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QUESTIONS AND ANSWERS
MTN-034 - The REACH Study

About REACH

What is the REACH study?
REACH (Reversing the Epidemic in Africa with Choices in HIV prevention), or MTN-034, is a Phase IIa open-label study designed to fill important gaps in information about the safety and acceptability of the monthly dapivirine vaginal ring and Truvada® as daily oral pre-exposure prophylaxis (PrEP) in girls younger than 18 and to supplement existing safety and acceptability data of these products in young women ages 18-21. REACH also seeks to understand how adolescent girls and young women use the ring and oral PrEP, their preferences for either or both approach and what kind of support they need to use them as best they can. To provide protection against HIV, both must be used consistently– daily, for oral PrEP, and for the ring, a full month at a time – which previous studies of these products found to be especially challenging for younger women. REACH has enrolled 247 adolescent girls and young women ages 16-21 at four sites in South Africa, Uganda and Zimbabwe, 86 or whom were under the age of 18 at the time of enrollment.

Who is conducting and funding the study?
REACH is being conducted by the Microbicide Trials Network (MTN), which is funded by the National Institute of Allergy and Infectious Diseases (NIAID), the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development and National Institute of Mental Health, all components of the U.S. National Institutes of Health. Gonasagrie (Lulu) Nair, MBChB, MPH, of Stellenbosch University in South Africa, is protocol chair. Protocol co-chairs are Connie Celum, MD, MPH, of the University of Washington, USA, and Kenneth Ngure, PhD, MPH, of Jomo Kenyatta University of Agriculture and Technology in Kenya.

Where is REACH being conducted?
REACH is being conducted at four MTN-affiliated clinical research sites (CRSs): the Makerere University-Johns Hopkins University (MU-JHU) CRS in Kampala, Uganda; the University of Zimbabwe Clinical Trials Research Centre Spilhaus CRS in Harare; and, in South Africa, at the Wits Reproductive Health and HIV Institute in Johannesburg, and at the Emavundleni CRS of the Desmond Tutu HIV Foundation in Cape Town.

Why is REACH important?
Globally, more than half of all people living with HIV are women, and in sub-Saharan Africa, women account for more than 60 percent of adults with HIV. Rates of infection are especially high among adolescent girls and young women. According to UNAIDS, in 2020, one in four new infections in sub-Saharan Africa were in young women ages 15-24, despite making up only 10 percent of the population. Ensuring that young women and girls can have access to and benefit from safe and effective HIV prevention methods is vitally important.

Daily oral PrEP is approved in many countries, and in some places, being offered to adolescent girls. The dapivirine ring is a new HIV prevention method currently under regulatory review in several countries. Neither of these methods can be effective if not used consistently, which in previous trials has been a challenge for young women. REACH aims to understand what kind of support adolescent girls and young women need to help them use these products better so they can have the benefit of being protected. Yet, for the ring to even be considered as an option for adolescent girls, specific data about its safety in this population is needed – data that the REACH study intends to provide. Not everyone will want to use the ring, and not everyone will want to use oral PrEP. Moreover, as circumstances change, so will needs and preferences for HIV prevention. That's why having both the ring and oral PrEP (and other methods) is so important, because the more HIV prevention options that are available to adolescent girls and young women, the more likely one can and will be used.

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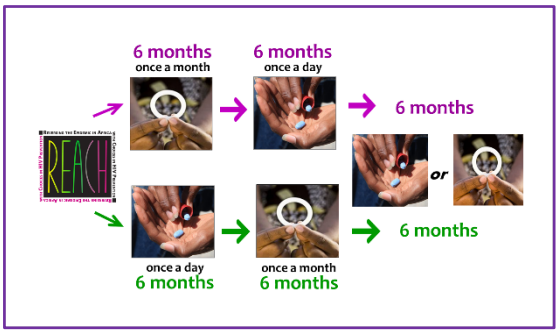
Why is safety data in adolescent girls so important?
When a new drug is being considered for its potential approval, regulatory authorities will examine data collected from multiple studies conducted over several years, from the animal and pre-clinical laboratory studies conducted during the drug's early development to the Phase I, II and III clinical trials in humans. It's the results of the Phase III trials – at least two are usually required – that perhaps carry the greatest weight, and seldom do these studies enroll participants who are under the age of 18. As a result, a drug that receives approval will, at least initially, be limited to the same population studied. The Phase III trials for the dapivirine ring were conducted among cisgender women ages 18-45, and, as such, additional data is needed to support the ring's use in women younger than 18. The ring's developer, the nonprofit International Partnership for Microbicides, plans to submit the data from REACH, as well as from the MTN-023/IPM 030 study among adolescent girls ages 15 to 17 in the United States, to regulators so that they can consider approving the ring for adolescent girls.

