CONTACT: Lisa Rossi
rossil@mwri.magee.edu
+1-412-916-3315

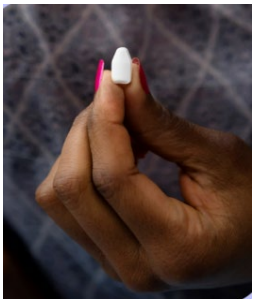
Questions & Answers

The TAF/EVG Fast-Dissolving Vaginal Insert and MATRIX-001 Phase 1 Study

About the TAF/EVG Fast-Dissolving Vaginal Insert

What exactly is the TAF/EVG fast-dissolving insert?

The TAF/EVG fast-dissolving insert is an on-demand HIV prevention product that women would insert into their vagina around the time of sex. The insert, which resembles a bullet-shaped tablet, contains the antiretroviral (ARVs) drugs tenofovir alafenamide (TAF) and elvitegravir (EVG). Once inside the vagina, the insert would begin to dissolve, and in doing so, release the two drugs, which by mixing with vaginal fluid, get dispersed inside the vagina. Animal and laboratory studies suggest the insert would provide protection against HIV for at least one day.



Who is developing the TAF/EVG fast-dissolving insert?

The insert is being developed by CONRAD, a nonprofit research organization affiliated with Eastern Virginia Medical School of Old Dominion University in Norfolk, Va., USA, for its use both vaginally and rectally. The two active ingredients, TAF and EVG, are being provided by Gilead Sciences for CONRAD's development in the insert product.

Why does the insert contain two ARVs, and, in particular, TAF and EVG?

Each insert contains 20 milligrams of TAF and 16 milligrams of EVG. Because TAF and EVG work against different steps in the HIV infection lifecycle, when used in combination, they would work synergistically together to provide a one-two punch, allowing for flexible, on-demand protection. TAF belongs to a class of ARVs called nucleoside reverse transcriptase inhibitors (NRTIs) that prevent HIV from making copies of itself inside human cells, therefore, preventing the spread of HIV inside the body. TAF has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of chronic hepatitis B and for the treatment and prevention of HIV in men who have sex with men when used in combination with another ARV drug called emtricitabine, or FTC. Laboratory and animal studies indicate TAF also has activity against herpes simplex virus (HSV). The insert's second drug, EVG, has been approved by the U.S. FDA for the treatment of HIV in combination with other ARVs. EVG belongs to a different class of ARV drugs known as integrase inhibitors that block HIV from being able to integrate its genetic code into human cells – a step that occurs later in the HIV lifecycle.

What is different about this product from other HIV prevention methods? What gaps would it fill?

The TAF/EVG fast-dissolving insert is the only female-controlled on-demand HIV prevention product in clinical trials. It is discreet and portable, and studies to date also suggest it is easy to use. Such a method could appeal to women who don't want or are unable to use daily oral pre-exposure prophylaxis (PrEP) or long-acting injectable methods, such as cabotegravir (CAB-LA), both of which deliver drug systemically, throughout the body. It may appeal especially to women who have infrequent or clustered sex and want only to use a product when they need it. Because has shown activity against HSV, using the insert could potentially protect against both HIV and HSV, which would be an added benefit. HSV is the most prevalent sexually transmitted infection (STI) worldwide and the most common cause of genital ulcers, which increases the risk of acquiring HIV through sex.

What is known about the TAF/EVG fast-dissolving insert? How far along is it in its developments?

Of the products being developed under MATRIX, the TAF/EVG fast-dissolving insert is the farthest along, having already been evaluated in placebo studies of the insert with no active drug and in first-in-human studies evaluating its safety and acceptability as a vaginal insert (CONRAD 146) and as a rectal insert (MTN-039). CONRAD-146, which was conducted among 16 women in the U.S., found single use as a vaginal insert safe and acceptable. Likewise, the MTN-039 study involving 23 participants found its single use as a rectal insert and two inserts used together posed no safety concerns. In both studies, results of laboratory tests of tissue and fluid samples showed drug levels compatible with protection against HIV for at least 24 hours although animal and laboratory studies suggest a single insert used vaginally and two inserts used rectally could provide protection against HIV for up to three days.

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What role is MATRIX playing in the development of the TAF/EVG insert?

MATRIX is evaluating the insert for its primary indication as a product to prevent HIV – and as a vaginal insert. Toward this end, it is conducting MATRIX-001. MATRIX-001 is the second Phase 1 trial of the TAF/EVG insert used vaginally and the first to enroll African women.

About the MATRIX-001 Phase 1 Study

What is the aim of MATRIX-001? And why is it important?

