Tenofovir Alafenamide / Elvitegravir (TAF/EVG) Fast Dissolving Insert

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PEPFAR
U.S. President's Emergency Plan for AIDS Relief

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Advancing R&D of Innovative HIV Prevention Products for Women

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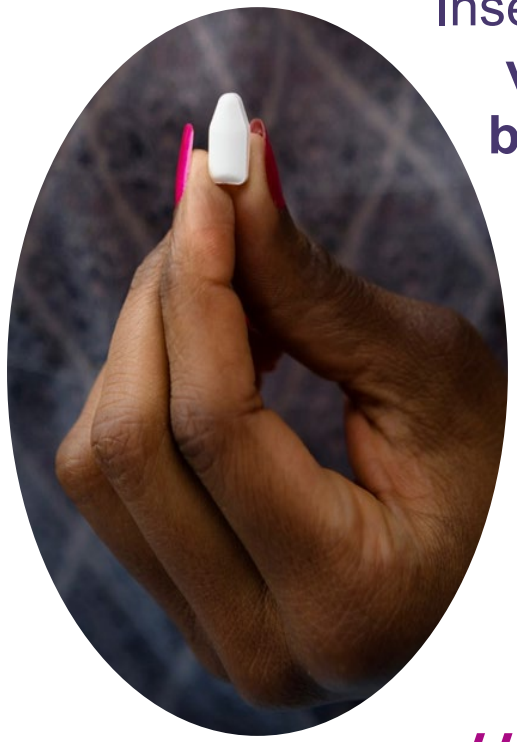
Macon & Joan Brock Virginia Health Sciences
Eastern Virginia Medical School
at Old Dominion University

What is the TAF/EVG Insert?

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



Inserted by user into the **vagina or rectum before or after sex**

2 proven, synergistic ARVs in **simple, scalable low-cost formulation**

Highly discreet, portable and easy-to-use

To **prevent HIV (and potentially HSV)** acquired vaginally or rectally

For **all ages and genders,** especially **AGYW** having infrequent or clustered sex

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

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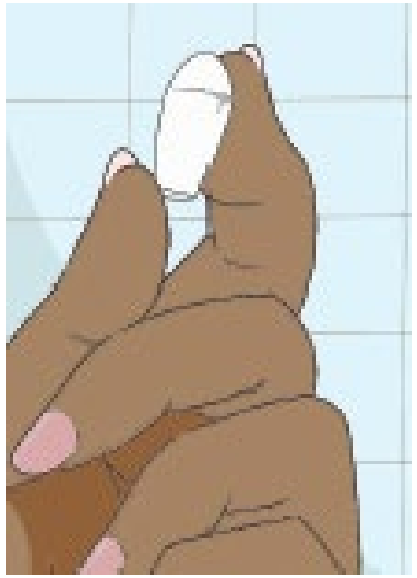
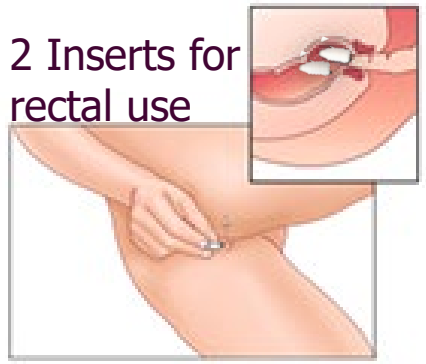
How does the insert work?

Insert within 4 hours before sex
(or within 4 hours after sex)



1 Insert for vaginal use

2 Inserts for rectal use



Repeat next day you have sex

Insert dissolves, **TAF** and **EVG** release and spread, delivering **high drug concentrations** locally

- Drug combination acts **synergistically** against HIV *("one-two punch")*
  - **TAF – Reverse Transcriptase Inhibitor**
  - **EVG – Integrase Inhibitor**
- TAF also acts against **HSV**
- Protection expected to **last at least a day**, regardless of number of sex acts

- ***Pharmacologically forgiving on-demand dosing regimen***

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How are the inserts made?