How is REACH designed?
In REACH, all participants use both the dapivirine ring and Truvada as oral PrEP, each for six months, the order of which is determined by randomization. After having experienced using both the ring and oral PrEP, participants then choose which one they want to use for the remaining six months of the study, or they may choose to use neither. Moreover, participants are free to change their minds. REACH is the first HIV prevention study incorporating the concept of informed choice into its design. Throughout the study, participants receive extensive support and counseling focused on helping them to use their assigned (or chosen) product as best they can.



To evaluate the safety of each product, researchers conduct medical exams and laboratory tests of blood, urine and vaginal fluid. To evaluate adherence and acceptability, participants answer questions about their use and experience with each product, both on a computer and in face-to-face conversations with site staff. Some participants may also be asked to take part in in-depth interviews or focus group discussions to help researchers gain additional insight into what motivates or is challenging about using each products. Laboratory tests for adherence are used to determine how well participants are using each product. Adherence to oral PrEP is based on levels of drug in blood samples taken at each monthly visit. For the ring, researchers look at the amount of residual drug left in rings participants return after a month of use.

Why hasn't REACH enrolled 300 participants, as originally planned?
While REACH was originally designed to enroll 300 participants, 100 of whom would be 16 and 17 years of age, in March 2020, in the face of the emerging COVID-19 pandemic, MTN and study leadership decided to close the study to further enrollment so that fullest attention could be paid to ensuring the safety of its current participants as well as clinic staff. By this time, REACH had already enrolled 247 participants, including 86 (35 percent) who were under the age of 18, such that the study would still be able to provide sufficient data about the safety of the dapivirine vaginal ring and oral PrEP in adolescent girls and young women, and to do so in less time as well.

When did REACH start? When will results be available?
REACH began in February 2019 and by April 2021 all participants had completed the first two periods, during which they were asked to the ring and oral PrEP each for six months. As of July 2021, most participants have also completed the choice period and exited the study. Follow-up of the remaining participants in the study is expected to be completed in October 2021, with final results anticipated early or mid-2022. Interim results, however, from the study's first two periods, were reported in July (2021) at IAS 2021 – the 11th IAS Conference on HIV Science. As such, REACH has already demonstrated that adolescent girls and young women can and will use oral PrEP and the dapivirine ring with consistency. The vast majority (97 percent) of the study's 247 participants used the vaginal ring and daily oral PrEP some or all of the time, and fewer than three percent of participants used neither of the products. Both approaches also received high marks from participants: 88 percent said they liked using the ring and 64 percent said they liked the daily pill-taking regimen of oral PrEP; and both were well tolerated with no safety concerns. As REACH is still an ongoing study, the safety of these products continues to be monitored by the research team.

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What do the study's interim results say about how well participants used each of the products?
Using laboratory measures for adherence, researchers determined that during the six months participants were assigned to use oral PrEP, 39.9 percent had drug levels that suggested they used oral PrEP at least some of the time, meaning they took the tablets between one and three times a week; and 58.6 percent were classified as high users, whose drug levels suggested they took the tablets at least four times a week, which among men who have sex with men has been associated with 100 percent protection. The threshold for protection in cisgender women has yet to be determined. For the ring, drug levels in returned rings suggested that 45.4 percent used it at least some of the time, and that 50.2 percent used the ring for the full month. Full compliance to oral PrEP, whereby blood levels indicate taking at least six pills per week, was evident for 22 percent of the participants. Because of the differing laboratory methods used for determining adherence to each product, direct comparisons between the two are not feasible, nor was not the intent of researchers anyway. Instead, researchers wanted to see how well REACH participants used oral PrEP and the ring compared to participants in previous studies of these products. What the data demonstrates is that, indeed, they used daily oral PrEP and the monthly ring more consistently than was seen in other studies and that *both* approaches are feasible options for adolescent girls and young women.

