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

Questions & Answers
The Non-ARV/Non-hormonal Contraceptive Dual-purpose Vaginal Ring and MATRIX-003 Study

About the Non-ARV/Non-hormonal Contraceptive Dual-Purpose Vaginal Ring

What is the Non-ARV/Non-hormonal Contraceptive Dual-Purpose Vaginal Ring?

The non-antiretroviral (non-ARV)/non-hormonal contraceptive dual-purpose vaginal ring is being developed as a method to protect women against both HIV and unplanned pregnancy for a month at a time. Women would insert and remove the ring themselves. The ring, which is 56mm (2.2") in diameter and 6.5mm (¼") thick and made of soft and flexible medical-grade materials, has two compartments. One contains the anti-HIV agent, an antiviral peptide (protein fragment), and the other a hormone-free contraceptive. When placed inside the vagina, the ring is designed to continuously release both drugs during the one month it is worn, with both agents acting locally in the vaginal fluids.

What is known about the two agents contained in the ring??

The anti-HIV agent is an antiviral peptide that blocks viruses from attaching to, penetrating, and infecting healthy cells in the body. Animal and laboratory studies suggest the antiviral drug also has activity against herpes simplex virus (HSV) and human papillomavirus (HPV). The non-hormonal contraceptive is a soluble adenylyl cyclase (sAC) inhibitor that impedes the movement of sperm and its ability to penetrate and fertilize eggs. The sAC inhibitor and antiviral peptide are new drugs and have not yet been evaluated in human clinical trials.

Who is developing the ring?

The non-ARV/non-hormonal contraceptive dual-purpose vaginal ring is being developed by the Oak Crest Institute of Science in Monrovia, Calif., in collaboration with scientists at Weill Cornell Medicine, the Medical College of Cornell University in New York City.

What is different about the ring from other HIV prevention methods? What gaps would it fill?

While similarly sized vaginal rings have been found to be safe and effective for use as a contraceptive (e.g., the NuvaRing) or for HIV prevention (e.g., the monthly dapivirine ring), the design of the Oak Crest dual-purpose ring, with its two cassette-like compartments, is unlike other rings studied to date. Whereas most biomedical HIV prevention methods that have been approved or are in development contain ARVs, Oak Crest's ring contains an anti-HIV agent that's a small peptide, not an ARV, and, hence, not used for the treatment of HIV. This means the development of drug resistance is less likely to be of concern should a woman be exposed to HIV while using the ring, though this will need to be confirmed in clinical trials. Similarly, because the ring's contraceptive targets sperm, researchers expect it would have little or no effect on a woman's menstrual cycle or fertility. Notwithstanding these potential benefits, a single product offering protection against both HIV and unwanted pregnancy would be attractive option for many women.

How far along in the development process is the dual-purpose ring.?

Thus far, researchers have conducted one study involving 12 women in the United States that evaluated short-term (one hour) use and ease of insertion and removal of placebo rings (containing no active drugs) that differed slightly in design, geometry and hardness/stiffness. Women were instructed to perform various physical activities while the ring was in place, such coughing, squatting and jumping up and down. The study, which found no safety or usability concerns, guided the ring designs to be evaluated in the MATRIX-003 study, in which women will use placebo rings for a month at a time and determine the ring design that would move forward into early phase clinical trials, including a first-in-human study of the vaginal ring containing the antiviral and non-hormonal contraceptive.

-more-

What role is MATRIX playing in the development of the ring?

The non-ARV/non-hormonal contraceptive dual-purpose vaginal ring is being developed through the U.S. Agency for International Development (USAID)-funded MATRIX program. MATRIX is supporting development of the vaginal ring for its primary indication to protect against HIV and unplanned pregnancy.

About the MATRIX-003 Study

What is the aim of MATRIX-003? And why is it important?

MATRIX-003 is designed to collect data on the acceptability, usability and safety of two placebo rings (with no active drug) when used for a month at a time. While the two placebo rings to be evaluated are identical in size and design, there are slight differences in their flexibility and stiffness. The study will help determine what women like or dislike about each of the rings, which of the two is easier for women to insert and remove, and how well the rings remain in place during normal daily activities. . The MATRIX-003 study will also assess sexual partners' attitudes toward and experiences with the vaginal ring, particularly within the context of sex. The overall goal of the study is to inform the final design of a ring containing an antiviral peptide and a non-hormonal contraceptive to be evaluated in a first-in-human Phase 1 clinical trial.

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

MATRIX-003 will enroll 100 HIV-negative women and approximately 30 sexual partners at five sites: one in the United States (University of Pittsburgh/Magee-Womens Research Institute, or MWRI); three in South Africa (Aurum Institute, Wits RHI and the Centre for the AIDS Programme of Research in South Africa, or CAPRISA); and one in Zimbabwe (Harare Health and Research Consortium, or HHRC). Protocol co-chairs are Kathryn Mngadi MBChB (Aurum Institute) and Krishnaveni (Surina) Reddy, MMedSci (Wits RHI). Dr. Mngadi also serves as the investigator of record of the Aurum site.

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

The study began enrolling participants at the U.S. site in March 2024. Pending regulatory and ethics approvals, the four African sites are expected to begin screening and enrollment of participants by mid-year. The study is anticipated to take approximately one year to conduct, with results early 2025.

How is the MATRIX-003 study designed? What's involved?

All women in the study will use both placebo rings, each for approximately four weeks. Which placebo ring women use first will be determined by randomization. With each ring, women will be asked to abstain from vaginal sex for the first two weeks of use and from use of all vaginal products throughout the duration of the study. Women will insert the rings 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 ring use. Approximately 30 participants will also be asked to participate in an in-depth interview at the end of the study so that the study can gain deeper insight into women's experience with and views about the ring. In-depth interviews will also be conducted with 30 sexual partners to better understand their opinions about the ring.

Who may enroll in the study?

To enroll in the study, participants must be between the ages of 18-45, have been assigned female sex at birth, be in a mutually monogamous relationship, using an effective contraceptive method (other than a vaginal ring) and be at low risk of acquiring HIV. Participants must also not be pregnant or breastfeeding and agree to refrain from vaginal sex during the first two weeks of use with each ring and vaginal products throughout the study.

What is being done to ensure the safety of participants in MATRIX-003?

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, Clinical Research Manager and a product developer representative. Based on its review, the PSRT may recommend continuing as planned, pausing or stopping the study. Both the Clinical Data Manager and 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 more often 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-003, 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 the 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 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.

What approvals are needed to conduct the MATRIX-003 study?

MATRIX-003 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.

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.

# # #

21 March 2024

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).