Primary HIV Prevention for Pregnant Women

Stakeholders Consultation on MTN-042

Phase 3B open-label safety study of the dapivirine vaginal ring and oral PrEP used during pregnancy

MEETING REPORT

AVAC
Global Advocacy for HIV Prevention

MTN
microbicide trials network

Meeting Report: Stakeholders consultation on MTN-042,
a Phase 3b safety study of the dapivirine vaginal ring and oral PrEP used during pregnancy
5-6 April 2018 – Johannesburg, South Africa

This report and additional information from the consultation is available at https://www.avac.org/stakeholders-consultation-mtn042

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To learn more about the MTN-042 study, as well as other studies of the Microbicide Trials Network, please go to www.mtnstopshiv.org

September 2018

MEETING REPORT

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Phase 3B open-label safety study of the dapivirine vaginal ring and oral PrEP used during pregnancy

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Acknowledgements

We would like to give special thanks to all meeting participants, who individually and collectively contributed to the success of this consultation. In particular, we would like to thank our speakers Renee Heffron, Paul Ndebele, Joseph Mfutso-Bengo, Henry Mugerwa, Sithembile Ruzario, Francesca Conradie, Frank Taulo, Richard Beigi, Petina Musara and John Steytler, together with our panelists Audrey Tasaranarwo, Lillian Mworeko, Maureen Luba and Thokokozile Budaza, for providing much of the context for the rich discussion about the MTN-042 study and the challenges and opportunities that lie ahead. Katie Bunge, Bonus Makanani and Lee Fairlie, who are leading the study, helped framed many of the questions with maximum effect. The insightful comments and suggestions made by meeting attendees have helped to improve the protocol and move it forward. Of course, if not for the vision of Sharon Hillier and others within the Microbicide Trials Network (MTN) or for the National Institutes of Health's support and belief in this vision, a conversation of this kind might not have taken place – at this juncture, at least. So, it is with much gratitude that we thank all the stakeholders who took part in this meeting for recognizing that, indeed, the time is right. The time is right to pursue a research agenda focused on HIV prevention in women during pregnancy.

The MTN has partnered with AVAC on many of its stakeholders' consultations, and we are grateful to be part of such a fruitful collaboration. As they have done numerous times before, the MTN-042 consultation was planned by Lisa Rossi (MTN) and Manju Chatani-Gada (AVAC).

Rapporteur for the consultation was Nicoletta Mabhena. This report, based in large part on her notetaking, was co-written and edited by Lisa Rossi. We thank those who reviewed earlier drafts of this report for their valuable input. Finally, a big thank you to Michelle Leszczewski who helped immensely with the formatting of this document.

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Acronyms and Abbreviations

AE	adverse event
ARS	Automated Response System
ART	antiretroviral treatment
ARV	antiretroviral medicine
ASPIRE	A Study to Prevent Infection with a Ring for Extended use
AVAREF	African Vaccine Regulatory Forum
CIOMS	Council for International Organizations of Medical Sciences
COMREC	College of Medicine Research and Ethics Committee (Malawi)
CRS	Clinical Research Site
DAIDS	Division of AIDS (of the US National Institute of Allergy and Infectious Disease)
DREAM	Dapivirine Ring Extended Access and Monitoring (open-label extension study for former Ring Study participants)
EC	Ethics Committee
EMA	European Medicines Authority
EMBRACE	Evaluation of Maternal and Baby Outcome Registry After Chemoprophylactic Exposure (also called MTN-016)
FDA	US Food and Drug Administration
HIV	Human Immunodeficiency Virus
HOPE	HIV Open-label Prevention Extension (open-label extension study for former ASPIRE participants)
HSV	herpes simplex virus
HREC	Human Research Ethics Committee
ICWEA	International Community of Women Living with HIV Eastern Africa
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials
IPM	International Partnership for Microbicides
IRB	Institutional Review Board
IRB/EC	Institutional Review Board/Ethics Committee
JCRC	Joint Clinical Research Centre (Uganda)
MOH	Ministry of Health
MRC	Formerly Medical Research Council (of South Africa) See *SAHPRA*
MRCZ	Medical Research Council in Zimbabwe
MTN	Microbicide Trials Network
NCST	National Commission for Science and Technology (Malawi))
NGO	nongovernmental organization
NHSRC	National Health Sciences Research Committee (Malawi)
NIAID	National Institute of Allergy and Infectious Diseases (part of NIH)
NICHD	*Eunice Kennedy Shriver* National Institute for Child Health and Human Development (part of NIH)
NIH	US National Institutes of Health
NIMH	National Institute of Mental Health (part of NIH)
NRA	National Regulatory Authorities
OLE	open-label extension
PK	pharmacokinetics
PMTCT	Prevention of mother-to-child transmission
PrEP	pre-exposure prophylaxis
PROMISE	Promoting Maternal and Infant Survival Everywhere (study)
PSRT	Protocol Safety Review Team
REACH	Reversing the Epidemic in Africa with Choices in HIV prevention (also known as MTN-034)
REC	Research Ethics Committee
SAE	serious adverse events
SAHPRA	South African Health Products Regulatory Authority
STI	sexually transmitted infection
TDF/FTC	tenofovir/emtricitabine (two ARVs in Truvada)
UZCHS	University of Zimbabwe College of Health Sciences
VOICE	Vaginal and Oral Interventions to Control the Epidemic (study)
WHO	World Health Organization
Wits RHI	Wits Reproductive Health and HIV Institute

