

MATRIX

Developing the next generation of
HIV prevention products for women

Kenneth Ngure MPH, PhD

JKUAT/KEMRI/UW

Co-lead D2D Pillar 1

HPTN - Socio-Behavioral and Structural Working Group Member



Presentation Highlights

- MATRIX is supporting early phase R&D for 9 products
- Three phase 1 or 0 studies are nearing implementation in the US, South Africa, Zimbabwe and Kenya
 - MATRIX-001 TAF/EVG insert used vaginally 14 days
 - MATRIX-002 Vaginal 30 day placebo film acceptability study
 - MATRIX-003 Placebo novel dual prevention monthly ring acceptability study
- The Design to Delivery (D2D) Hub Pillar 1 has generated feedback from end-users through design consultations (DCs) and is planning a use of the rapid response network (RRN)
- The Business, Market Dynamics and Commercialization (BACH) hub is supporting the MATRIX PDs through estimating of cost of goods and the feasibility of eventual manufacturing of products in South Africa and Kenya
- The Capacity Strengthening, Engagement and Mentorship (CaSE) mentoring program is providing short and mid term training for approximately 28 scholars and planning in underway for launch of a in depth fellowships for product development

MATRIX

Microbicide Research and Development (R&D) to **A**dvance HIV
Prevention **T**echnologies through **R**esponsive
Innovation and e**X**cellence

What is MATRIX?

- A USAID Project to Advance the Research and Development of Innovative HIV Prevention Products for Women – funded in Dec. 2021 for 5 years
- Brings together partner organizations from sub-Saharan Africa and North America, with expertise in **product development, clinical trials, social and behavioral research and market and business case development**
- Led by Sharon Hillier (University of Pittsburgh/ Magee-Womens Research Institute - USA) and Thesla Palanee-Phillips (Wits RHI - South Africa)

MATRIX Goals

Through North-South partnerships, MATRIX goals include development of a range of HIV and pregnancy prevention products that are

acceptable, affordable, scalable and deliverable

to meet the unmet needs of women at risk of HIV infection and unplanned pregnancy

How MATRIX is structured

5 Activity "Hubs"

Technology Accelerator

- Manages development process of products, and with input of an independent **Scientific Advisory Group**, advises on a product's next steps
- Provides support to other research and development endeavors through seed funding and other grants, including of projects led by African investigators

Clinical Trials

- Oversees design and implementation of placebo studies and Phase 1 trials of products at partner clinical trial sites in the U.S., Kenya, South Africa and Zimbabwe

Design to Delivery (D2D)

- Conducts end-user research to understand women's and stakeholders' preferences for products and product attributes
- Designs and implements behavioral studies & socio-behavioral research within trials
- Seeks stakeholder feedback on products, proposed studies and regulatory process.

Business, Market Dynamics and Commercialization (BACH)

- Conducts business case & market analysis; seeks linkages with possible investors

Capacity Strengthening, Engagement and Mentorship (CaSE)

- Matches African investigators with mentorship and fellowship opportunities, with an emphasis on early R&D

4 Product Developers






(currently)

- **CONRAD/Eastern Virginia Medical School**
- **Oak Crest Institute of Science**
- **Population Council**
- **University of Pittsburgh/ Magee-Womens Research Institute**





What does the MATRIX product portfolio include?

- A *range* of HIV prevention products to ensure women can have options:
 - Dual-purpose products for prevention of both HIV and pregnancy
 - Products designed to provide protection for six months to a year
 - On-demand vaginal products meant to be used around the time of sex
 - Vaginal products that would be used for a month at a time
- Some are new formulations of existing ARV-based products; others contain novel antiviral agents
- **Most have not yet been tested in clinical trials**

