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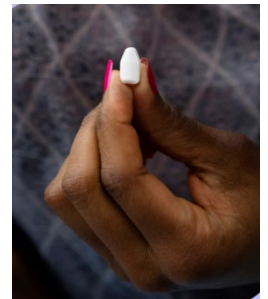
Questions & Answers

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 up to three days.



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 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?

The idea is that by using TAF and EVG together they would work hand-in-hand against HIV to provide a "one-two punch." TAF belongs to a class of ARVs called nucleoside reverse transcriptase inhibitors (NRTI) 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 emtricitabine. Laboratory and animal studies have shown that TAF also acts against herpes simplex virus (HSV). 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 on-demand HIV prevention product for use by women currently being evaluated in clinical trials. 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 products like the monthly dapivirine vaginal ring or cabotegravir injections given every two months. It may especially appeal to women who have infrequent or clustered sex and only want to use a product when needed, and also like that it delivers drug locally (inside the vagina), with little drug going elsewhere in the body. Because, in addition to HIV, TAF has shown activity against HSV (herpes), 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 nine 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.

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.

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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. Specifically, the study is evaluating 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 are being conducted to assess 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 to Phase 2 studies of its safety and acceptability when used as designed – at or around the time of sex.

Who is leading the study and where is it being conducted?

MATRIX-001 will enroll 60 women at three sites in Kenya, South Africa and the United States: the Kenya Medical Research Institute (KEMRI) Centre for Clinical Research Thika clinical research site (CRS); Centre for the AIDS Programme of Research in South Africa (CAPRISA) eThekweni CRS; and Eastern Virginia Medical School (EVMS) in Norfolk, Va. Protocol co-chairs are Leila Mansoor, B.Pharm, PhD, from CAPRISA, and Nelly Mugo, MBChB, Mmed, MPH, from KEMRI, both of whom also serve as the investigator of record at their respective sites.

When did the study start – and how long will it take to conduct?

The study enrolled its first participant in early December 2023 and is expected to take approximately one year to conduct, with results anticipated mid-2025.

How is MATRIX-001 designed? What's involved?

Women in the study will be randomly assigned to use either the TAF/EVG fast-dissolving insert or a placebo insert with no active drug. Each participant will use 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 will be timed to not coincide with a participant's menstrual cycle. Participants will insert the products themselves, the first time in the clinic with guidance from study staff. During the two to three months they are in the study, participants will undergo different tests and procedures and will be asked questions about product acceptability prior to, during and following insert use.

Who may enroll in the study?

To enroll in the study, participants must be between the ages of 18-50, assigned female sex at birth, be in general good health and not be HIV-infected, pregnant, or breastfeeding an infant under 6 months of age. Among other requirements, participants must 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 will be done to ensure the safety of participants in the study?

Several measures are in place to ensure the safety of participants, beginning at the site level. In addition, monthly (or more often as needed) reviews of safety data will be 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. Based on its review, the PSRT may recommend pausing or stopping the study. An Independent Safety Physician (ISP) with no interest (financial or otherwise) in the outcome of the study will also review participant safety data as part of regular study progress reviews. The ISP may choose to convene a panel of other experts to review study findings with the PSRT and, likewise, may recommend that the study proceed as designed, proceed with design modifications, or be discontinued.

Will women participating in the study provide informed consent?

Participants must provide informed consent to ensure they understand 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 will receive HIV and STI risk reduction counseling and testing, physical and pelvic exam, 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 will be 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 five-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 the Wits Reproductive Health and HIV Institute (Wits RHI) and University of Witwatersrand, South Africa, serving as deputy director.

What kind of products is MATRIX developing?

Diversity is the hallmark of MATRIX's product portfolio, which includes long-acting systemic products designed to provide protection for six months to a year; on-demand vaginal products meant to be used around the time of sex; and vaginal products that would be used for a month at a time. Some products are new formulations of existing ARV-based methods, while others contain novel antiviral agents. Four of the nine HIV prevention products being developed under MATRIX are dual-purpose products that in addition to providing protection against HIV would also provide contraception to prevent unplanned pregnancy.

How is MATRIX unique?

Research and development is a long and complex process that can take up to 10-12 years, with relatively few products advancing from pre-clinical research to human trials, and fewer still succeeding all the way to regulatory approval. MATRIX has adopted a unique approach that aims to improve the odds of success for the products in its portfolio, which includes seeking feedback from potential end-users and stakeholders much earlier in the process than is customary. As such, not only must its products show promise in laboratory and animal studies, they must also be products that women are likely to use, can be manufactured locally and at low cost, will be feasible and practical to introduce with minimum burden on healthcare systems, and align with the priorities of Ministries of Health and national HIV prevention programs. And while the first trials of HIV prevention products, particularly those involving women, are usually conducted in the United States or Europe, MATRIX will be conducting these studies in parallel in both the U.S. 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. Indeed, though most Phase 1 studies focus on safety and where and how drug is taken up in the body, under MATRIX, understanding whether women find the product acceptable is a primary objective as well.

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

According to UNAIDS, women and girls accounted for 63 percent of all new HIV infections in sub-Saharan Africa in 2022, versus 46 percent globally, and every week, an estimated 4,000 adolescent girls and young women aged 15–24 years became infected, 3,100 of whom were in sub-Saharan Africa. In much of Africa, daily oral PrEP, which requires taking an ARV tablet every day, is the only biomedical prevention method available. Daily pill-taking has been especially challenging for adolescent girls and young women. 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 approved and/or under regulatory review in several African countries. Presently, the only means of access to these products is through implementation studies,

such as Catalyzing Access to New Prevention Products to Stop HIV (CATALYST), which is being implemented by the USAID-funded Maximizing Options to Advance Informed Choice for HIV Prevention (MOSAIC) program. Even so, women have different preferences and needs, and at different times in their lives, which is why additional options are needed. As we've learned with contraception, the more options there are, the more likely there will be one that can and will be used.

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, at most, only 50 will 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. Failure may happen at any step along the way, and may be due to, among other things, poor efficacy, safety concerns, poor adherence, or cost. While MATRIX has adopted a unique approach to improve the odds of success for its products – ensuring that only the most promising will enter clinical trials – there are no guarantees. Given these realities, researchers are hopeful that at least one or two of the products in its current pipeline will succeed.

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

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The content and views in this document are those of MATRIX and its partners and do not necessarily reflect the views of the U.S. President's Emergency Plan for AIDS Relief, the U.S. Agency for International Development or the U.S. Government.

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