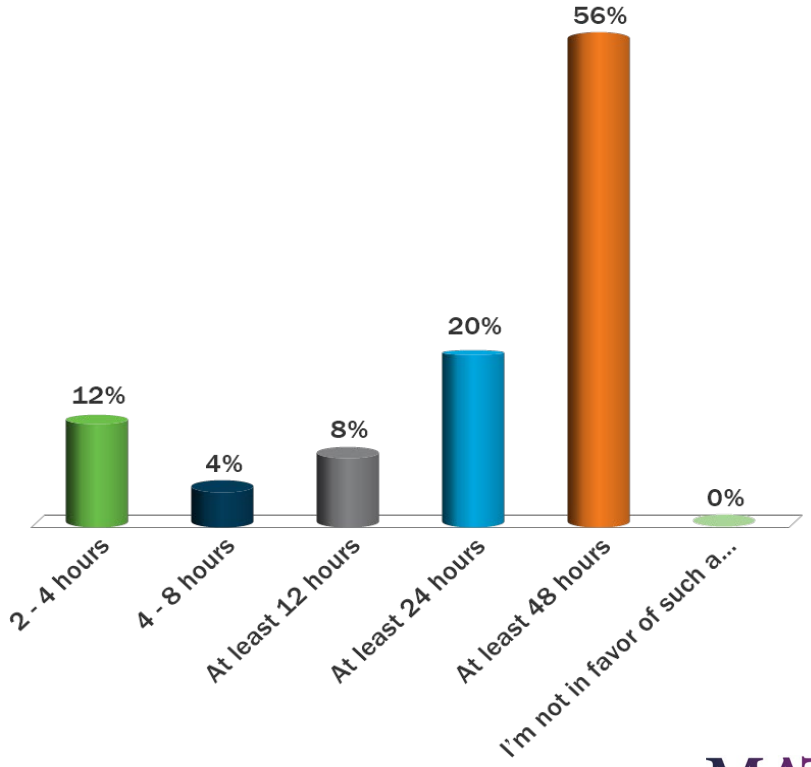
B. 4 - 8 hours

C. At least 12 hours

D. At least 24 hours

E. At least 48 hours

F. I'm not in favor of such a method.



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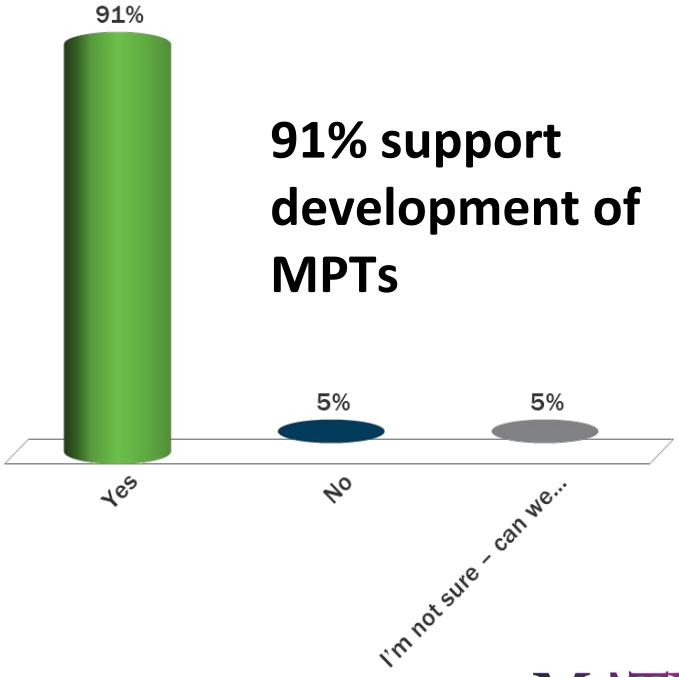
Should MPTs be a priority?