MATRIX Product Pipeline Overview

Product	Developer	Product Type	Active Ingredient(s)	How used	Protection Goal	Unique Features/ Additional Information	Development Status	
Products for Prevention of HIV								
1 	TAF/EVG Fast-dissolving vaginal insert	CONRAD (USA)	Fast-dissolving insert	TAF/EVG <i>tenofovir alafenamide & elvitegravir</i> <i>NRTI & integrase inhibitor (ARVs)</i>	On-demand <i>(women insert themselves at or around time of sex)</i>	Up to 3 days	TAF has also shown activity against HSV, which could be added benefit. CONRAD also evaluating the insert's rectal use.	MATRIX-001 to evaluate the safety and acceptability of insert at sites in Kenya, South Africa & US –the first Phase 1 study in African women. Expected start 2023.
2 	Griffithsin Fast-dissolving vaginal insert	Population Council (USA)	Fast-dissolving insert	Griffithsin antiviral protein (non-ARV) <i>Viral entry inhibitor</i>	On-demand <i>(women insert themselves at time of sex)</i>	4-8 hours	Animal and laboratory studies indicate Griffithsin also has activity against HPV and HSV, which could be added benefit.	Pre-clinical
3 	Dapivirine vaginal film	Univ of Pittsburgh (USA)	Vaginal film	Dapivirine <i>NNRTI (ARV)</i>	Women insert themselves	1 month	Film would slowly release drug until it completely dissolves. <i>Also being developed as dual-purpose product</i>	MATRIX-002 to evaluate acceptability and usability of 2 placebo films at sites in Kenya, South Africa, Zimbabwe & US. Expected start 2023; will determine film to be used in first-in-human trial of monthly dapivirine film.
4 	Cabotegravir hydrogel injectable	CONRAD (USA)	Injectable depot	Cabotegravir <i>Integrase strand inhibitor (ARV)</i>	Injection given under the skin	4-6 months	Initially a liquid, hydrogel forms into a small ball that would slowly release drug as it dissolves. (If needed, removable in first month) <i>Also being developed as dual-purpose product</i>	Pre-clinical
5 	Cabotegravir dissolvable pellets	CONRAD (USA)	Pellet implant	Cabotegravir <i>Integrase strand inhibitor (ARV)</i>	Inserted under skin	Up to 1 year	8-9 pellets would be inserted in a row that slowly release drug as they dissolve in course of a year. (If needed, removable in first 1-2 mos) <i>Also being developed as dual-purpose product</i>	Pre-clinical

MATRIX Product Pipeline Overview

Product	Developer	Product Type	Active Ingredient(s)	How used	Protection Goal	Unique Features/ Additional Information	Development Status	
Products for Prevention of HIV and Pregnancy (Dual Purpose)								
1 	Non-ARV/ nonhormonal contraceptive dual-purpose vaginal ring	Oak Crest Inst of Science (USA)	Vaginal ring	Antiviral peptide (non-ARV) <i>(protein fragment)</i> Non-hormonal contraceptive <i>A soluble Adenylate Cyclase (sAC) inhibitor; affects sperm's ability to move, fertilize eggs</i>	Women insert themselves	1-3 months	The antiviral also shows activity against HSV and HPV, which could be an added benefit.	MATRIX-003 to evaluate acceptability of 2 placebo rings at sites in South Africa, Zimbabwe & US. Expected start 2024. Will determine ring to be evaluated in first-in-human trial of active ring.
2 	Dapivirine and levonorgestrel vaginal film	Univ of Pittsburgh (USA)	Vaginal film	Dapivirine <i>NNRTI (ARV)</i> Levonorgestrel (LNG) <i>hormonal contraceptive</i>	Women insert themselves	1 month	As film slowly dissolves it would release both dapivirine and LNG until film completely dissolves	Pre-clinical
3 	Cabotegravir/ levonorgestrel hydrogel injectable	CONRAD (USA)	Injectable depot	Cabotegravir <i>Integrase strand inhibitor (ARV)</i> Levonorgestrel (LNG) <i>hormonal contraceptive</i>	Injection given under the skin	4-6 months	Initially a liquid, hydrogel forms into a small ball that would slowly release drug as it dissolves. (If needed, could be removed in first month)	Pre-clinical
4 	Cabotegravir/ levonorgestrel dissolvable pellets	CONRAD (USA)	Pellet implant	Cabotegravir <i>Integrase strand inhibitor (ARV)</i> Levonorgestrel (LNG) <i>hormonal contraceptive</i>	Inserted under skin	Up to 1 year	8-9 pellets would be inserted in a row that slowly release drug as they dissolve in course of a year. (If needed, could be removed in first 1-2 mos)	Pre-clinical