MATRIX-001 is a Phase 1 study that will provide critical information about the TAF/EVG insert as a vaginal product, including its use by African women. More specifically, the study will provide information about the safety of the insert used vaginally multiple times over several days, as well as user acceptability and how and where the two drugs are taken up in the body. In addition, laboratory tests of tissue samples will provide additional insight into its potential activity against both HIV and HSV. The TAF/EVG fast-dissolving insert is the only on-demand HIV prevention product for women in clinical trials. MATRIX-001 will help determine whether the product should advance and other studies be conducted.

Who led and funded the study?

The MATRIX-001 study is being conducted by MATRIX, a nine-year program funded in 2021 by the United States Agency for International Development that is focused on the early development of HIV prevention products for women. . Protocol co-chairs are Leila Mansoor, B.Pharm, PhD, from the Centre for the AIDS Programme of Research in South Africa (CAPRISA), and Nelly Mugo, MBChB, Mmed, MPH, from Kenya Medical Research Institute (KEMRI, both of whom also served as the investigator of record at their respective sites.

Where was MATRIX-001 conducted and what is its current status?

MATRIX-001, which began in December 2023, enrolled 60 women at three sites in Kenya, South Africa and the United States: in Kenya, at the KEMRI Centre for Clinical Research Thika clinical research site (CRS); in South Africa, at the CAPRISA eThekwini CRS; and in the United States, at the Eastern Virginia Medical School at Old Dominion University in Norfolk, Va. Follow-up of all participants was completed in December 2024. Results are anticipated to be available late 2025.

How was MATRIX-001 designed?

Women in the study were randomly assigned to use either the TAF/EVG fast-dissolving insert or a placebo insert with no active drug. Each participant used a total of 10 inserts – at first, every day for three consecutive days, and then every other day (every 48 hours) for two weeks. Product use was timed to not coincide with a participant's menstrual cycle. Participants inserted the products themselves, the first time in the clinic with guidance from study staff. During the two to three months they were in the study, participants underwent different tests and procedures and asked questions about product acceptability prior to, during and following insert use.

Who could enroll in the study?

To enroll in the study, participants had to be between the ages of 18-50, assigned female sex at birth, in general good health and not be HIV-infected, pregnant, or breastfeeding an infant under 6 months of age. Among other requirements were that participants use contraception (except for vaginal rings) and agree not to use vaginal products or engage in vaginal and/or anal sex or activity at specific times during the study.

What was done to ensure the safety of participants in the study?

Several measures served to ensure the safety of participants, beginning at the site level. In addition, monthly (or more often as needed) reviews of safety data were conducted by a Protocol Safety Review Team (PSRT), which is made up of the Protocol Co-Chairs, Protocol Safety Physician, Clinical Data Team, Clinical Research Managers and representatives of CONRAD as the product developer. An Independent Safety Physician (ISP) with no interest (financial or otherwise) in the outcome of the study also reviewed participant safety data as part of regular study progress reviews.

Did women participating in the study provide informed consent?

Participants were required to provide informed consent to ensure they understood the study procedures, time commitment and potential risks and benefits of taking part in the study. A research study is not for everyone – especially a Phase 1 study, in which there are more potential risks and fewer benefits. Participation is voluntary – likewise, participants may choose to leave the study at any time.

What approvals were needed to conduct the study?

MATRIX-001 underwent extensive review by its funder, the U.S. Agency for International Development (USAID), and the U.S. FDA. Moreover, before any site could begin enrolling women into the study, approvals were required of national regulatory authorities in the trial site country and by the site's Institutional Review Board (IRB) or Ethics Committee (EC). IRBs and ECs ensure that studies are scientifically valid and ethically sound and provide oversight throughout the duration of the trial.

What are the benefits to enrolling in this kind of study?

Participants received HIV and STI risk reduction counseling and testing, physical and pelvic exams, Pap smears, STI treatment and/or referrals free of charge, and referrals for care for any other medical issues identified. If a participant tests positive for HIV after enrollment, she is referred to local care and treatment services and may return to the research clinic for additional counseling and other support services as needed.

About MATRIX

What is MATRIX?

MATRIX is a nine-year program funded in 2021 by USAID that aims to expedite the research and development of HIV prevention products for women-- including products designed to protect against both HIV and pregnancy – that addition to being safe and effective, will be acceptable, affordable, scalable and deliverable in the settings where they are needed most. MATRIX activities are focused on the early research and development of products, which involves both pre-clinical research (the animal and laboratory studies needed to support a product's evaluation in humans) and the first clinical trials of products. Through its North-South partnerships, MATRIX also aims to strengthen the capacity of African investigators to facilitate full and sustainable ownership of this work into the future.