- ✓ Simple manufacturing using conventional tablet press technology
- ✓ Each insert contains 20 mg TAF and 16 mg EVG
- ✓ All excipients are "generally regarded as safe" (GRAS) by FDA
- ✓ 3 year shelf life capable (> 2yr demonstrated)
- ✓ No cold chain storage required

➢ **Affordable, Scalable, Deliverable, Transferable**

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Why TAF/EVG Inserts?

How is it different from existing/approved PrEP products?

- ✓ **Would provide women a new PrEP option – on-demand PrEP**
  - *On-demand (event-driven) oral PrEP currently approved for MSM only*
  - No other user-controlled, on-demand biomedical HIV prevention product
- ✓ **Fewer doses and side effects** expected than oral/systemic PrEP
  - *Low systemic exposure → drug where and when you need it → Potential future OTC*
- ✓ Potential for additional protection against **HSV-2** acquisition and dual compartment **(vaginal/rectal)** use
- ✓ **Most advanced product** in MATRIX's product portfolio, with:
  - **Preclinical** proof-of-concept in non-human primates
  - **Clinical** proof-of-concept (CONRAD-146, MTN-039)
  - **Expanded Phase I** ongoing (MATRIX-001 [vaginal use], RITE-PrEP [rectal use]); Phase II planning underway
  - **User acceptability & ease-of-use** demonstrated

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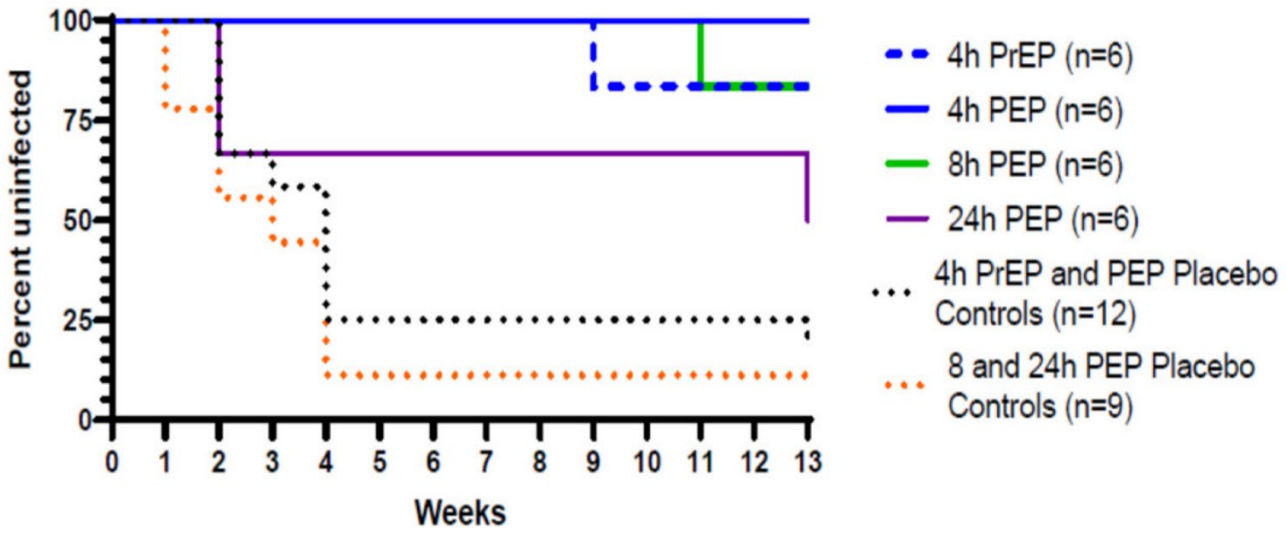
Preclinical Proof-of-Concept in Non-Human Primate Models – *highly effective pre- or post-exposure*

- **Highly effective after single vaginal dose or double rectal dose**
- **Results support forgiving dosing window for on-demand use pre- or post-coitus** *(at least 4hr pre to 8-24hr post vaginally)*