Meet the TAF/EVG Insert

"The Weekend Special"

A dual-compartment (vaginal/rectal) insert for flexible, user-controlled, on-demand HIV prophylaxis



- + For all sexually-active ages and genders, especially AGYW
- + Highly discreet and portable
- + Low systemic exposure → drug where and when you need it
- + Designed to be used on-demand pre- or post-coitus
- + Provides potential added benefit of HSV prophylaxis

Under MATRIX, product development focused on vaginal use for primary indication of HIV prevention

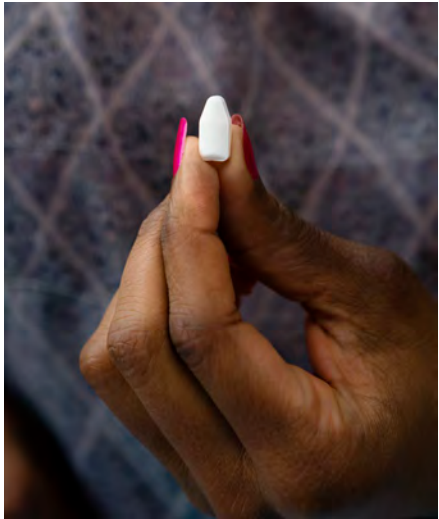
Through other/future funding would be pursuing rectal use and prevention against HSV-2 and other STIs

Why TAF/EVG Inserts?

How is it different from existing/approved PrEP products?

- ✓ No other user-controlled, on-demand HIV prevention product **in clinical trials**
- ✓ **Provides new event-driven PrEP option for women** (*ED oral PrEP currently approved for MSM only*)
- ✓ **Fewer doses and side effects** expected than oral/systemic PrEP
- ✓ Potential for additional protection against **HSV-2** acquisition and dual compartment (**vaginal/rectal**) use
- ✓ **Most advanced product** in MATRIX's current product portfolio, with:
 - **Preclinical** proof-of-concept in non-human primates
 - **Clinical** proof-of-concept (CONRAD-146, MTN-039)
 - **User acceptability & ease-of-use** demonstrated
- ✓ **Simple manufacturing** = readily **affordable, scalable, deliverable**

MATRIX-001: Overview



- Phase I study : Evaluate safety of the TAF/EVG (NRTI/ integrase inhibitor) fast-dissolving insert(FDI) used vaginally
 - Will also evaluate user acceptability, how and where the two drugs are taken up in the body, and potential activity against HIV and herpes simplex virus (HSV)
- Will enroll 60 women at 3 trial sites
- The first study of the TAF/EVG fast-dissolving insert in African women. Study to open in October 2023
- **Dosing** : daily for 3 days, then every other day for 14 days



Why MATRIX-001?

- Researchers need to know about **the safety** of the TAF-EVG insert **with more frequent vaginal use** (not just one time)
- Need to understand **safety and acceptability in African women**, not just women in the US
- Will provide information about **where the drugs go in the body**– and **how long they remain there** – when used consecutive days as a vaginal insert, as well as insight into the product’s **potential effectiveness** against HIV and HSV
- Study results will determine **whether the TAF/EVG insert should proceed to Phase 2 studies** to evaluate its safety and acceptability when used as designed – at or around the time of sex, and vaginally



Why Vaginal films?

