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Questions & Answers

The Monthly Dapivirine Vaginal Film and MATRIX-002 Study

About the Monthly Dapivirine Vaginal Film

What is the monthly dapivirine vaginal film?

The monthly dapivirine vaginal film is being developed as a discreet, user-controlled HIV prevention method for women. The film is designed so that when placed inside the vagina, and comes in contact with vaginal fluid, it slowly begins to dissolve, and in doing so, releases the antiretroviral (ARV) drug dapivirine. The drug continues to be slowly released over the course of a month until the film completely dissolves and all of the drug has been delivered in the vagina. This means that there is nothing to remove or discard before inserting a new film for another month of protection.

Who is developing the dapivirine vaginal film?

The monthly dapivirine film is being developed by a team of researchers from the University of Pittsburgh and Magee-Womens Research Institute (MWRI). They are also developing a dual-purpose vaginal film for one month protection against both HIV and pregnancy, which, in addition to dapivirine, contains the contraceptive hormone levonorgestrel (LNG). The University of Pittsburgh/MWRI team is collaborating with the Population Council, a global nonprofit research organization, which has acquired the dapivirine product pipeline from the International Partnership for Microbicides, in the development of both film products.

What is known about vaginal films – in particular for HIV prevention?

Similar to thin breath mint strips that dissolve in the mouth, vaginal films are products designed to dissolve after being inserted in the vagina. The use of vaginal films as a drug delivery platform is not new – a film containing the spermicidal agent Nonoxynol-9 (N-9) has been available over the counter in U.S. pharmacies for more than 40 years. The use of films for HIV prevention has been explored in a number of studies conducted in the United States and several African countries, including acceptability studies of fast-dissolving films containing no active drug, finding that many women are both willing to and interested in using films to protect against HIV. Researchers have also conducted Phase 1 studies of films containing different ARVs as the active drug, including daily quick-dissolve films containing tenofovir or dapivirine, and a film containing an experimental ARV called MK-2048 designed to dissolve over the course of seven days. In each of these studies, the film was found to be safe, acceptable to use and to release drug as it dissolves within the desired timeframe.

What is known about dapivirine??

Dapivirine belongs to a class of ARVs called non-nucleoside reverse transcriptase inhibitors that prevent HIV from making copies of itself. Dapivirine is already known to be safe and effective for preventing HIV when formulated as a vaginal ring. The dapivirine vaginal ring has been recommended by the World Health Organization as an additional HIV prevention option for women and approved for use in several African countries, including Kenya, South Africa and Zimbabwe.

What is different about the dapivirine film from other HIV prevention methods, particularly the monthly dapivirine ring? What gaps would it fill?

A vaginal film for HIV prevention would offer several advantages in that films are inexpensive to make, easy to store and environmentally friendly. An applicator is not needed for insertion and because the film dissolves, there is nothing to remove and discard as waste. Vaginal films are also discreet methods designed specifically for women, similar to vaginal rings. Unlike daily oral pre-exposure prophylaxis (PrEP) and cabotegravir injections, which deliver drug systemically (throughout the body), vaginal films and vaginal rings are designed to deliver drug locally, within the vagina, with little drug going elsewhere in the body. The dapivirine ring contains 25 mg of active drug, 4-5 mg of which is released during the month it is worn. The vaginal film, on the other hand, will contain about 35 mg of dapivirine, **all** of which will have been released by the end of the month, when the film is completely dissolved. What impact this may have on safety and efficacy is not yet known.

How far along in the development process is the monthly dapivirine film?

The monthly dapivirine film has undergone extensive laboratory and animal (nonhuman primate) studies demonstrating that it is able to release drug over 30 days, and importantly, with no safety concerns. However, before evaluating the monthly

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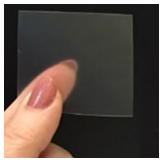
dapivirine film for its safety, drug release and distribution in a first-in-human Phase 1 trial, researchers want to be sure that women – particularly women in Africa – are comfortable with the idea of using a film that takes one month to dissolve. The MATRIX-002 study of two prototypes of a monthly film containing no active drug will help answer this question. The study will also help determine the film design to be evaluated in subsequent trials of dapivirine film products, beginning with a monthly film containing dapivirine only, followed by the dapivirine and LNG dual-purpose film, which is earlier in its development.

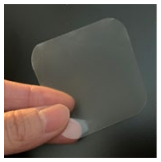
What role is MATRIX playing in the development of the two dapivirine film products?

Both the monthly dapivirine vaginal film and the dual-purpose monthly dapivirine and LNG contraceptive film are being developed through the U.S. Agency for International Development (USAID)-funded MATRIX program.

About the MATRIX-002 Study

What is the aim of MATRIX-002? And why is it important?





MATRIX-002 was designed to assess the acceptability, usability and safety of two prototype monthly vaginal films containing no active drug that are similar in size (2"x2") but differ in their shape – one has rounded corners, while the other has straight corners. As the first study of a vaginal film made to dissolve over the course of a month, MATRIX-002 will be important for understanding how participants feel about using a monthly film, whether they are able to insert the films themselves, which film is easier to insert, as well as what sexual partners think about the films. MATRIX-002 will help researchers understand what refinements may be needed in the film's design, including to its shape, before conducting a first-in-human study of a monthly film containing the ARV dapivirine. The study will also help to understand the kind of support and counseling women may need to use film and how best to address questions and concerns male partners may have.

Who led and funded the study?