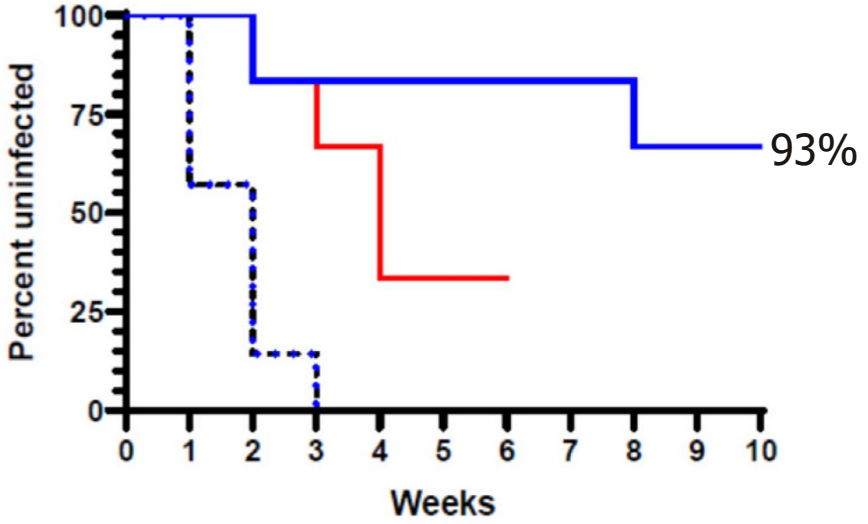
Vaginal dose/SHIV challenge model

Single dose 4h PrEP or 4-24 hr PEP



Rectal dose/SHIV challenge

Single or double rectal dose 4h PrEP

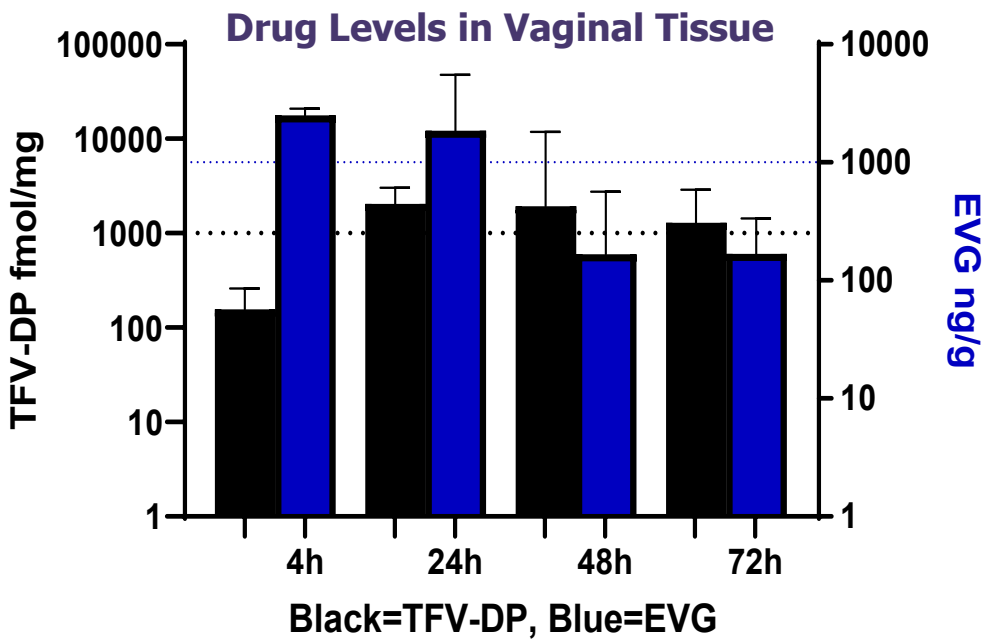


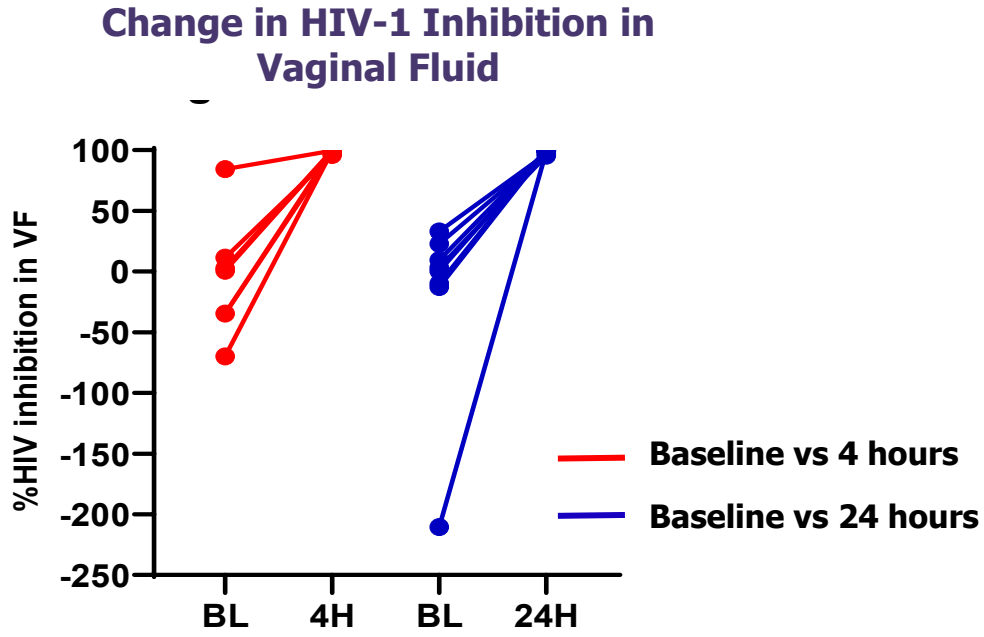
***Assessment of rectal post-exposure efficacy in NHPs in progress*

Dobard et al., eBioMedicine, 2022; Makarova et al. eBioMedicine. 2022; Peet et al., 2024

Clinical Proof-of-Concept in First-in-Human Study in Women – *High drug concentrations, anti-HIV activity ex vivo*

Data from CONRAD-146, FIH vaginal PK/PD, single dose study





- **High local drug concentrations** in cervicovaginal or rectal fluids and tissues
- **Modeled pharmacodynamics supports** antiviral activity against **HIV-1 and HSV-2** (vaginal) **for up to 24** (vaginal) **or 72 hours** (rectal) compared to baseline

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Thurman et al., Front. Cell. Infect. Microbiol. 2023; Riddler et al. J. Infect Dis. 2024

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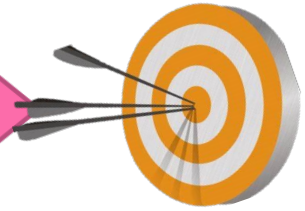
How is MATRIX Advancing the TAF/EVG Insert for vaginal use?

- Expanded clinical testing
- Engaging end-users & key stakeholders in SSA throughout product development process
- Assessing cost, manufacturability & transferability
- Advancing product development in preparation for future pivotal studies

Outcome:
Ensure the TAF/EVG insert is **safe, acceptable, affordable, scalable, deliverable, &** ***relevant to African women***

2022 2023 2024 2025 2026



MATRIX-001
Phase I safety, PK/PD & acceptability study in women in SA, Kenya & US
Started Q4 2023
To complete Q4 2024
Results expected mid 2025

Future Studies in Planning/ Development Stages
Impact of sex on PK (MATRIX-004)
Drug-Drug Interaction Study
Phase II proof-of-concept trial