Ease of Use & Privacy:

Women control use and insertion of film
Can be used discreetly and inserted
anytime in private
Not expected to impact sex

Unique & Convenient Platform:

Removal not required
Complete drug release
Small and portable



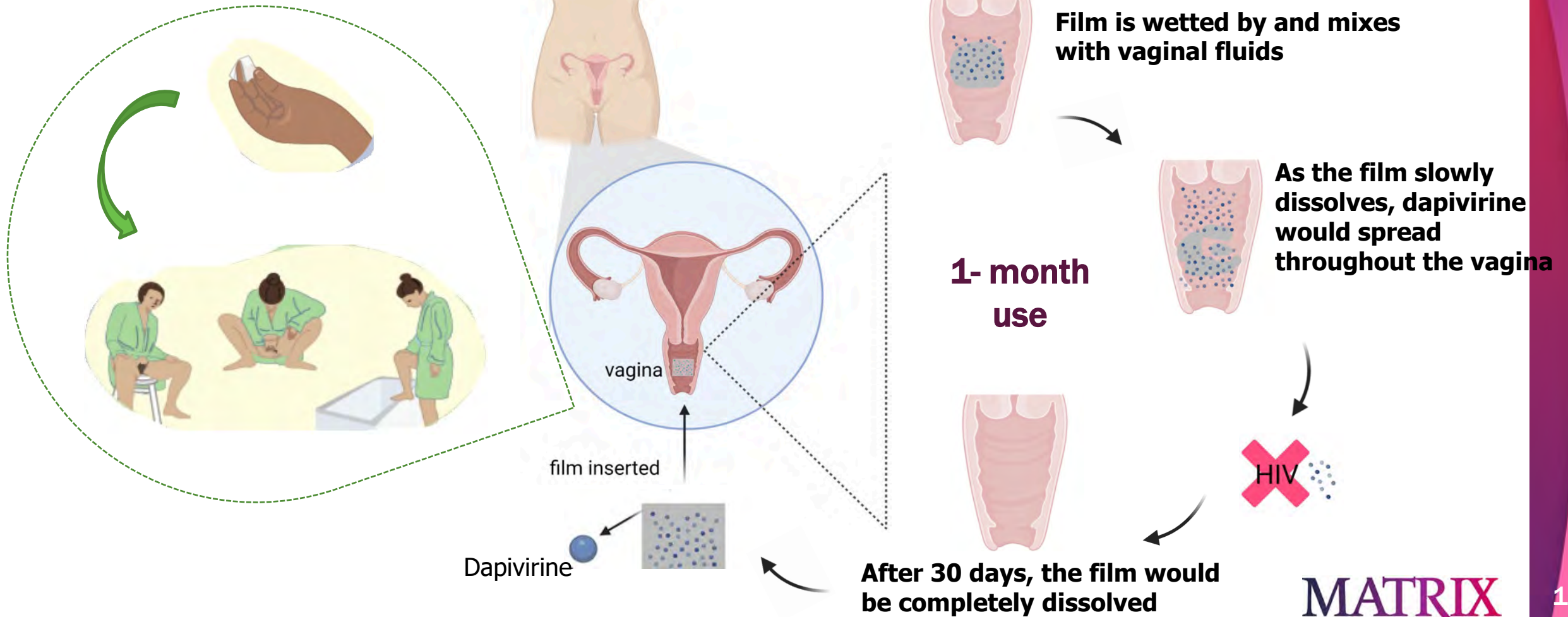
Low Cost:

Inexpensive to manufacture
No applicator required

Safe with No Messiness:

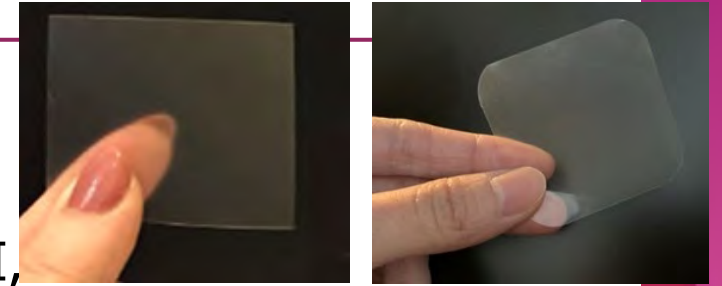
Minimal impact on vaginal health
Minimal to no additional vaginal
discharge

How would the film work?