Executive Summary

Background: Context is Key

Developing the MTN-042 Study: Seeking Input from Stakeholders

Executive Summary

Women acquire HIV at disproportionally higher rates than do their male counterparts, especially in regions like sub-Saharan Africa. While the development of safe and effective prevention methods for women has long been a priority, much less attention has been paid to women's HIV prevention needs during periods of pregnancy or breastfeeding, when their HIV risk is estimated to be three to four times greater than if they were not pregnant or breastfeeding. For many women, this represents a significant portion of their reproductive years. Clearly, there is the need for women to be protected at all times of their lives.

Daily use of a daily antiretroviral (ARV) pill by HIV-negative people, an HIV prevention method known as PrEP, or pre-exposure prophylaxis, is now approved in many countries, with Truvada® the ARV most commonly used. Whether it is offered for use to women during pregnancy differs from country to country. No controlled studies have been conducted in this population, hence, the reason that some countries, such as South Africa, are hesitant to recommend its use during pregnancy. Most of the information about the safety of Truvada – a combination of both tenofovir and emtricitabine – during pregnancy is in HIV-infected women using tenofovir or Truvada as part of treatment. Though limited, observational data to date suggest Truvada is safe in HIV uninfected women as well. Recognizing there is still a need for more safety data, the World Health Organization recommends PrEP during pregnancy based on the view that the benefits of preventing HIV outweigh any potential risks.

Much less is known about the safety of the ARV dapivirine – the active drug in a monthly vaginal ring that is currently under regulatory review. If approved, national drug regulatory agencies and programs will require specific data about the safety of the dapivirine ring during pregnancy before considering expanding its approval to pregnant women.

Why the paucity of data about either PrEP or the dapivirine ring in pregnancy is no mystery. Clinical trials typically exclude participation of women during pregnancy, and in studies involving women, participants must use contraception throughout and if they become pregnant, must stop using the study product immediately. The basis for not including pregnant women in clinical research is to avoid potential risk to the developing fetus. Yet, without clinical trial data in this population, drugs receiving approval are typically contraindicated for use by women during pregnancy and lactation, who nonetheless may end up using the drug anyway, without the benefit of data showing this is safe to do so. Whether a drug is safe to use during pregnancy, when the body undergoes numerous changes, is a question best answered in a controlled clinical trial setting with utmost attention to the safety of both mothers and their babies, rather than in the "real-world" *after* a drug is already widely available.

The U.S. National Institutes of Health-funded Microbicide Trials Network (MTN) is planning a Phase IIIb study called MTN-042 that would help answer key questions about the safety of oral PrEP and the dapivirine ring when used during pregnancy. The study will be conducted at four trial sites in Malawi, Uganda, South Africa, and Zimbabwe, and enroll 750 women at different stages of pregnancy who would be randomly assigned to use either oral PrEP or the dapivirine ring until the time they deliver. Researchers will monitor women's safety, pregnancy outcomes and the safety of infants.

The trial design involves a stepwise backwards approach, starting with women late in pregnancy (about 36 weeks). Provided there are no safety concerns, the study will proceed to enroll the second group – women who will be 30-35 weeks pregnant, and so on. The fourth and last group of women will be about 12-19 weeks into their pregnancy and will use their assigned product the longest – up to 30 weeks.

As part of the protocol development process, the MTN, in partnership with AVAC, held a consultation with key stakeholders in Johannesburg, South Africa, 5-6 April 2018, to hear their views about the study's design and objectives and to seek their opinions about specific aspects of the study. The timing of the consultation was deliberate, so that stakeholder feedback could be considered by the study team and site investigators at its protocol development team meeting a few days later.

Meeting participants included stakeholders with expertise in bioethics, maternal and fetal health, HIV prevention clinical trial design, regulatory affairs and health policy, as well as civil society and community representatives. Most of the attendees were from countries where MTN-042 will be conducted. Regional and international experts participated as well.

