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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 study that seeks to understand the HIV prevention needs and preferences of adolescent girls and young women in sub-Saharan Africa, who are among those most vulnerable to HIV. Specifically, the study is evaluating how adolescent girls and young women use the monthly dapivirine vaginal ring and Truvada® as daily oral pre-exposure prophylaxis (PrEP) and their preferences for each, as well as evaluating the safety of both approaches in this population. REACH will enroll 300 HIV-negative adolescent girls and young women ages 16-21, with at least 100 being under the age of 18 at 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 the Desmond Tutu HIV Centre in South Africa is protocol chair. Protocol co-chairs are Connie Celum, MD, MPH, of the University of Washington, USA, and Kenneth Ngure, PhD, 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) in sub-Saharan Africa: in Uganda, the Makerere University-Johns Hopkins University CRS, Kampala; in South Africa, at both the Wits Reproductive Health and HIV Institute in Johannesburg and the Emavundleni CRS of the Desmond Tutu HIV Foundation in Cape Town; and in Zimbabwe, at the University of Zimbabwe College of Health Sciences Clinical Trials Research Centre Spilhaus CRS, Harare.

Why is REACH important?
Globally, more than half of all people living with HIV are women, and in sub-Saharan Africa, women account for nearly 60 percent of adults with HIV. Rates of infection are especially high among adolescent girls and young women. In parts of Africa, it's estimated that 1,000 girls and women aged 15-24 get HIV every day. Ensuring that young women and girls have access to and benefit from safe and effective HIV prevention methods is vitally important. REACH aims to fill important gaps in information about the safety and acceptability of two methods – Truvada as daily oral PrEP and the dapivirine ring – that could potentially make a difference.

The dapivirine ring is a new method undergoing regulatory review that, if approved, would be the first biomedical prevention method specifically for cisgender women – who are 18 and older. REACH will provide information about the ring's safety among girls as young as 16 so that regulatory bodies can consider expanded approval to include a younger population. While Truvada as oral PrEP is already approved in many countries, relatively little data is available about its safety in young women – REACH will contribute additional data about this as well. Both methods must be used consistently and regularly to be effective – daily for oral PrEP, and monthly for the ring – which has been a challenge for younger women in clinical trials. REACH also seeks to understand what support young women need to use these products better, which is important for broader implementation of both PrEP and the ring, as well as the development of other HIV prevention methods.

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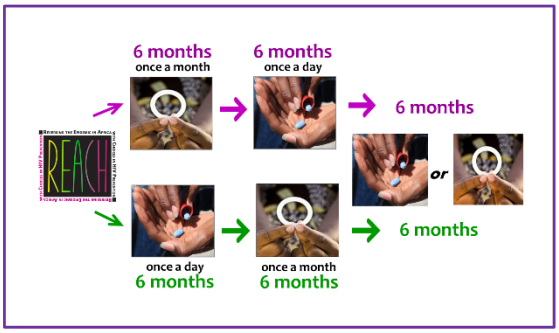
When did REACH start and how long will it take to be conducted?
REACH, which began in February 2019, is expected to take about three years to conduct, with results anticipated in late 2022. (*On 19 March 2020, screening and enrollment into the study was paused in response to the global COVID-19 pandemic. As of this date, 247 of 300 participants were enrolled, including 85 under the age of 18. While follow-up of these participants is continuing to the extent that it is both feasible and safe for participants and staff, study timelines may shift depending on the length of time that enrollment is paused*.)

How is REACH designed?
REACH is a type of clinical trial called an open-label study. Open-label means the study participants and site staff know which products they are receiving. In REACH, there are two active products: the dapivirine vaginal ring, which is used for a month at a time, and an oral tablet called Truvada taken daily, a regimen often referred to as oral PrEP. All participants will use each product for six months. Random assignment will determine the order in which products are used. Participants will either use oral PrEP for the first six months and then the ring for the following six months, or the ring first and then PrEP. After experiencing both methods, participants will have a choice of using either the ring or oral PrEP – or neither – for an additional six months.