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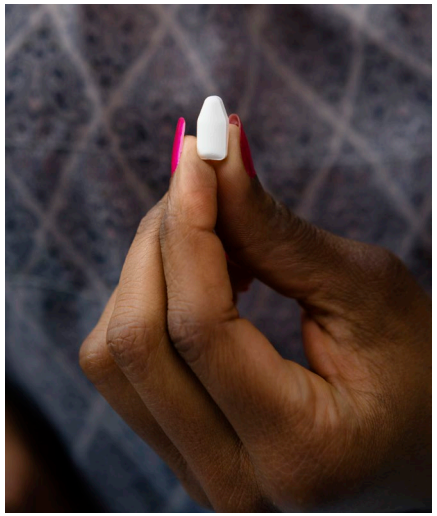
What is MATRIX-001?



- The MATRIX-001 Phase I study is evaluating:
  - Safety of the insert used vaginally and multiple times
  - Acceptability
  - How and where the two drugs are taken up in the body (PK)
  - Potential activity against HIV and HSV (PD)
- To enroll 60 women at 3 trial sites in Kenya, South Africa and the U.S.
- Protocol Chairs: Nelly Mugo (KEMRI), Leila Mansoor (CAPRISA)

- ❖ The first study of the TAF/EVG insert in African women
- ❖ A key study that will help determine the product's safety and PK in target population after repeated vaginal doses in preparation for Phase II clinical testing

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How is the study designed?

- Women are **randomly assigned** to use either the **TAF/EVG fast-dissolving insert** (containing 20 mg TAF; 16 mg EVG) or a **placebo insert** with no active drug
- Each participant **uses a total of 10 inserts**:
  - At first, **every day for 3 consecutive days**; and then **every other day** (every 48 hours) for two weeks
  - Participants **insert the products themselves** – the first time is in the clinic; Study staff provide guidance and instructions
  - Product use is timed to **not coincide with menstruation**
- Participants undergo **different tests and procedures** and are asked **questions about acceptability** prior to, during and following insert use
- Participants are in the study for approximately 2-3 months

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What are the study's objectives?

Primary Objective

Is the insert safe to use vaginally multiple times?

- Safety is assessed by physical exam and laboratory tests

Secondary Objectives

Where do the drugs go, how long do they stay there, and are they active? *(Pharmacokinetics – PK and Pharmacodynamics - PD)*

- Researchers will conduct laboratory tests of blood, vaginal fluid, rectal fluid and cervical tissue samples before participants have used the product and at different study visits after dosing

Does use of the insert result in changes in the types of immune cells and/or bacteria in the vagina?

- Researchers will characterize vaginal mucosal and microbiome changes from baseline

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What are the study's objectives?

Secondary Objectives

Do women find it acceptable to use?

- Questions are asked about satisfaction, comfort and ease of insertion, willingness to use in the future and what may be challenging or help facilitate use
- Some women (approx 8 at each site) will take part in in-depth interviews

Exploratory Objectives

Does it protect vaginal tissues against HIV infection? *(Modeled in vitro pharmacodynamics - PD)*

- Through laboratory tests of cervicovaginal tissue taken at the beginning of the study (before product use) and after dosing

MATRIX-001 Status Update

EVMS

- Activated Nov 2023
- 21 enrolled
- 15 completed

CAPRISA

- Activated Dec 2023
- 23 enrolled
- 20 completed
- Last Patient Last Visit (LPLV): Aug 2024

KEMRI

- Activated Mar 2024
- 19 enrolled
- 11 completed

- >75% participants completed
- Study completion anticipated in October 2024; results expected Q2 2025