Stakeholders were very supportive of the study and its design incorporating interim reviews as an extra measure of safety. There was consensus that pregnant women deserve safe, effective and equitable access to prevention. After all, protecting pregnant women from acquiring HIV would mean protecting also their babies from getting infected. And though another study, called IMPAACT 2009, will be evaluating the safety of PrEP in adolescent and young women during pregnancy, stakeholders felt that, together, both studies would contribute much needed data about the safety of PrEP in pregnant women. Stakeholders supported further study of the dapivirine ring as well and were unanimous in their view that the time is right to move forward with this agenda.

The researchers received several recommendations, including to lengthen the follow-up time of infants from six weeks to up to a year.

Given that there is no placebo group (women who would use a product without active drug), stakeholders were concerned that it will be difficult to determine whether adverse pregnancy and infant outcomes that occur during the study are due to the use of the ring or PrEP or a pregnancy complication that could be considered within the norm for that community or region. In lieu of a placebo control group, stakeholders suggested other approaches for obtaining or collecting background data for comparison purposes.

The recommendation was also made to harmonize clinical and laboratory definitions of safety outcomes within the protocol with those published by the GAIA project (Global Alignment of Immunization safety Assessment in pregnancy) as well as with IMPAACT 2009. This would enable comparisons of significant findings from each study as well as help identify the presence of important trends in outcomes.

Consideration was given to the challenges in and ethical and regulatory framework for conducting research among pregnant women, and the socio-cultural barriers and belief structures within communities. Engagement will need to consider the roles that male partners and family members play as well. Ongoing communication with stakeholders and communities throughout the study will be essential, particularly between cohorts when interim reviews are being conducted. Women will need to understand the potential risks and benefits of study participation, as will the community at large. Moreover, meeting participants emphasized how it will be important that both women and communities understand there are inherent risks with pregnancy and that serious complications may occur – with or without the study. It was strongly recommended that study teams establish partnerships with local hospitals where study participants are likely to deliver, as this will be key for collecting some of the trial's most important data. Concerns about the potential for social harms were discussed at length and how the site and study teams might help avert this problem and offer support and counseling to participants.

Please see **Study Update and Next Steps: Getting Ready to Deliver** *for a summary of changes made to the protocol since the stakeholders consultation as well as current status and projected timelines for the study.*

Background: Context is Key

HIV Risk During Pregnancy

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. Worldwide, HIV is the leading cause of death in women age 15-49. Compared to men, women are at greater risk of acquiring HIV, and that risk increases during pregnancy and breastfeeding. Indeed, women may be two to three times more likely to become infected during pregnancy and four times more likely during the postpartum period compared to non-pregnant times, according to new findings based on analysis of data from The Partners in Prevention HSV/HIV Transmission Study and The Partners PrEP Study.

The analysis, which calculated a woman's chance of acquiring HIV every time she had sex, accounted for decreases in sexual activity and the use of condoms as pregnancy progressed. Although both behavioral and biological factors are assumed to contribute to heightened risk during pregnancy, the study was not designed to assess what role biological changes during pregnancy and postpartum may have played.

Women in many African countries will spend considerable time either pregnant or breastfeeding or both, equating to periods of heightened risk that can be measured in years. In Uganda, women can be expected to be pregnant or breastfeeding for about 10 years. Similarly, in Malawi, the total amount of time spent pregnant or breastfeeding is nine years. Even in South Africa and Zimbabwe, where fertility rates are lower, women will on average spend four years and seven years either pregnant or lactating, respectively. (*See details below*)

As a global priority, women need safe and effective biomedical HIV prevention strategies they can use during pregnancy – a time when they are especially vulnerable to infection. Indeed, protecting mothers against HIV infection would mean their babies would be protected as well, averting the possibility of mother-to-child transmission.

Duration of Increased Risk for Women is Substantial

	Malawi	South Africa	Uganda	Zimbabwe
A woman's average life expectancy	60 years	66 years	64 years	62 years
Total fertility rate per woman	5 children	2.3 children	5.7 children	3.9 children
Years pregnant/breastfeeding per pregnancy	1.75 years	1.75 years	1.75 years	1.75 years
Total time pregnant or breastfeeding	About 9 years	About 4 years	About 10 years	About 7 years
	15% of lifetime 26% of reproductive years	6% of lifetime 12% of reproductive years	16% of lifetime 29% of reproductive years	11% of lifetime 20% of reproductive years

Sources: World Bank; http://www.worldlifeexpectancy.com

Both Overlooked and Overprotected

The usual path in the development of biomedical interventions is clinical research, yet studies typically exclude participation of women during pregnancy. Most studies require female participants to use contraception throughout, and if they get pregnant to stop using the study product immediately. The basis for not including pregnant women in clinical trials is to avoid potential risk to the developing fetus. Lacking data from clinical trials, many drugs are therefore contraindicated during pregnancy and lactation. This places the burden on health care providers for deciding the potential benefits and risks in prescribing drugs for pregnant women who may require treatment for a chronic condition or fall ill during pregnancy. Many pregnant women will also take over-the-counter medications. The body undergoes many changes during pregnancy, which could affect the bioavailability and distribution of drugs. They may work differently or not be as effective. Of great concern is the potential that drug could pass to the placenta and cause harm to the developing fetus.