To evaluate the safety of each product, researchers will conduct medical exams and laboratory tests of blood, urine and vaginal fluid. To evaluate adherence and acceptability, participants will answer questions about their use and experience with each product, both on a computer and in face-to-face conversations with site staff. In-depth interviews and focus group discussions will provide additional insight into what motivates or is challenging about using each product. Objective measures of adherence will also help to evaluate how well participants are using each approach. Oral PrEP use will be measured by drug levels in blood samples taken at each monthly visit. For the ring, researchers will look at the amount of residual drug left over in used rings participants return each month.

How is REACH unique?
REACH is the first HIV prevention study incorporating the concept of informed choice into its design – after having experienced both oral PrEP and the ring, each for six months, participants are able to choose which of the two they want to use for the remaining six months of the study, or they may choose neither. Moreover, participants may change their minds during these last six months as often as they like. Researchers designed the study this way to be able to collect what data is needed about the safety and acceptability of the monthly dapivirine ring and Truvada as daily PrEP, as well as to understand the HIV prevention preferences of adolescent girls and young women.

Having choice is important, because no single method will suit everyone, nor suit everyone all the time. As a person's circumstances change, so do needs and preferences. As with contraception, the more HIV prevention options available to women, the more likely one can and will be used. For adolescent girls and young women, choice may also be empowering by being able to make decisions on their own and taking control of their own health and behaviors.

About the Dapivirine Ring and Oral PrEP

What exactly is the dapivirine vaginal ring?
The dapivirine vaginal ring is made of a flexible silicone material containing 25mg of an antiretroviral (ARV) drug called dapivirine. Women can insert and replace the dapivirine ring themselves each month. When placed inside the vagina, the ring delivers the drug directly to the site of potential infection over the course of a month, with low absorption elsewhere in the body, which could help minimize side effects. Dapivirine, also known as TMC-120,

belongs to a class of ARVs called non-nucleoside reverse transcriptase inhibitors (NNRTI) that block HIV's ability to replicate itself inside a healthy cell. The ring was developed by the International Partnership for Microbicides (IPM), which holds an exclusive worldwide license for dapivirine from Janssen Sciences Ireland UC, one of the Janssen Pharmaceutical Companies of Johnson & Johnson, designed to ensure that women in low-resource settings have affordable access to any dapivirine-based microbicide. IPM is seeking regulatory approval of the ring for women ages 18-45. If approved, the dapivirine ring would be the first biomedical prevention method designed specifically for cisgender women and the first long-acting method.

What do we know about the dapivirine vaginal ring?
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, conducted by the MTN, and The Ring Study, led by IPM – involving approximately 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. Higher levels of protection were seen in women who used the ring most regularly, and among participants under 21, who used the ring least, it was not effective. In 2019, results of two open-label extension studies – HOPE for former ASPIRE participants and DREAM for former Ring Study participants – found women's uptake of the ringer was higher than in the Phase III trials. Together, the results also suggest a greater reduction in HIV risk (about 50 percent), though researchers caution that without a placebo group, these findings cannot be viewed with the same level of confidence.

The MTN has conducted several other studies of the dapivirine ring, including a Phase I trial called MTN-023/IPM 030 among adolescent girls in the United States. Current trials – DELIVER (MTN-042) and B-PROTECTED (MTN-043) – will provide information about the safety of the ring in pregnant and breastfeeding women, respectively.

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 US sites. Participants were randomly assigned to use either the dapivirine ring or a placebo ring each month for a total of six months. Results, which were reported in 2017, found no differences in safety outcomes between the dapivirine ring and the placebo ring. Adherence to ring use was also high, with 95 percent of the rings that participants brought back to the clinic having drug levels that suggested regular use during the previous month. Most participants said the ring was easy to use and they were not aware of it during daily activities. While some were worried that their partner would feel it during sex, overall, the majority of participants (93 percent) said they liked the ring.