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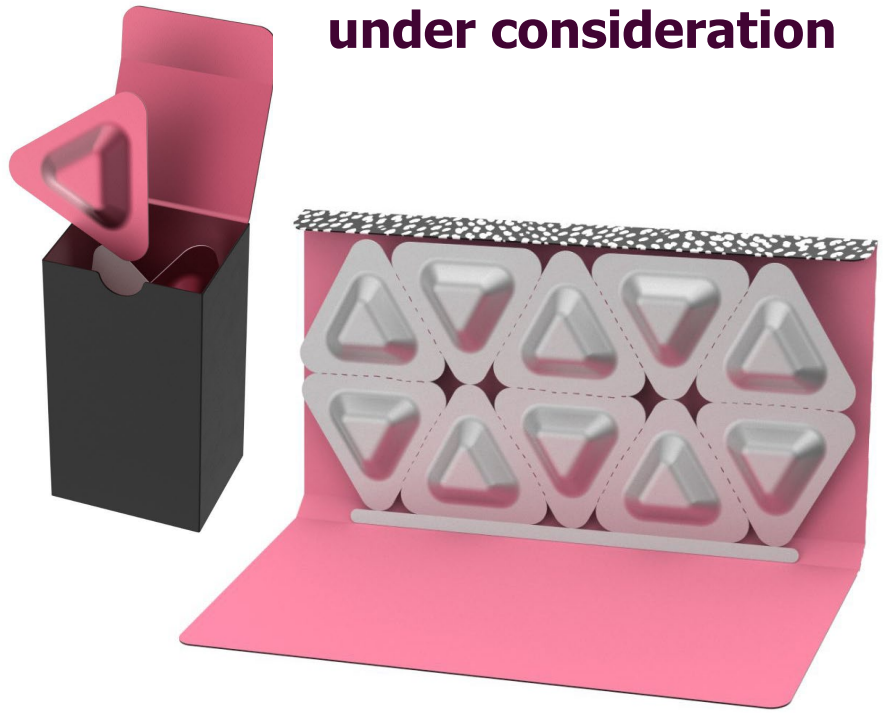
Designing Product Packaging for End-User Needs

- *For discreet, portable, user-friendly, on-demand use*
- *Ensuring product remains stable, affordable, minimizes waste, transferable to LMIC manufacture, suitable for end-user storage needs*

Key End User Preferred Attributes

- Not similar to pills or condoms yet familiar
- Size, portability, travel-friendly
- Ease of use
- Product ambiguous
- Private
- Secure

Two multi-pack designs under consideration



Key Product Requirements

- Common packaging line technology
- High moisture barrier materials
- Single dose units for max portability; secondary packaging for convenient storage
- No cold chain storage

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Next steps?

- Additional Phase I clinical studies
  - MATRIX-004: impact of vaginal sex on PK, PD, safety and acceptability of TAF/EVG insert
  - Drug-Drug Interaction Study of TAF/EVG insert and 3 commonly used vaginal products (antifungal, antibiotic, contraceptive)
- With MATRIX hubs
  - Expanded discussions with local manufacturers
  - Cost-of-goods and cost-effectiveness analyses
  - Finalize product packaging design for pilot testing
  - Refined messaging for target market segments
- Preparing for Phase II clinical trial
  - Clinical study design
  - Engaging with FDA and African regulators
  - Planning for scale up manufacturing

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Acknowledgements

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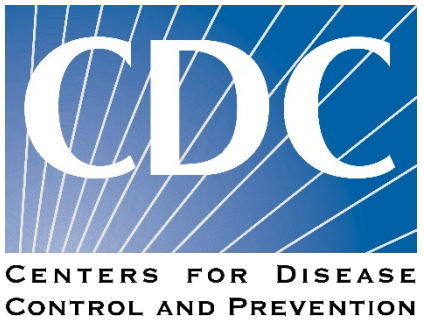

TAF/EVG Fast-Dissolving Insert

Questions and Discussion

Daily oral PrEP is very effective but sustained adherence to daily dosing is a challenge for many people. Using a product only around the time of sex (on-demand) is one approach that women have said they would like. As an on-demand topical product, the TAF-EVG fast-dissolving insert is expected to have a high barrier to resistance and minimal or no systemic side effects. It is also likely to be low cost and easy to manufacture locally.

- What are your views on the need and value for an on-demand HIV prevention product?
- What do you see the main challenges for regulatory approval and implementation might be for this type of product?
- If approved, do you see a path for eventually dispensing this product directly in the pharmacy?