The MATRIX-002 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 chairs are Nyaradzo Mgodi, MBChB, MMed, from Harare Health and Research Consortium (HHRC) Zengeza clinical research site (CRS) and Alexandra Minnis, PhD, from RTI International, Berkeley, California.

Where was MATRIX-002 conducted and what is its current status?

The study, which began in November 2023, enrolled 100 women and 26 sexual partners at five sites in four countries: In Kenya, at the Kenya Medical Research Institute (KEMRI) Centre for Clinical Research Thika CRS; in South Africa, at the Aurum Institute Klerksdorp CRS and the Wits Reproductive Health and HIV Institute (Wits RHI) CRS, Johannesburg; in Zimbabwe, at HHRC Sengeza CRS; and in the United States, at the University of Pittsburgh/MWRI CRS. Follow-up of all participants was completed in December 2024. The study's final results are anticipated mid-2025.

Why conduct a study with placebo products?

Previous studies have been of quick-dissolve or weekly vaginal films. A monthly film designed to dissolve over the course of 30 days has never been tested in women before. By conducting a study of placebo films with no active drug, researchers will be able to learn whether a monthly film will be acceptable for women to use. They will also be able to determine whether women prefer a film with rounded or straight corners and whether other refinements in film design may be needed so that when it comes time to evaluating a monthly film containing dapivirine in a first-in-human study, it will be of a product that has a greater chance of being acceptable and used correctly. In this way, the study will be better able to answer critical questions about safety and how and where the drug is released over the course of one month.

Why does the shape of the film matter?

In 2022, MATRIX convened stakeholder consultations in Kenya, South Africa, and Zimbabwe that included policymakers, advocates, civil society, providers, regulators, ethicists, former trial participants, and potential end-users, including young women, during which square placebo prototype films were passed around for meeting participants to touch and feel. Many of the stakeholders, in particular advocates and young women, disliked the straight corners of the film (echoing the views of some of the African women in previously conducted acceptability studies.) Based on this feedback, the product developer modified the shape of the film to round the film's corners, recognizing also that this modification in shape would result in a slightly higher product cost. While cost is an important factor to consider, this must be balanced with the preferences of end-users, insight into which the MATRIX-002 study will provide.

How was the MATRIX-002 study designed?

Women who enrolled into the study were randomly assigned to use one of two placebo films – either a film with straight corners or one with rounded corners. Participants used their assigned film twice – for one month each. During the first month of film use, women were to refrain from vaginal sex and use of vaginal products. During the second month of film use, there

were no such restrictions. Women inserted the films themselves in the clinic with study staff providing guidance and instructions. As part of the study, participants underwent physical and pelvic exams and different laboratory tests and procedures and asked questions about their experience and likes and dislikes with film use. Thirty participants also took part in an in-depth interview (conversation-style interview) at the end of the study so that researchers can gain deeper insight into women's experience with and views about the film. In-depth interviews were conducted with 26 sexual partners as well to better understand their opinions on the film.

Who could enroll in the study?

To enroll in the study, participants must have been between the ages of 18-45, assigned female sex at birth, in a mutually monogamous relationship, using an effective contraceptive method (other than a vaginal ring) and at low risk of acquiring HIV infection. Participants could not be pregnant or breastfeeding and had to agree to refrain from vaginal product use and vaginal sex during the first month they use their assigned film.

What was done to ensure the safety of participants in MATRIX-002?

Several measures were 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 were conducted by a Protocol Safety Review Team (PSRT), which includes the Protocol Co-Chairs, Protocol Safety Physician, USAID Medical Officer and the product developer representatives from the University of Pittsburgh/MWRI. An Independent Safety Physician with no interest (financial or otherwise) in the outcomes of the study also reviewed participant safety data on a regular basis.

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 study like MATRIX-002, which offers few direct benefits . Participation is voluntary – likewise, participants could choose to leave the study at any time. Separate informed consent was required of those participants who agreed to take part in in-depth interviews at the end of the study. In addition, participants were asked if their partner might be interested in participating in an in-depth interview Partners who agreed to participate provided written consent.

What approvals were needed to conduct the MATRIX-002 study?

MATRIX-002 underwent extensive review by USAID. Moreover, before any clinical research site can begin enrolling women into the study, approvals are required of national regulatory authorities in the trial site country and by the site's Institutional Review Board (IRB) and/or Ethics Committee (EC). IRBs and ECs ensure that studies are scientifically valid and ethically sound and provide ethical 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 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 is referred to local care and treatment services and may return to the research clinic for additional counseling and other support services as needed.

What is expected to happen after MATRIX-002?

Based on the results of the MATRIX-002 study, researchers will proceed with the manufacturing of the film design that is to be evaluated moving forward, with the next study – MATRIX-006 – being a phase 1 first-in-human clinical trial that will evaluate the safety, drug release and acceptability of the monthly dapivirine film at trial sites (to be determined) in the US and sub-Saharan Africa. Pending ethics and regulatory approvals in each trial site country, the study could potentially begin early 2026. In parallel, researchers will be working to refine production of the dapivirine/LNG dual-purpose film, which, because it contains a hormonal contraceptive, will require a more specialized manufacturing process, and begin exploring regulatory requirements for evaluating the dapivirine/LNG film. There is currently no guidance on the regulatory pathway for dual-purpose products or MPTs (multi-purpose prevention technologies).

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 in 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.

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

MATRIX is being implemented by MWRI of the University of Pittsburgh Medical Center (USA), 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 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 we have 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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