What is the timeline for regulatory review and approval of the ring?
The dapivirine ring is under review by the European Medicines Agency (EMA) through the Article 58 procedure, which allows the EMA, in cooperation with the World Health Organization (WHO), to provide a scientific opinion on the ring's use in developing countries, where women face the highest HIV risk. A scientific opinion is expected in 2020. IPM also plans to submit applications to the US Food and Drug Administration (FDA) and the South African Health Products Regulatory Agency, followed by other national regulatory authorities in Africa. IPM is working across sectors to prepare for the ring's possible introduction, initially in eastern and southern Africa. Approvals would not apply to girls under the age of 18 or pregnant and breastfeeding women. Additional data will be needed before regulators would consider expanded approval for these populations. The REACH, DELIVER and B-PROTECTED studies are designed specifically to provide this kind of information in the respective populations.

What is PrEP?
Oral 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 getting HIV. The WHO recommends oral PrEP for anyone at significant HIV risk.

The ARV pill most commonly used as PrEP is called 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 is still used for the treatment of HIV, in combination with other ARVs. Truvada's use for prevention of HIV (PrEP) in adults was approved by the US FDA in 2012. Approval was expanded to include adolescents at risk of HIV in 2018. While Truvada as PrEP is approved in many countries, this primarily applies to adults. However, some national programs are targeting services for adolescent girls and young women as well.

In 2019, Gilead obtained FDA approval of a second drug for oral PrEP called Descovy®, which contains emtricitabine and tenofovir alafenamide (F/TAF). Its approval does not apply to people at risk of getting HIV through receptive vaginal sex, however, because effectiveness in this population has not been evaluated. Gilead is planning a trial to begin sometime in 2020 to collect data about the safety and efficacy of F/TAF among cisgender women in Africa.

What is known about oral PrEP in women?
In the Partners PrEP Phase III study, daily use of Truvada helped reduce HIV risk by 70 percent among women living with an HIV-positive partner. Yet, the VOICE and FEM-PrEP studies, which enrolled mostly single and younger women, were not able to demonstrate efficacy because most study participants did not take the tablets. Interviews with some of the participants revealed that they had been worried about potential side effects and not knowing if they'd been assigned to use an active product or placebo. They also feared being stigmatized or wrongly labeled as being HIV-positive. In the context of open-label studies and demonstration projects, however, oral PrEP has been found to be at least 90 percent effective when used consistently and regularly.

Daily pill taking can be a challenge for many people, especially so for adolescents and young adults. Indeed, a study called HPTN 082, which reported results in 2019, highlighted the struggles young women in South Africa and Zimbabwe had in using an HIV prevention method that requires daily use.

What exactly did the HPTN 082 study learn about oral PrEP in adolescent girls and young women?
HPTN 082 enrolled 471 adolescent girls and young women aged 16 to 25 years in South Africa and Zimbabwe. Women were eligible to be in the study even if they did not want to start taking oral PrEP right away, but the majority (95 percent) were eager to start PrEP at enrollment.

All participants who accepted oral PrEP received standard adherence support services, including counseling, and text messaging reminders. Approximately half were randomized to also receive counseling that included information about their drug-level results (as a measure of adherence), which the researchers hypothesized would help motivate better use, though it appeared to make no difference. While drug blood levels indicated most (85 percent) participants were taking PrEP in the first three months of the study, by month nine, this had declined to 31 percent. In both groups, adherence declined significantly after month three, when clinic visits were reduced from monthly to every three months. No safety concerns were observed.

Is there need for the dapivirine ring when oral PrEP is already approved in many countries?
No one HIV prevention method will work for everyone – people's needs and preferences are different and can change over time. As with contraception, the more HIV prevention options available to women, the more likely one will and can be used. Daily use of an ARV tablet, most commonly Truvada, an approach called oral PrEP, is approved in many countries, including countries in Africa, and recommended by WHO for persons at substantial HIV risk. Oral PrEP is highly effective with consistent use. But daily pill-taking can be challenging for some people or not desired. If approved, the monthly dapivirine ring could fill an important gap with a long-acting prevention method for women who are unable to use daily oral PrEP consistently. At the same time, a vaginal ring may not be suited for everyone either. Controlling the epidemic will only be possible with a comprehensive HIV prevention portfolio that includes multiple options.

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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.