What did the earlier trials of PrEP and the ring show in terms of younger women's use of these products?
In the two Phase III trials of the ring, younger women used the ring least regularly, and as a group, had the lowest rates of risk reduction. In ASPIRE, for example, the ring was not shown to be effective among women ages 18-21, with levels of drug in returned rings also indicating low adherence to use. Likewise, daily pill taking was more challenging for younger women in the Phase III trials of oral PrEP (VOICE and FEM-PrEP). In the HPTN 082 open-label study among adolescent girls and young women in South Africa and Zimbabwe, found that 85 percent of the participants used oral PrEP with some regularity at the beginning of the study, but when clinic visits changed from monthly to every three months, there was a steep decline. Three months into the study, fewer than 25 percent were using oral PrEP, and by month 12, it was only nine percent.

Why do you think REACH participants used the ring and oral PrEP so well?
The research team attributes the study's interim findings of high product adherence and acceptability to the ongoing support measures, tailored specifically for adolescent girls and young women, and nonjudgmental counseling approach provided as part of the study.

At the Trial Site

What kind of approvals were required to conduct this study?
REACH underwent extensive and rigorous review by NIAID and the US 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.

Did participants provide informed consent?
The legal age at which an individual may provide informed consent to enroll in a research study is 18. As such, in REACH, a participant under the age of 18 could only provide informed assent (agreement) with the permission of her parent and/or legal guardian also being required. Participants who turned 18 during the study were re-consented as an adult. A participant who was under the age of 18 but considered to be an emancipated minor (because they are married, a mother or head of a household) could legally provide consent. Regardless, all participants who volunteered to join REACH (and their parents and/or guardians, if they were minors) were informed about all the study procedures, any possible risks, benefits and alternatives to participation, as well as the study's requirements. Study staff also explained that they did not have to take part in the study and may leave it at any time, without consequence. All information was provided in simple terms and translated into local languages.

Who could enroll in REACH?
To enroll in REACH, women must have been between 16 and 21 years old and HIV-negative as well as have been using an effective form of contraception for at least two months before starting the study and agree to use a contraceptive throughout participation. Potential participants who weren't already using a contraceptive were counseled by site staff on different options and provided their method of choice prior to enrollment.

Why were participants required to use contraception for at least two months before they could enroll?
The reason for requiring that women be using a contraceptive for at least two months prior to enrollment was to allow enough time for initial side effects to subside before beginning use of the dapivirine ring or oral PrEP. In this way, researchers – and participants – would be more certain that any side effects or changes that occur during product use were due to the ring or PrEP and not the contraceptive.

What does participation in the study involve?
Participants are in the study for about 19 months, with monthly clinic visits throughout. Each study visit includes a meeting with a counselor to discuss their experience using the dapivirine ring or oral PrEP and strategies that may help improve their use. Participants also answer questions about their use and experience using the products on a computer. Some may be asked to take part in in-depth interviews and focus group discussions to help researchers better understand what motivates or is challenging about using each product. To monitor the health and safety of participants, various tests and exams are conducted. Visits also include HIV testing and risk-reduction counseling, including the provision of condoms; testing and treatment of other sexually transmitted infections (STIs); and pregnancy testing and contraceptive counseling. At some visits, physical and pelvic exams are conducted.