Highly regulated trials conducted in controlled settings with rigorous monitoring of its participants would pose far less risk than if safety were left to chance in the general population of women.

Developing the MTN-042 Study: Seeking Input from Stakeholders

Why MTN-042? Why now?

While oral PrEP, which involves daily use of an antiretroviral (ARV) tablet called Truvada®, has been approved for HIV prevention in many countries, guidelines on its use in pregnant women differ. The World Health Organization (WHO) recommends its use during pregnancy and breastfeeding, but in some countries, such as South Africa, PrEP is contraindicated. This is mainly because there is relatively little information about the safety of Truvada in HIV uninfected women during pregnancy — much more is known about Truvada in HIV-infected pregnant women — or about the safety of PrEP to the developing fetus.

Another potential HIV prevention approach is a monthly vaginal ring containing the ARV dapivirine. Unlike Truvada, dapivirine is a new drug entity that is not used in the treatment of HIV. The International Partnership for Microbicides (IPM), which developed the dapivirine ring, is in the process of seeking regulatory approval for its use by women ages 18-45. Specific data on the ring's safety and use among pregnant women will be required for the ring to be considered for and made available to this population.

For its part, the Microbicide Trials Network (MTN) is planning a Phase IIIb study called MTN-042 that would help answer key questions about the safety of oral PrEP and the dapivirine ring for both mothers and their babies when used during pregnancy. MTN-042 will be the first study to provide safety data about the dapivirine vaginal ring in pregnant women and will provide additional information about the safety of Truvada as PrEP in this population. Ultimately, the goal of the study is to ensure that women will have safe and effective HIV prevention methods they can use throughout their lives, including during pregnancy.

Stakeholders Consultation for the MTN-042 Study

To help inform development of the MTN-042 protocol, the MTN, in partnership with AVAC, held a consultation with key stakeholders in Johannesburg (Sandton), South Africa, on 5 and 6 April 2018. At the time of the consultation, the protocol was still very much in draft form (Version 0.3). Feedback from the consultation would in turn be considered by the study team and site investigators who were to be meeting in the coming days. The overall objectives of the consultation were to:

- Engage with key stakeholders in order to seek their views and input about the MTN-042 study overall and specific aspects of its proposed design.
- Assess how stakeholders view MTN-042 within the context of the current HIV prevention landscape, especially with regard to PrEP and differing opinions about its use during pregnancy.
- Solicit stakeholders' views about how best to overcome the ethical, sociocultural and structural challenges inherent in a study of this kind as well as challenges unique to MTN-042.
- Establish new ties and strengthen existing relationships between researchers and key in-country stakeholders and create a framework for continued engagement on issues of relevance in each country.

The meeting was attended by 35 stakeholders who included Institutional Review Board (IRB)/Ethics Committee (EC) members and administrators, Ministry of Health (MoH) representatives, WHO representatives, researchers, ethicists, national HIV program officers, and non-governmental organization (NGO)

representatives with experience working with pregnant women, and civil society, and advocates focused on HIV prevention, women's reproductive health and empowerment.

MTN researchers attending included Sharon Hillier, MTN principal investigator (University of Pittsburgh); MTN-042 protocol chairs Katherine Bunge (University of Pittsburgh) and Bonus Makanani (University of Malawi College of Medicine); and MTN-042 protocol co-chair, Lee Fairlie (Wits Reproductive Health and HIV Institute). Also participating were lead investigators from MTN-042 trial sites as well researchers leading a related qualitative study called MTN-041.

(*See Appendix 2 for a list of all meeting participants.*)

Agenda Synopsis

The meeting began with Sharon Hillier, MTN principal investigator, and Manju Chatani-Gada, director of partnerships and capacity strengthening at AVAC, welcoming meeting participants. Renee Heffron, an assistant professor at the University of Washington, then helped to set the stage with a presentation about HIV risk during pregnancy. This was followed by an overview of the MTN-042 study presented by protocol chairs Katie Bunge and Bonus Makanani, and protocol co-chair, Lee Fairlie.

The last session on day one explored the legal and ethical framework and considerations for conducting clinical trials in pregnant women. It began with Paul Ndebele, director of the Medical Research Council of Zimbabwe (MRCZ), who described the evolution in thinking and current international guidance for conducting research involving pregnant women. Country-specific presentations were given by: Joseph Mfutso-Bengo, professor of ethics from the University of Malawi College of Medicine; Francesca Conradie, who serves on the University of Wits Human Research Ethics Committee, representing South Africa; Henry Mugerwa, a member of the Research and Ethics Committee of the Joint Clinical Research Centre in Kampala, Uganda; and Sithembile Ruzario, senior research compliance officer at MRCZ. Ensuing group discussion focused on a myriad of legal and ethical issues, with conversations continuing into the informal dinner that followed.