MATRIX-002 Overview

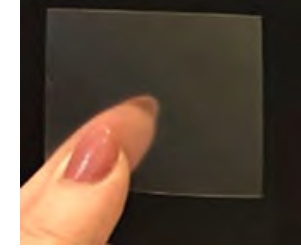
- Trial to assess acceptability, usability and safety of two placebo prototype vaginal films which differ in shape
- To be conducted at five clinical sites (MWRI, KEMRI, Aurum, Wits RHI, HHRC)
 - 100 participants (18-45 y/o) and up to 30 sexual partners
 - No sexual activity or product use in 1st month, no restrictions in 2nd month. Study to launch in October 2023
- Key questions to be addressed:
 - Do women like the vaginal film?
 - Which film shape is better?
 - Can women insert the vaginal films themselves?
 - What do sexual partners think about the film?
 - Will sex or vaginal products/practice interfere with film use?



Why MATRIX-002?

The concept of a vaginal film is unfamiliar to many women – perhaps especially, African women.

The idea of a monthly vaginal film is brand new



- **Quick-dissolve vaginal films** and a **7-day film** have been evaluated in US women
- In the QUATRO study, women in South Africa and Zimbabwe tried a **quick-dissolve placebo film**

Before evaluating the monthly dapivirine film in a first-in-human Phase 1 study:

- Researchers need to **know that women will be comfortable with the idea of using a monthly film** and are **able to insert it**
- They also want to be sure that **the “right” film is the one that moves forward:** which of the two films do women find easier to use? Which is safest?

OneRing – An Innovative Dual-purpose Prevention Product



Highlights of activities to date:

- Antiviral agent (peptide) formulation development
- Contraceptive agent formulation development
- Bioanalytical method development
- Safety and pharmacokinetics in sheep
- Antiviral activity studies in mice
- Ring design and formulation
- Regulatory
- Studies to support regulatory

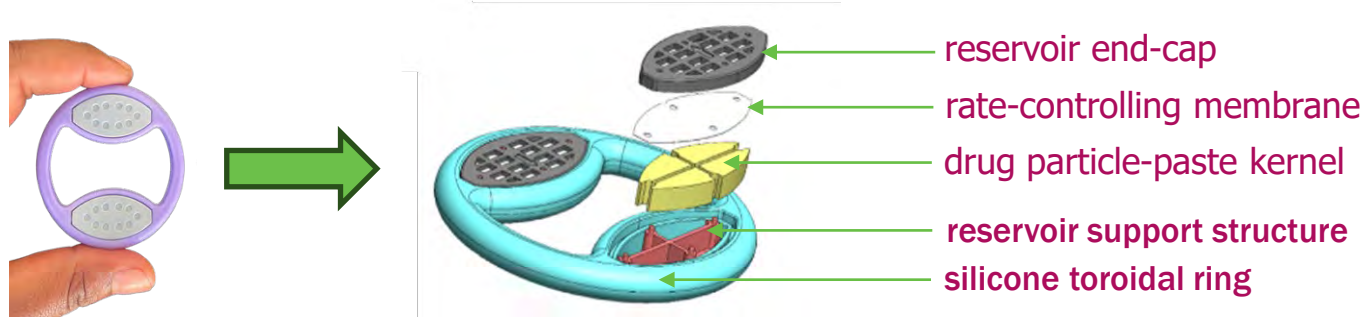
 **ONE RING**
Dual-Purpose Ring to Prevent HIV and Pregnancy