Six of the nine products in the MATRIX pipeline are being designed to not only protect against HIV but also against other sexually transmitted infections (herpes simplex virus – HSV; and/or human papillomavirus - HPV) and/or unwanted pregnancy – products often referred to as an MPT, short for multi-purpose technology. **What is your opinion about MPTs – should their development be a priority for the HIV prevention field?**

A. Yes

B. No

C. I'm not sure – can we talk about this some more?



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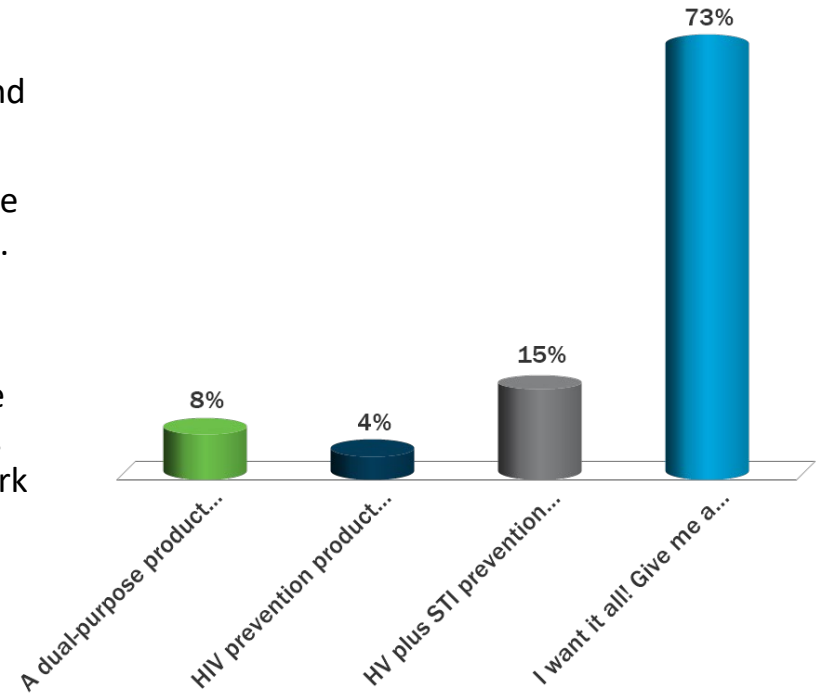
What's more important: Having an HIV prevention product that includes contraception, an HIV prevention product that protects against other STIs or a product that is solely for HIV prevention?

A. A dual-purpose product that protects against HIV and offers contraception would be a game-changer.

B. HIV prevention product only – Women already have a number of contraceptive methods to choose from. Why can't they continue with what they're already using and just use something else for HIV?

C. HV plus STI prevention product – It's about time we did something to address the high incidence of STIs. I'm all for an HIV prevention method that would work against HPV and/or HSV as well.

D. I want it all! Give me a single product that protects women against HIV, STIs and unwanted pregnancy!



- While there was overwhelming enthusiasm for MTPs, a representative of the NDoH cautioned that developers should consider how they will be delivered:

> "*For example, combining contraceptives with ARVs – think about how it will be delivered, who can prescribe it, where to obtain it, also whether it can be self-administered, because protocol or guidelines for delivering ARVs are much more rigorous than for Family Planning.*"

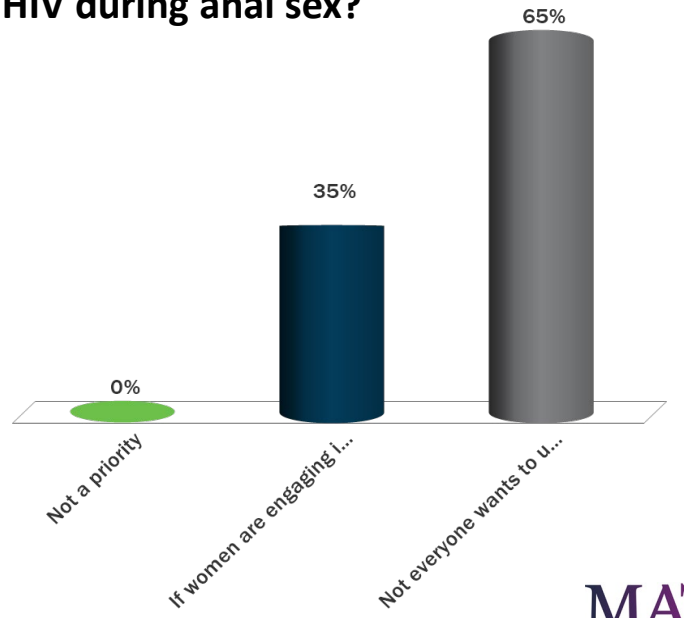
Rectal microbicides for women?