Who is leading MATRIX, and where are its activities taking place?

MATRIX is being implemented by Magee-Womens Research Institute (MWRI) of the University of Pittsburgh Medical Center in the U.S., in collaboration with partner organizations in Kenya, South Africa and Zimbabwe. Leading the project is Sharon Hillier, Ph.D., of MWRI and the University of Pittsburgh School of Medicine, with Thesla Palanee-Phillips, Ph.D., from Wits RHI and University of Witwatersrand, South Africa, serving as deputy director.

What kind of products is MATRIX developing?

In order to meet the diverse needs of women, MATRIX aims to develop a range of HIV prevention products, including dual-purpose products for the prevention of both HIV and unplanned pregnancy. The current portfolio of critical path products includes a short-acting, on-demand product intended to be used at the time of sex (TAF/EVG fast-dissolving insert); and three monthly products: dapivirine vaginal film, a dual-purpose vaginal film containing dapivirine and levonorgestrel; and a non-antiretroviral/nonhormonal contraceptive dual-purpose vaginal ring. MATRIX is also supporting research seeking to develop products that could potentially provide protection for up to a year.

How is MATRIX unique?

Early research and development is an unpredictable process – of hundreds of potential products evaluated in pre-clinical research, only a handful will make it into early-phase clinical studies, and fewer still can expect to progress all the way to regulatory approval. To increase the odds of success, MATRIX is taking a unique approach that prioritizes only those products that have the greatest chance to succeed and add value. It's not enough that laboratory and animal studies suggest a product will be safe and effective in humans. There must also be evidence that potential end-users will likely use the product; it can be manufactured and distributed locally and at low cost; it will be easy to deliver, with minimal burden on healthcare systems; will meet the needs of Ministries of Health and national prevention programs; and serve to enhance the existing toolbox of options. It's a deliberately nimble and responsive approach to product development guided by clearly defined milestones, benchmarks and "Go/No-Go" criteria," with an independent scientific advisory group that provides unbiased assessment of a product's progress in meeting its timelines and milestones and considers developments within the broader field as well. Unlike most other HIV prevention programs, MATRIX is conducting Phase 1 studies, including first-in-human studies, in parallel in both the US and sub-Saharan Africa in order to gain important insight into the safety and acceptability of new products in the populations that are most important.

Why do we need more HIV prevention products when there's already oral PrEP, CAB-LA and the dapivirine ring?

According to UNAIDS 2024 global AIDS report , 44 percent of all new HIV infections globally in 2023 were among women and girls (all ages). In sub-Saharan Africa, women and girls accounted for 62 percent of all new HIV infections, with adolescent girls and young women (aged 15–24 years) accounting for 27 percent of new HIV infections and being three times as likely to acquire HIV as their male counterparts. Daily oral PrEP (pre-exposure prophylaxis), which requires taking an ARV tablet every day is the only biomedical prevention method generally available in Africa. Not everyone finds taking a daily pill easy or desirable, perhaps because of the side effects or the stigma associated with taking an ARV. Two other methods – the monthly dapivirine vaginal ring and cabotegravir long-acting injectable, or CAB-LA, which involves receiving an intramuscular injection every two months –are recommended by the World Health Organization (WHO) as additional prevention options for women and are approved and/or under regulatory review in several African countries. In many places, the only means of access to these products is through implementation studies. Although another method – lenacapavir given by injection every six months – was found to be highly effective in two large-scale trials and its approval is

likely, women will still need additional options. As has been learned from family planning, women have different preferences and needs, which can change at different times in their lives. Moreover, efficacy is not the only consideration in choosing which product to use. The best product is the one that can and will be used, which is why providing choice is important.

How likely is it that any of the products being developed under MATRIX will succeed?

Of some 5,000-10,000 compounds that might be considered for investigation for HIV prevention, only 50, at most, typically make it to Phase 1 trials, and of these, perhaps only one will advance through Phase 2 and Phase 3 trials and eventually be licensed for use.. While MATRIX has adopted a unique approach to improve the odds of success of its products – ensuring that only the most promising will enter clinical trials – there are no guarantees. Research and development is inherently risky, and products can fail at any step along the way due to, among other things, poor efficacy, safety concerns, poor adherence or cost. Given the realities, MATRIX researchers are hopeful that at least one or two of the products in its current pipeline will make it all the way to regulatory approval.

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For more information about MATRIX please visit www.matrix4prevention.org

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