MATRIX

MATRIX-003



- **MATRIX-003** will gather acceptability, usability, and safety data of 2 placebo prototypes of a new type of ring (OCIS OneRing) which differ in firmness
- The rings' size is similar to that of approved devices and multiple clinical trials (like the dapivirine vaginal ring), but the design is different as it includes two cassettes (cartridges)



- Designed for simultaneous delivery of two medications (non-ARV antiviral and non-hormonal contraceptive) for HIV and pregnancy prevention
- Each participant will use each ring for ~28 days - allow assessment of ring use and preference for the different rings (without the impact of drug related side effects)

MATRIX-003

- This data collected in **MATRIX-003** will guide the final design of a dual-purpose vaginal ring that
 - Contains non-ARV and non-hormonal drugs that act locally – fewer side effects, less concern about viral resistance, rapid return to fertility
 - Could offer long-term protection from both pregnancy and HIV (30 days)
 - Women can use discretely and insert and remove themselves
 - Goal is low cost and easy to manufacture



MATRIX Products Not Yet in Trials

- Cabotegravir implantable pellets (with and without LNG)
- Cabotegravir depot injectable (with and without LNG)
- Griffithsin Fast dissolving insert

Acknowledgements

This program was made possible by the generous support of the American people through the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) and the U.S. Agency for International Development (USAID).

The contents in this presentation are those of the presenter and do not necessarily reflect the view of the U.S. President's Emergency Plan for AIDS Relief, the U.S. Agency for International Development or the U.S. Government.



Additional Slides to be used if necessary



CAB Bioresorbable Pellets and Hydrogel Injectable in Development by CONRAD

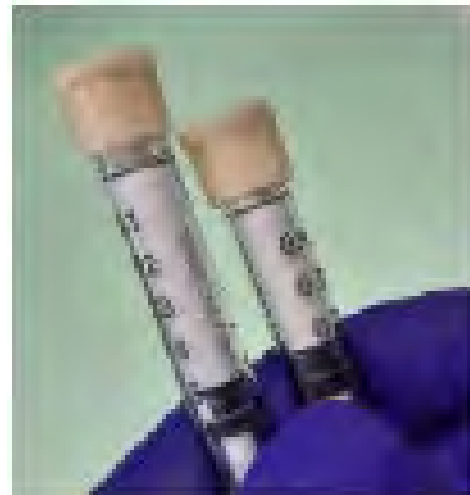
For users of **all ages and genders**

Administered under the skin by healthcare provider **similar to contraceptives**



Option for 2-in-1 Dual Purpose Product with added contraceptive to meet needs of more users

Longer duration (~6-12 months)



CAB Hydrogel Injectable CAB Pellets



Reduce clinic visits, costs, time, monitoring efforts

MATRIX

CAB Pellet Attributes



Small (3x5-10mm) cylindric solid dosage form; GRAS excipients



CAB Pellets



LNG pellets

(with or without color)



Commercial trocar
(for FIH studies)