The risk of acquiring HIV through anal sex is much greater than through vaginal sex. **What are your thoughts about the need for products that women could use to protect themselves against HIV during anal sex?**

A. Not a priority

B. If women are engaging in both anal and vaginal sex they should be taking oral PrEP (or another systemic product like cabotegravir injectable PrEP)

C. Not everyone wants to use a systemic method like oral PrEP or injectable cabotegravir, so I'd support having rectal products – in additional to vaginal products.



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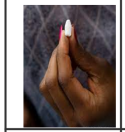
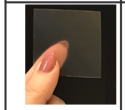
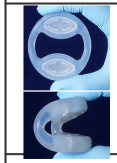
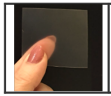
Overall MATRIX Product Pipeline

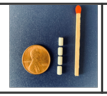
Stakeholders Views

MATRIX Product Pipeline Overview

	Product	Developer	Product Type	Active ingredient	How used	How long protected?	MPT?	Unique features	Status
1	 TAF/EVG Fast-dissolving insert	CONRAD (USA)	Fast-dissolving insert	**TAF/EVG** tenofovir alafenamide & elvitegravir (NRTI and integrase inhibitor)	On-demand (at the time of sex)	Up to 3 days	HIV *and* HSV	Could be used vaginally or rectally - as PrEP or PEP	US/North American studies conducted – first Phase 1 study in African women planned for 2023
2	 Griffithsin Fast-dissolving vaginal insert	Population Council (USA)	Fast-dissolving insert	**A protein -Griffithsin** Viral entry inhibitor	On-demand (at the time of sex)	4 hours	HIV *and* HPV HSV	Active ingredient derived from seaweed	Pre-clinical
3	 One month dapivirine vaginal film	Univ of Pittsburgh (USA)	Vaginal film	**Dapivirine** NNRTI	Women insert themselves	1 month		Releases drug until film completely dissolves	Placebo study being planned for 2023
4	 Non-ARV/ nonhormonal contraceptive multipurpose vaginal ring	Oak Crest Inst of Science (USA)	Vaginal ring	**2 Peptides** (protein fragments) – one acts against HIV (& HSV/HPV), the other inhibits movement of sperm & ability to penetrate & fertilize egg	Women insert themselves	1-3 months	HIV *and* HPV HSV pregnancy	Non-ARV and nonhormonal Could be used with or without contraceptive	Placebo trial being planned for 2023
5	 Cabotegravir injectable depot	CONRAD (USA)	Injectable depot (storage bubble)	**Cabotegravir** Integrase strand inhibitor	Injection given under the skin	4-6 months		May be less burden on healthcare system and users	Pre-clinical
6	 Cabotegravir dissolvable pellets	CONRAD (USA)	Pellet implant	**Cabotegravir** Integrase strand inhibitor	Implanted under skin	9-12 months		Slowly dissolves over course of a year (biodegrades) Can be removed after 1-2 mo if needed	Pre-clinical

7  One month dapivirine vaginal film plus levonorgestrel (LNG)

8  Cabotegravir injectable depot plus LNG

9  Cabotegravir dissolvable pellets plus LNG

Three products also to be developed as an MPT with the addition of a hormonal contraceptive

The Need to Manage Expectations

- The consultation focused on the six products in the main table (previous slide)
- The initial impression of stakeholders was that all six products would be introduced – and within a timeframe of just a few years.
- Need to temper expectations about the products we are evaluating with messages about how the process is a very long, and not all products will succeed.