Do 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 can only provide informed assent (agreement), with the permission of her parent and/or legal guardian also required. If a participant turns 18 during the study, she will need to provide her consent as an adult. A participant who is under the age of 18 but considered to be an emancipated minor (because they are married, a mother or head of a household) may legally provide consent. Regardless, all participants who volunteer to join REACH (and their parents and/or guardians, if they are minors) are informed about all the study procedures, any possible risks, benefits and alternatives to participation, as well as the study's time requirements. Study staff also explain that they do not have to take part in the study and can leave it at any time, without consequence. The process begins prior to joining the study and continues throughout the duration of their participation in the study. All information is provided in simple terms and translated into local languages.

Who may enroll in REACH?
To enroll in REACH, women must be between 16 and 21 years old and be HIV negative. Participants should also be willing to try each product – and to try using them as best they can.

To be eligible, women must also 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 aren't already using a contraceptive will be counseled by site staff on different options and be provided their method of choice prior to enrollment. The reason for requiring that women be using a contraceptive for at least two months prior to enrollment is to allow enough time for initial side effects to subside before beginning use of the dapivirine ring or oral PrEP. In this way, researchers can be more certain that any side effects or changes that occur during product use are due to the ring or PrEP and not the contraceptive.

What does participation in the study involve?
Participants will be in the study for about 19 months, with monthly clinic visits throughout. At each of these visits, participants will receive their assigned product (ring or PrEP), meet with a counselor to discuss their experience using their assigned product and strategies that may help improve its use, and undergo various tests and exams for monitoring their health. Visits will 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 will be conducted. Participants will answer questions about their use of and experience with each product both on a computer and in face-to-face conversations with site staff. 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.

How will participants be supported to use the ring and oral PrEP?
REACH study participants will receive extensive support and counseling focused on helping them to use their assigned product, and they will be 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 will help participants recognize that these products won't be for everyone, and the reasons why are just as important for researchers to understand.

Counselors will work with participants to develop individual adherence plans and use a menu of options to support them in achieving their goals and overcoming any challenges they anticipate might stand in the way. For

instance, participants may choose to receive daily text messages or weekly check-ins by phone or text, to be connected with another participant – a so-called Peer Buddy – for mutual support, or to take part in adherence support groups. At some sessions, participants will also receive individual adherence tests results – for oral PrEP, drug levels in blood samples taken at the previous visit, and for the ring, the amount of residual drug in the ring they had returned after that month – to help facilitate discussion about adherence and how it relates to protection. Results will be 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 will provide encouragement and offer to help in whatever way they can.

Can women choose not to use the product they've been assigned?
REACH is designed so that all participants will use the monthly dapivirine ring and daily oral PrEP – each for six months. Whether they use the ring for the first six months and then switch to PrEP for the second six-month period, or vice versa, will be determined by chance (randomization). Participants will be encouraged to use their assigned study products as best they can so that the study is able to answer questions about the safety of these products in young women, especially in girls under age 18. REACH also aims to answer questions about the acceptability of these products, so if a participant doesn't want to or cannot use either the ring or PrEP, researchers will want to understand the reasons why (while also seeing what kind of support may help). After trying each product for six months, participants will then have a choice of what they want to use for the last six months of the study – the dapivirine ring or oral PrEP, or neither – and they may change their mind as often as they like, at their discretion.

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. The PSRT includes the REACH protocol chair and co-chairs, an MTN safety physician, the medical officer for NIAID's Division of AIDS and representatives of Gilead and IPM. 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 will instances of these be managed by study sites?
The study team recognizes that social harms or intimate partner violence could be experienced by some study participants. All sites have processes in place to address any instance that may occur. Intimate partner violence is an unfortunate reality for many women in the communities where REACH is being conducted. Any participant experiencing intimate partner violence will be provided appropriate support and counseling by site staff and referred to any services not available at the site, and measures will be taken to protect her safety.

Some participants could experience social harms 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. Site staff will make every effort to work with participants on ways to address the problem. 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 will provide 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?
Contraceptive counseling and the provision of a range of methods is provided at each trial site. While long acting reversible contraceptives (LARCs), such as intrauterine devices (IUDs) and implants, will be encouraged, the choice in method will be up to the participant. As a precaution, all participants will be tested for pregnancy each month.

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.

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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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