High CAB drug loading of up to 90% per pellet; supports longer duration

Scalable, affordable, stable; no cold-chain storage required

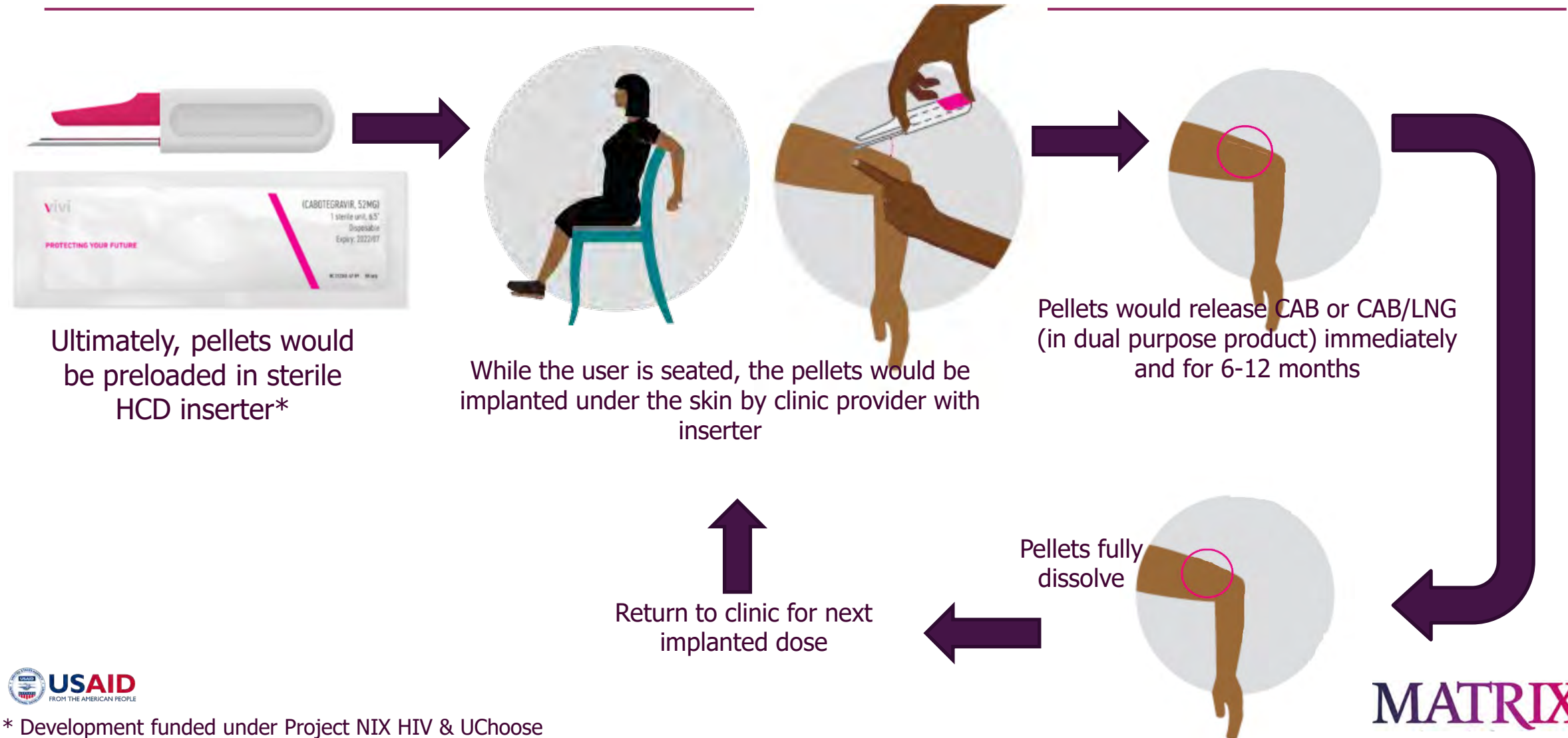
Controlled release; supports long-term PK profile

Bioresorbable; no need for removal, CAB and LNG have good safety profiles

User-friendly insertion; administrable with commercial trocar, but designed for ultimate delivery in pre-loaded, HCD inserter