Day two of the consultation commenced with a brief summary of the previous day's discussions which was followed by a session focused on PrEP, with Renee Heffron providing an overview of what is known and not known about PrEP in women during pregnancy, and Frank Taulo from the University of Malawi, describing the IMPAACT 2009 Study of PrEP in pregnant adolescent girls and young women. A group discussion about possible implications for MTN-042 was facilitated by Lee Fairlie.

The next session focused on the dapivirine vaginal ring as well as MTN's framework for conducting studies in pregnant and breastfeeding women. John Steytler, IPM director for medical safety, summarized results of the dapivirine ring Phase III trials and the regulatory pathway and timelines for possible licensure of the ring. His presentation also included a summary of data from animal toxicology studies as well as data derived from women who became pregnant while using the dapivirine ring. Richard Beigi, professor of obstetrics and gynecology at the University of Pittsburgh, provided context for understanding the rationale for the MTN-042 study design, including MTN's previous studies involving both pregnant and breastfeeding women. Bonus Makanani facilitated a group discussion on the implications for the MTN-042 study.

Community attitudes, sociocultural norms and behavioral practices during pregnancy were topics explored next. Petina Musara, protocol co-chair of a related qualitative study (MTN-041), described how that study aims to learn about the social and cultural factors that may affect uptake of the monthly dapivirine ring and daily oral PrEP in pregnant and breastfeeding women. A panel discussion on community perspectives and perceptions about research and pregnancy, which was facilitated by Manju Chatani-Gada, explored personal views and possible community perceptions. Panelists included Audrey Tasaranarwo, a Community Advisory Board member from the University of Zimbabwe College of Health Sciences Clinical Trials Research Centre, Lillian Mworeko from Uganda's International Community of Women Living with HIV Eastern Africa (ICWEA), Maureen Luba from AVAC and the Center for Development of People in Malawi, and Thokokozile Budaza, Soul City Institute for Social Justice in South Africa.

There was ample time for rich discussion throughout the meeting, but the final session, led by Katie Bunge, ensured all voices were heard. Meeting participants registered feedback in real-time using handheld remote devices and then discussed their views and thoughts on specific aspects of the MTN-042 study. Questions stimulated extensive dialogue and suggestions relevant to both the study's design and implementation. The consultative meeting ended with Sharon Hillier summarizing the major feedback received on the MTN-042 study.

(*See Appendix 1 for the full agenda*)

About this Report

This report attempts to capture, to the extent possible, a rich, two-day discussion in which there were multiple narratives and threads. Organizationally, it begins with an overview of the MTN-042 study. The sections that follow then describe discussions about the study in the context of four general topic areas: oral PrEP, the dapivirine ring, socio-cultural issues and ethics. The next section reports feedback received in response to specific questions asked of stakeholders and is followed by a summary of key discussion themes and recommendations across the two days. The report concludes with an update on the study's status, including how feedback was incorporated into the protocol

From Concept to Design: The MTN-042 Study

From Concept to Design: The MTN-042 Study

Study Overview and Design

The information outlined below describes the study design at the time of the consultative meeting.

MTN-042 is a Phase IIIb open-label study that will evaluate two different HIV prevention approaches in pregnant women — the dapivirine vaginal ring, which is used for a month at a time, and daily use of the ARV tablet Truvada, an approach commonly referred to as PrEP (pre-exposure prophylaxis). Both PrEP and the ring have been found to be safe and effective in trials involving non-pregnant women.

The study plans to enroll 750 healthy, HIV-uninfected pregnant women ages 18-40 who are at different stages in pregnancy. As an open-label study, all participants will use an active product — there is no placebo. Women will be randomly assigned to use either the monthly dapivirine ring or daily PrEP. For each woman assigned to use PrEP, two will use the ring.