> *"We have to avoid over-promising, over-hyping a product, and be realistic about expectations, because they generate a lot of excitement."*
>
> (Advocate)

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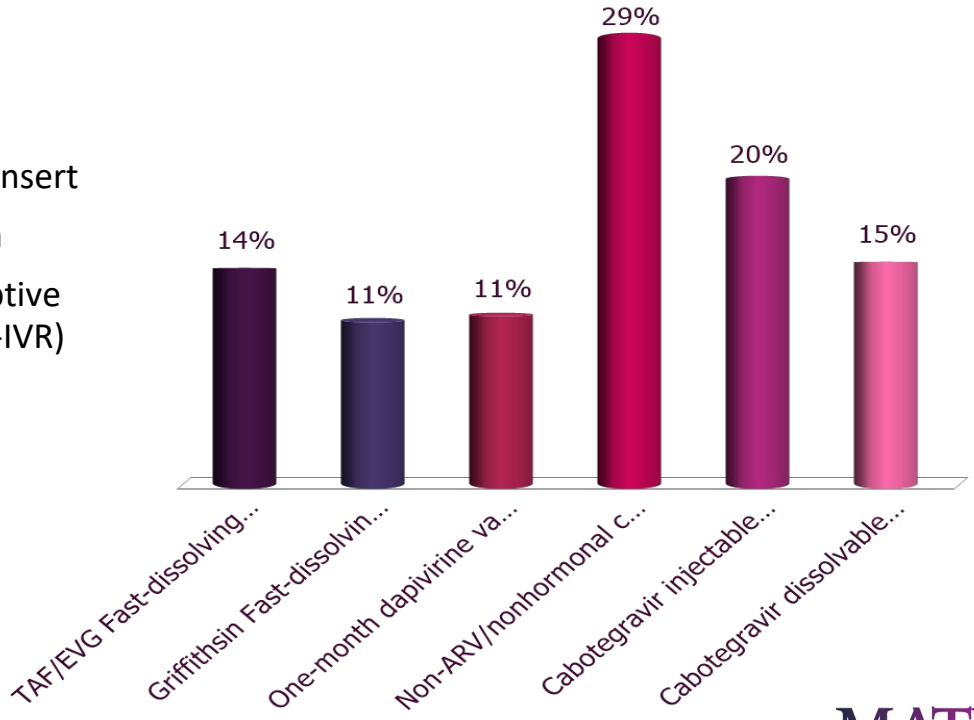
How products were presented

- All product videos were shown
  - Individual sessions were devoted to TAF-EVG fast-dissolving insert, the 30-day dapivirine vaginal film, and MPT ring (LAMP-IVR)
  - Griffithsin fast-dissolving insert and CAB dissolvable pellet implants and CAB injectable depot were featured in a session, "Looking farther ahead"
  - Videos were generally well received but stakeholders cautioned that some messaging was too optimistic
- There was support of each of the products, as well as several questions (NOTE: Specific feedback about each product will be shared with individual PDs)
- At the end of the meeting, stakeholders were asked to select the 3 products they were most excited about or felt were most needed

Which three products are you most excited about or feel are needed the most?

A. TAF/EVG Fast-dissolving insert
B. Griffithsin Fast-dissolving vaginal insert
C. One-month dapivirine vaginal film
D. Non-ARV/nonhormonal contraceptive multi-purpose vaginal ring (LAMP-IVR)
E. Cabotegravir injectable depot
F. Cabotegravir dissolvable pellets



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- Some stakeholders didn’t vote because they felt all products were important – or that it was too early to say.
- Others didn’t vote because they said it didn’t matter what they preferred when there would be other women who would prefer something else.
- Of note, young women, especially, commented on the need for products to be fun, flavored and they recommended that PDs should learn from sex-friendly toys.

Many considerations

"Consider how acceptable these products will be, would they be feasible for implementation? Would there be demand for it? Also cost-effectiveness, compared to what else is available – who would benefit from it?"

(NDoH representative)

Views on conducting early phase clinical trials and placebo studies in SSA

Should early phase studies be conducted in SSA?