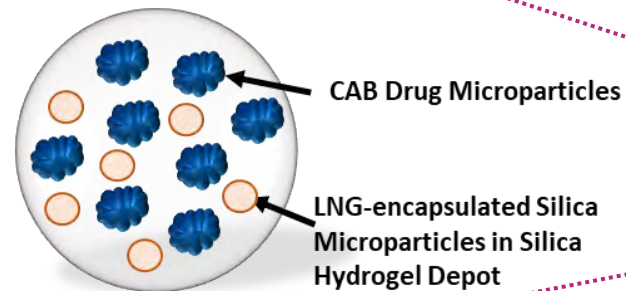
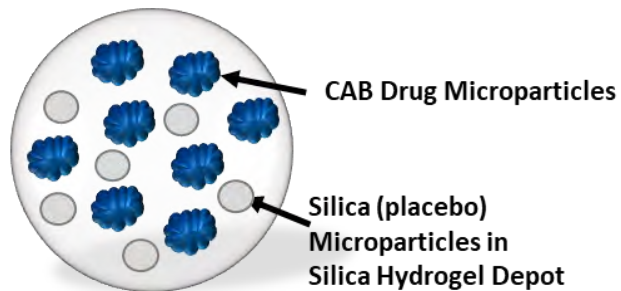
Target: protective plasma levels for 9-12 months (CAB only)
and 6-12 months (CAB/LNG)

How would CAB & CAB/LNG Pellets be inserted?



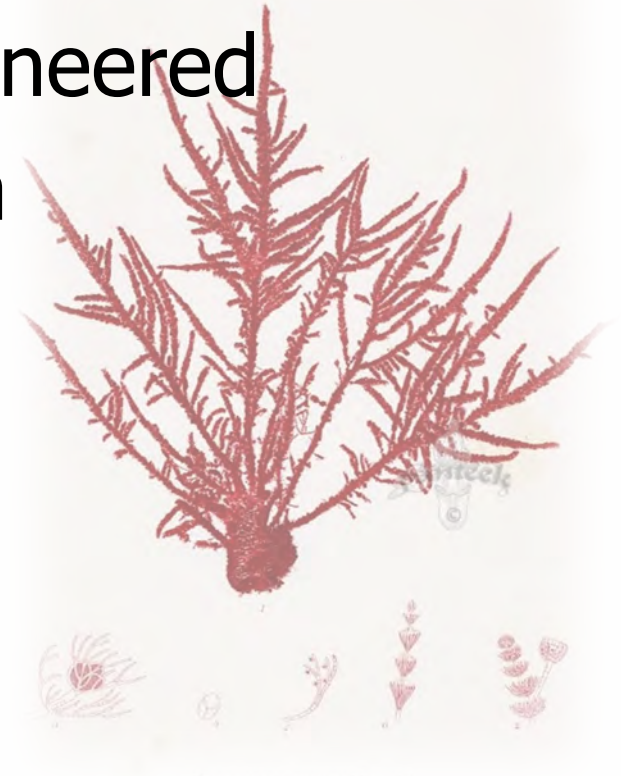
CAB and CAB/LNG Hydrogel Injectable

- Uses a hydrogel drug delivery technology that is:
 - Made of natural ingredients (silica and water)
 - Shear thinning, so may be injected either under skin (SC) or into muscle (IM) using a small needle
 - Forms a bubble-like “depot” where injected that slowly degrades (dissolves) over time
 - As it dissolves, the drug payload is slowly released and absorbed into bloodstream
 - **CAB only** 6 month target duration for protection **CAB/LNG**



Why and What is Griffithsin (GRFT)?

- Non-ARV with broad antiviral properties
- Protein discovered in algae — now bioengineered
- Promising preclinical and early clinical data
- Highly potent against HIV — effective at sub-nanomolar concentrations
- Topically-active/non-systemic



Why Fast-dissolving Insert (FDI)?

User Acceptance

- Endorsed as highly desired by end-users
- Discreet, easy to use, portable
- Anticipate minimal impact on vaginal discharge → lower risk of partner detection

Product Characteristics

- Relatively simple manufacturing and capacity to scale-up production
- Optimal for wide distribution

Our Product

- Quick onset (<20 minutes)
- **12+** hours duration of protection
- Portable, stable at room temperature
- No inserter
 - Discreet placement with finger
 - Reduced waste/cost
- Could possibly use with other prevention methods
- Manufacturing of GRFT being optimized for possible phase 1 in 2024