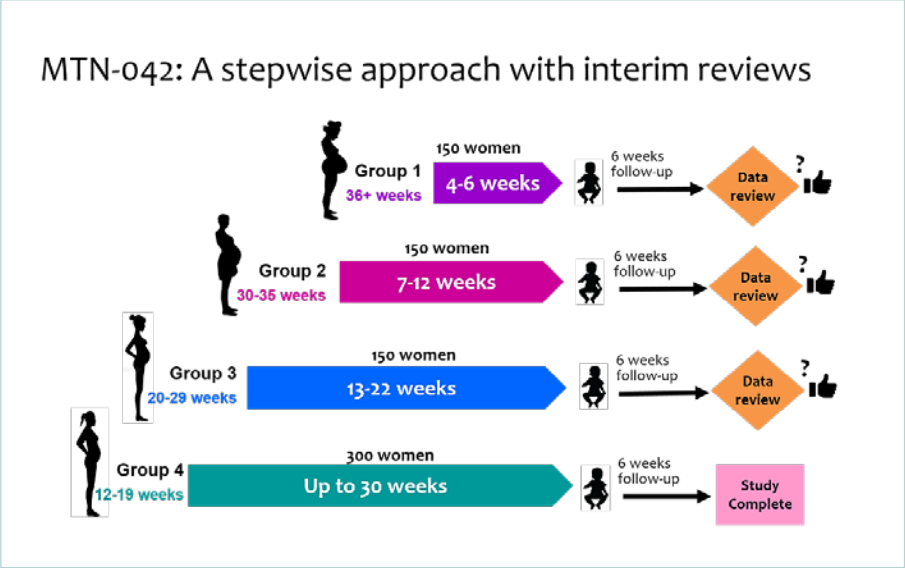
The primary objective of MTN-042 is to understand whether PrEP and the ring are safe and well-tolerated when used during pregnancy — safe for the mother, her pregnancy and her baby. The study is designed to answer other questions as well. (*See textbox: Study Objectives*)

The study consists of four discreet phases defined by the gestational age of the women to be enrolled and will be conducted in a stepwise, backward fashion, beginning with women who are closest to the time of delivery. Interim reviews of study data will take place after completion of each phase and before determining whether to proceed to the next.

The first group will consist of 150 women late in pregnancy (36 or more weeks) who will use their assigned product until delivery — approximately four to six weeks. During this time, women will undergo physical exams and different laboratory tests, including for HIV infection, and be asked questions about their health and their experience in using the ring or PrEP. Similar assessments will take place within the first week of giving birth and six weeks after. Likewise, newborns will be examined at birth and at six weeks.

A review of study data will occur after follow-up of all 150 women and their babies has been completed. Provided there are no safety concerns, the study will proceed to enroll the second group — 150 women who are 30-35 weeks pregnant who would also use their assigned product (the ring or PrEP) until delivery — about seven to 12 weeks. As before, after all women and their babies have completed follow-up, an interim review will be conducted to determine whether it is safe to continue with the third group of 150 women, who will be 20-29 weeks pregnant and use their assigned product for between 13 and 22 weeks. Likewise, the fourth group would only proceed if there are no concerns with the previous group. This fourth group will comprise 300 women who are 12-19 weeks into their pregnancies and who would use the products the longest — up to 30 weeks until the outcome of the pregnancy.

The study will be conducted at four MTN-affiliated trial sites: the College of Medicine-Johns Hopkins University Research Project (Blantyre, Malawi); Makere University-Johns Hopkins Research Collaboration (Kampala, Uganda); Wits Reproductive Health and HIV Institute Shandukani Research Centre (Johannesburg, South Africa); and University of Zimbabwe College of Health Sciences Clinical Trials Research Centre, Zengeza (Harare, Zimbabwe). Each site will work closely with nearby hospitals and health centers where women in the study are likely to deliver.



As part of the study, all women will receive HIV risk-reduction counseling and testing, and, as needed, be referred for any medical or counseling services not provided through the study or at the site.

Women planning to use PrEP outside the confines of the study may not enroll in MTN-042. Taking part in the study is voluntary, but women should be willing to accept and use the product to which they have been randomly assigned.

All About Safety

While on the one hand MTN-042, researchers are conducting the study to know whether the dapivirine ring and oral PrEP are safe to use during pregnancy, multiple measures will also be taken to ensure participation in the study is as safe as possible. Site staff will monitor participants' safety, health and wellbeing at each visit. A Protocol Safety Physician will also provide near daily monitoring of adverse events and social harms reported across sites, and a Protocol Safety Review Team (PSRT) will conduct regular, and as needed, expedited reviews of safety information. The MTN Study Monitoring Committee will provide oversight with routine reviews of study conduct and safety data. Local IRBs/ECs will also provide ongoing oversight, as will the study's funders: the National Institute of Allergy and Infectious Diseases (NIAID) Division of AIDS (DAIDS); the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) and National Institute of Mental Health.

Perhaps the study's most important safety feature is the study design itself, moving backwards in stepwise fashion with pauses to allow for reviews of study data between each cohort. One reason for this design is to be attentive to the potential risks and complications that can occur at different times during pregnancy and fetal development and ensure that the use of the dapivirine ring or oral PrEP is not posing additional risk or undue harm to either the mother or her fetus. The interim reviews, which will be conducted by a special panel of experts, will ensure that the study continues only if the data indicate it is safe to do so.