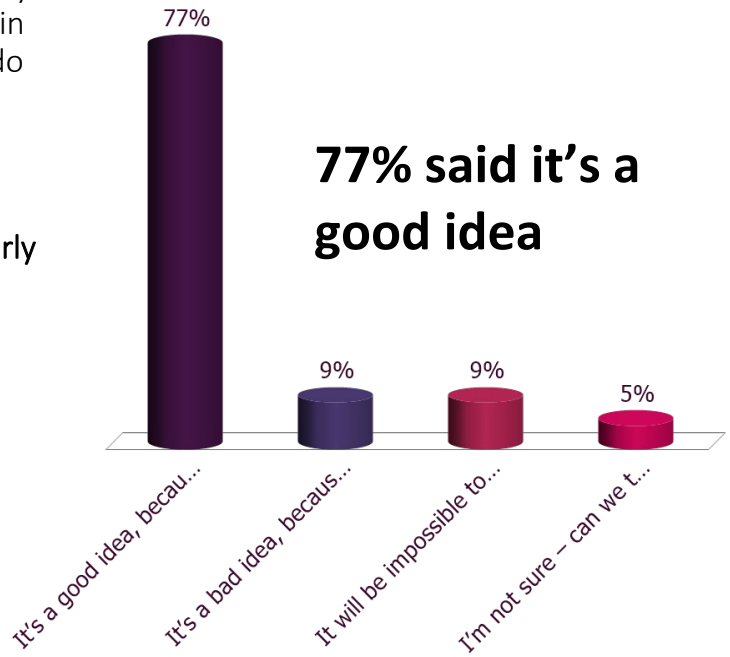
Most HIV prevention studies that have taken place in Africa have been later phase studies (Phase 2 or 3),and were conducted only after Phase 1 safety studies among women (at low risk of HIV) in the United States or Europe had indicated it would be safe to do so. MATRIX intends to conduct early-phase studies here in Africa, in addition to the US. The MATRIX-001 Phase 1 study of the TAF/EVG fast-dissolving insert, for example, will enroll women at three trial sites – in the US, Kenya and South Africa. **What are your views about including African women in these early phase studies?**

A. It's a good idea, because early safety and acceptability data from African women will result in products that African women want.

B. It's a bad idea, because safety should be assured in US women before the studies are done in African women.

C. It will be impossible to do early safety studies in African women because the women in early phase studies have to be at very low risk of HIV.

D. I'm not sure – can we talk about this some more?



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Some helpful advice

- SAHPRA supports Phase 1 studies being conducted in South Africa but **only** if the first-in-human trials had already been conducted in the US (or Europe) or if these trials were to be conducted in parallel
- Although MATRIX studies would be enrolling women who are low HIV risk, protocols should justify/ensure there is an ethical argument for conducting placebo studies that would not be providing participants with an active product (either through the study or as standard of prevention)
- Site investigators should request pre-submission meetings with SAHPRA and IRB/ECs

"There is increasing scrutiny of studies by Ethics Committees and since these are early phase studies, this would even be more rigorous. It is very important to secure their understanding of the intended studies."

(Ethicist)

A need for clear and nuanced messaging

- Participants (and communities) need to understand what's involved in early phase studies – the many tests and procedures
- They must also understand the research process – that Phase 1 studies are the beginning of the road and that the product being evaluated may not succeed, but that their participation was valuable nonetheless, because it is much better to learn these things earlier rather than later (i.e., in Phase 3 trials)
- Sites are advised to engage with partners so they don't hinder women's successful participation in studies

A need for clear and nuanced messaging

- For placebo studies, it will be especially important to use simple language to ensure understanding of the purpose of study

> *"A young girl is going to think, okay I have this placebo, it is going to protect me from HIV".*
>
> (Clinical trial site community educator)

Views about MATRIX and its approach

Listening to stakeholders and end-users

- There was appreciation for MATRIX considering what end-users think early in the process, which stakeholders felt had not been the case before

  "The PrEP pill is big, and some women find it hard to swallow, which could affect use."

  (Young woman advocate and former trial participant)

- Getting communities involved in the research process early ensures ownership of the end product

  "I am not going to own something I was not part of."

  (Clinical trial site community educator)

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"We often feel the research community don't really care that we are the ones who take these products and sometimes they don't really work [for us]. Take community needs and questions seriously. Do women want this?"

(Advocate)

Other considerations

- Support for looking at the feasibility of products from many angles

  It's good that MATRIX is considering *"the pricing issues … early enough, because many times we talk to communities about new products, then when it is approved, there [are challenges] regarding the prices. When developers are developing these products, they know who they are targeting, so can they just think about pricing as well? "*

  (Advocate)

- General agreement that North-South collaboration in early phase studies is critical, both for sustainability and to build capacity in SSA

Acknowledgements

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