How are participants supported to use the ring and oral PrEP?
As part of REACH, study participants receive extensive support and counseling focused on helping them to use their assigned (or chosen) product as best they can. Every monthly visit includes a meeting with a counselor, and participants can also choose from a menu of additional forms of support, including daily text messages or weekly check-ins by phone; having a "Peer Buddy"; and adherence support groups. At some sessions, participants receive their individual adherence test results as a way to help facilitate discussion about adherence and how it relates to HIV risk reduction. Results are presented in terms of what they mean for level of protection they are receiving – either low, medium or high – and without judgement. No matter what the results suggests, counselors provide encouragement and offer to help in whatever way they can. Study participants are also encouraged to be open with study staff about any concerns or difficulties they may have. If participants aren't willing or able to use the ring or oral PrEP, researchers want to understand why so that other measures of support might be considered. At the same time, the study intends to help participants recognize that these products won't be for everyone, and the reasons why are just as important for researchers to understand.

What measures are being taken to ensure the safety of study participants?
REACH is being conducted with numerous measures to protect the safety and well-being of participants. First, potential volunteers are carefully screened by site teams to ensure that only women for whom it would be safe to participate are enrolled. During the study, thorough evaluations of the health, safety and welfare of participants are conducted at each study visit. In addition to these protections at the site level, participant safety is also monitored by MTN's Statistical and Data Management Center, which assesses incoming reports on a daily basis, and by a Protocol Safety Review Team (PSRT) that meets monthly. A Study Monitoring Committee (SMC) responsible for general study oversight will also conduct periodic reviews of study conduct, including participant safety. Based on its review the SMC may at any time recommend that the study proceed as designed, proceed with design modifications, or be discontinued.

Is there concern about social harms or intimate partner violence? How are instances of these managed by study sites?
Intimate partner violence is an unfortunate reality for many women in the communities where REACH is being conducted. As such, the study team recognizes that social harms or intimate partner violence could be experienced by some study participants. Other participants could experience social harms simply as a result of being in the study, or because they are using PrEP or a vaginal ring. They may feel undue pressure from partners, family members or friends, or experience stigma or discrimination from family members and members of their community. All sites have processes in place to address any instance of intimate partner violence or social harms that may occur to ensure the participant is provided appropriate support and counseling by site staff and referred to any services not available at the site, and that measures are taken to protect her safety. Moreover, all sites are required to have a social harms committee with members who have expertise in areas such as research ethics, protection of minors, women's rights law and gender-based violence response and prevention to ensure adequate

support is provided to any participant who experiences social harm. The committee provides advice and guidance on possible referral organizations, legal obligations, and any other relevant resource or information with the goal of supporting participant autonomy and wellbeing while ensuring ethical obligations of the study.

What if a participant becomes pregnant?
While participants must use contraception while in the study, as precaution, pregnancy tests are conducted at each monthly clinic visit. If a participant gets pregnant during the study, she will stop use of the ring or oral PrEP, but can remain in the study and continue with routine study visits. She will also be referred by study staff to available sources of medical care and other services that she or her baby may need. Depending on the timing and outcome of pregnancy relative to the study's progress, she may be able to resume use of the ring or oral PrEP. If a participant gets pregnant and also acquires HIV, she will also be referred to specialized services aimed at preventing HIV transmission to her infant, and be offered expedited resistance testing that may be useful for identifying optimal treatment regimens.

What happens if a participant acquires HIV during the study?
A comprehensive HIV prevention package is provided to all women throughout the trial. This includes HIV risk-reduction counseling, free condoms, regular HIV testing and testing for and treatment of other STIs. Despite these intensive efforts, some women may still acquire HIV while they are participating in REACH. Women in the trial who test positive for HIV will immediately stop using their assigned product – the dapivirine vaginal ring or Truvada as PrEP – and be counseled and referred by study staff to local HIV care and support services. Women are encouraged to remain in the study and continue with routine study visits.

About the Dapivirine Ring and Oral PrEP

What exactly is the dapivirine vaginal ring?
The dapivirine ring is the first biomedical HIV prevention product designed specifically for women. The ring is made of a flexible silicone material containing 25mg of the ARV drug dapivirine, about 4 mg of which is released into the vagina when used continuously for 28 days with low absorption elsewhere in the body. Women can insert and replace the ring themselves each month. IPM, the ring's developer, is seeking its regulatory approval in several African countries as well as in the United States.