MTN-042 Study Objectives

The version of the study protocol discussed at the time of the consultation included the following study objectives:

Primary objectives:

- To describe the maternal, peri-partum (pregnancy-related) and infant safety profile associated with use of PrEP and the dapivirine ring during pregnancy

Secondary objectives:

- To describe pregnancy outcomes associated with use of PrEP and the dapivirine ring during pregnancy (i.e., number of full-term live births versus premature births, stillbirths and miscarriages)
- To describe how the body takes up the active drug (pharmacokinetics) in PrEP and the dapivirine ring during pregnancy
- To characterize adherence – how well women use daily PrEP and the monthly ring during pregnancy
- To characterize acceptability – do women find using PrEP and the ring acceptable during pregnancy?

Exploratory objectives:

- To describe the vaginal microbiome (good and bad bacteria in the vagina) with use of oral PrEP and the vaginal ring during pregnancy

How the Idea was Born: MTN's Pregnancy and Breastfeeding Research Agenda

It could be said that MTN-042 has been 12 years in the making, a vision of the Microbicide Trials Network (MTN) as itself came into being in 2006. MTN researchers, including Richard Beigi, an obstetrician/gynecologist from the University of Pittsburgh, recognized that women needed safe and effective products for *all* stages of life. As such, its scientific portfolio has included a comprehensive program purposefully designed to take incremental steps for evaluating the safety of HIV prevention products in pregnant and breastfeeding women. Each study is carefully designed and implemented so that vital information can be collected while also ensuring the safety and well-being of women and their babies.

"Many of the products being developed are intended specifically for sexually active women, who, not surprisingly, are likely to become pregnant. With pregnancy and breastfeeding being periods of greater HIV risk, we saw this as a public health imperative," explained Dr. Beigi.

MTN's first studies focused on tenofovir gel, which at the time, was being evaluated in trials to support its potential licensure. There was reassuring data from animal reproductive toxicity studies of tenofovir and from registries that followed HIV-infected women who had used tenofovir during pregnancy, but the study being proposed, called MTN-002, would be the first time an ARV-based product would be administered to pregnant women who did not have HIV. The researchers took a necessarily conservative approach, enrolling 16 women who received a single dose of gel within eight hours of scheduled cesarean delivery. Finding the gel safe for both mothers and infants, the researchers designed a second study, MTN-008, in which women in their third trimester of pregnancy received a daily dose for one week. The first group was 45 women between 37 and 39 weeks gestation who were randomized to receive tenofovir gel or a placebo gel. After an interim safety review found no concerns, the study proceeded to enroll a second group of women, between 34 and 36 weeks gestation. (The study also included a cohort of breastfeeding women.) Results supported taking the next step — a larger Phase II study called MTN-019, with a design very similar to MTN-042, aiming to enroll women in three cohorts of progressively earlier gestational ages based on interim safety reviews. The study, which was to be conducted in Africa, did not proceed, however, after results of Phase III trials indicated tenofovir gel was not viable for licensure.

With the dapivirine ring, MTN's first step was MTN-029/IPM 039, in which women who were no longer nursing their babies but still producing milk used the ring for 14 consecutive days, allowing data to be collected without exposing infants to drug. Finding dapivirine was absorbed at very low concentrations in breastmilk, the MTN is planning a study of the ring in women who are actively breastfeeding. The study, called MTN-043, will be conducted at the same sites as MTN-042.

In parallel, MTN has been conducting an observational study and data registry called MTN-016, or EMBRACE, in which women who became pregnant in MTN's large trials (e.g., VOICE, ASPIRE and HOPE) and their babies are followed for one year. To date, the study has collected data on 449 women and 391 infants. Of note, researchers have yet to observe significant differences in pregnancy and infant outcomes between women using the dapivirine ring at the time they became pregnant and women from the placebo group who fell pregnant during the ASPIRE study.

Oral PrEP and Pregnancy: What We Know and Don’t Know

Oral PrEP and Pregnancy: What We Know and Don't Know

WHO and National Guidelines: Different Views About PrEP in Pregnancy

When the U.S. Food and Drug Administration (FDA) approved Truvada (a combination of tenofovir and emtricitabine) for use as prevention, or PrEP, in 2012, it had already been an approved drug for use in the treatment of HIV as part of ART. Although not specifically indicated for use in pregnant women, there was nonetheless a fair amount of information about the use of Truvada or tenofovir in HIV-infected women who became pregnant while on ART and continued using it off-label, with most studies finding no adverse effects to mothers or their infants.

The only information available at the time about Truvada's safety in HIV-uninfected women during pregnancy was limited to cases in which women in Phase III trials who were randomized to receive PrEP became pregnant and discontinued its use as soon as pregnancy was known — usually around six weeks. Researchers followed their pregnancies, and their infants, providing information about the possible effects that exposure to drug may have during the time of conception and early in the first trimester. No safety concerns with either the pregnancy or infant outcome were observed, which was reassuring, especially when coupled with data from the treatment arena.

