



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

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 hormonal contraceptive 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.

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.

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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 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.

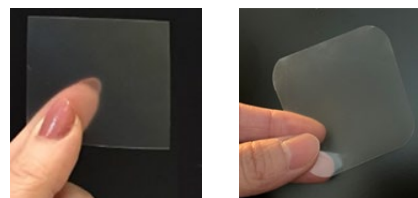
What role is MATRIX playing in the development of the two dapivirine film products?

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 will 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 designed 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 is leading the study and where is it being conducted?

MATRIX-002 will enroll 100 women and 30 sexual partners at five sites in four countries: In Kenya, at the Kenya Medical Research Institute (KEMRI) Centre for Clinical Research Thika clinical research site (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 Harare Health and Research Consortium (HHRC) Zengeza CRS; and in the United States, at the University of Pittsburgh/MWRI CRS. Protocol chairs are Nyaradzo Mgodzi, MBChB, MMed, from HHRC, who also serves as that site's investigator of record; and Alexandra Minnis, PhD, from RTI International, Berkeley, California.

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

The study began screening and enrolling participants in October 2023 at the University of Pittsburgh/MWRI CRS. Pending ethics and regulatory approvals, African sites are expected to begin before the end of 2023. Follow-up of all participants is expected to be completed in July or August 2024, with study results anticipated by the end of the year (2024).

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 on which will be provided through the MATRIX-002 study.

How is the MATRIX-002 study designed? What's involved?

Women will be randomly assigned to use one of two placebo films – either a film with straight corners or one with rounded corners. Participants will use their assigned film twice – for one month each. During the first month of film use, women are to refrain from vaginal sex and vaginal product use. During the second month of film use, there will be no such restrictions. Women will insert the films themselves in the clinic with study staff providing guidance and instructions. As part of the study, participants will undergo physical and pelvic exams and different laboratory tests and procedures and be asked questions about their experience and likes and dislikes with film use. Up to 35 participants will also be asked to participate in an in-depth interview (conversation-style interview) at the end of the study so that the study can gain deeper insight into women's experience with and views about the film. In-depth interviews will also be conducted with approximately 30 sexual partners to better understand their opinions on the film.

Who may enroll in the study?

To enroll in the study, participants must be 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 must also not be pregnant or breastfeeding and agree to refrain from vaginal product use and vaginal sex during the first month they use their assigned film.

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

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 includes the Protocol Co-Chairs, Protocol Safety Physician, USAID Medical Officer and the product developer representatives from the University of Pittsburgh/MWRI. Based on its review, the PSRT may recommend continuing as planned, pausing or stopping the study. An Independent Safety Physician with no interest (financial or otherwise) in the outcomes of the study will also review participant safety data on a regular basis and as needed.

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

What approvals are 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 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 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.

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?

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 of 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 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. 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 to use is also a primary objective.

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 (pre-exposure prophylaxis), 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 are 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 the Catalyzing Access to New Prevention Products to Stop HIV (CATALYST) study, 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, 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. 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 of its products – ensuring that only the most promising will enter clinical trials – there are no guarantees. Given the realities, researchers are hopeful that at least one or two of the products in the current pipeline will succeed.

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23 October 2023

MATRIX was established through 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).

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