What is the regulatory status of the ring?
In July 2020, the ring received a positive opinion from the European Medicines Agency (EMA) for its use among women ages 18 and older in developing countries, an important first step toward its potential approval by regulatory authorities in countries where women are especially vulnerable to HIV. Soon after, the ring was added to the World Health Organization's (WHO) list of pre-qualified medicines. IPM is seeking approval of the ring in eastern and southern Africa, including in countries where REACH is being conducted. In July 2021, the ring received its first approval, from the Medicines Control Authority of Zimbabwe. IPM is also seeking regulatory approval from the US Food and Drug Administration.

In anticipation of the ring's potential approval, WHO's updated guidelines for HIV prevention, published in March 2021, recommend the ring as an additional HIV prevention choice for women at substantial risk of HIV, while also acknowledging that studies like REACH will help to better understand ways to support consistent and persistent use of both PrEP and the ring in adolescent girls and young women.

What do we know about the dapivirine vaginal ring? Is it effective?
Multiple studies of the ring conducted in Africa, Europe and the US have shown it to be well-tolerated in HIV-negative women, with no safety concerns. The largest of these were two Phase III clinical trials – ASPIRE (MTN-020), conducted by the MTN, and The Ring Study (IPM 027), led by IPM – involving more than 4,500 women ages 18-45 in Malawi, South Africa, Uganda and Zimbabwe. Results, reported in 2016, found the dapivirine ring reduced the risk of HIV by approximately 30 percent overall. Higher levels of protection were seen in women who used the ring most regularly. Results of the HOPE (MTN-025) open-label extension (OLE) study for former ASPIRE participants, and the DREAM (IPM 032) OLE for former Ring Study participants,

which were first reported in 2019, showed increased ring use and suggested a greater reduction in HIV risk (about 50 percent) than in the Phase III trials. Without a placebo group, however, these findings don't have the same strength of evidence.

What did the previous study of the ring in adolescent girls, MTN-023/IPM 030, find?
MTN-023/IPM 030 was a Phase IIa study that evaluated the safety and acceptability of the dapivirine vaginal ring among 96 girls between the ages of 15-17 at six sites in the United States. Results, which were reported in 2017, found no differences in safety outcomes between the dapivirine ring and the placebo ring. Adherence to the ring was also high, with 95 percent of the rings participants returned to the clinic having drug levels suggesting regular use during the previous month.

What is oral PrEP?
PrEP, which stands for pre-exposure prophylaxis, is an HIV prevention method in which people who don't have HIV take an ARV pill daily to reduce their risk of being infected. WHO recommends oral PrEP for anyone at significant HIV risk.

The ARV pill most commonly used as PrEP is Truvada, the brand name for a tablet containing the ARVs tenofovir disoproxil fumarate and emtricitabine that is marketed by Gilead Sciences of Foster City, California. Truvada was originally developed (and still used) for the treatment of HIV, in combination with other ARVs. Truvada was first approved for use as PrEP by the US FDA in 2012 and has since been approved in more than 50 countries.

In 2019, Gilead obtained FDA approval of a second drug for PrEP called Descovy®, which contains emtricitabine and tenofovir alafenamide (F/TAF). Approval does not apply to people at risk of getting HIV through receptive vaginal sex, because effectiveness in this population has not yet been evaluated. The safety and efficacy of F/TAF among cisgender adolescent girls and women will be evaluated as part of a trial Gilead is planning in South Africa and Uganda.

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Click here to watch a short video about REACH. Additional information about REACH can also be found at https://mtnstopshiv.org/reach-study and www.mtnstopshiv.org/news/studies/mtn034.

About the Microbicide Trials Network

The Microbicide Trials Network (MTN) is an HIV/AIDS clinical trials network established in 2006 by the National Institute of Allergy and Infectious Diseases with co-funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the National Institute of Mental Health, all components of the U.S. National Institutes of Health. Based at Magee-Womens Research Institute and the University of Pittsburgh, the MTN brings together international investigators and community and industry partners whose work is focused on the development and rigorous evaluation of promising microbicides – products applied inside the vagina or rectum that are intended to prevent the sexual transmission of HIV – from the earliest phases of clinical study to large-scale trials that support potential licensure of these products for widespread use. More information about the MTN is available at http://www.mtnstopshiv.org.

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