In fact, it is based primarily on data derived from studies of HIV-infected pregnant women using tenofovir or Truvada for treatment that WHO deems PrEP safe for use during pregnancy in HIV-uninfected women. While also acknowledging that more safety data is needed, WHO's 2016 guidelines argue that the benefits to women outweigh any potential risks, including any risks associated with drug exposure to the fetus and infant, and that PrEP should therefore be used by women during pregnancy and breastfeeding in areas where there is a high HIV prevalence. Its guidelines also recommend that countries implementing PrEP include active surveillance of pregnant and breastfeeding women receiving PrEP.

WHO GUIDANCE ON PREP USE DURING PREGNANCY AND BREASTFEEDING

- *The existing safety data support the use of PrEP in pregnant and breastfeeding women who are at continuing substantial risk of HIV infection.*
- *While the data for PrEP use in HIV-negative pregnant women are reassuring, and the benefits of preventing HIV infection outweigh the risks during pregnancy and breastfeeding, more safety data are needed.*
- *The choice to start, continue or discontinue PrEP when a woman becomes pregnant should be made by the woman, following discussion of the risks and benefits with her health-care provider. PrEP also should be considered as part of a safer conception package for women wanting to become pregnant and who are at high risk of acquiring HIV.*

Source: WHO TECHNICAL BRIEF: Preventing HIV during pregnancy and breastfeeding in the context of PrEP, July 2017 Available at: http://www.who.int/hiv/pub/prep/en/

PrEP is now approved in a number of countries, but not all have adopted WHO recommendations or developed country-specific guidance about the use of PrEP during pregnancy. Uganda is among the few countries that recommend PrEP during pregnancy. Zimbabwe and Malawi recognize that pregnant women are a high-risk group but neither have instituted specific guidance for PrEP or its use during pregnancy.

In South Africa, on the other hand, the use of PrEP during pregnancy is currently contraindicated, with its national guidelines stating:

> *"TDF/FTC is contra-indicated for use as PrEP in pregnant or breastfeeding women. However, as the risk of seroconversion during pregnancy is high, the risks and benefits of PrEP should be discussed with potential PrEP users, allowing these women at high risk of HIV acquisition to make an informed decision regarding PrEP use."*

What exactly is the evidence so far?

WHO guidelines are based on a review of 33 studies—26 involving HIV-positive pregnant women taking tenofovir or Truvada as part of treatment and/or prevention of mother to child transmission; five studies of HIV-negative women taking tenofovir to treat hepatitis B; and two HIV prevention studies in which HIV-negative women were randomized to use a placebo or PrEP (tenofovir or Truvada). In the two PrEP studies (Partners PrEP and VOICE) women stopped use of their assigned product when it was learned they were pregnant, and there were no significant differences in pregnancy and infant outcomes between women who received PrEP and those who received placebo.

Across all studies, outcomes are overall reassuring, with no differences in rates of stillbirths, birth defects, neonatal death, pre-term delivery, low birth weight or pregnancy loss.

Results of the PROMISE study, however, showed higher rates of preterm delivery and infant death when HIV-infected pregnant women used a Truvada-based regimen for prevention of mother-to-child transmission, compared to two other regimens (zidovudine and lamivudine). The interpretation of the results has differed widely. While the British HIV Association has gone so far as to recommend that HIV-infected women not use any ART during pregnancy, others, including the researchers who conducted the PROMISE study, believe such action is grossly ill-advised until more is understood about the possible reasons for the results.

Additional insight could come out of the Partners Demonstration Project, as well as other demonstration projects, in which researchers are following women, who upon learning they are pregnant, still want to continue using PrEP. Though, until more data are available about maternal and infant safety, especially from studies specifically designed to evaluate safety outcomes, there will continue to be reticence about the provision of PrEP to women during pregnancy, and even

where available, reluctance by some women to use it. Both the MTN-042 study and IMPAACT 2009, which will evaluate oral PrEP among pregnant adolescent girls and young women, should hopefully help to fill some of the knowledge gaps.

The IMPAACT 2009 Study

IMPAACT 2009 is a study being planned by another NIH-funded network called International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) that will evaluate the pharmacokinetics (PK), feasibility, acceptability, and safety of oral PrEP during pregnancy and breast feeding in adolescents and young women ages 16-24. The study will be conducted in Malawi, Uganda, South Africa and Zimbabwe — at many of the same sites as MTN-042.

The IMPAACT 2009 study consists of two components. The first is a small PK study that seeks to establish plasma drug levels associated with daily use of oral PrEP during pregnancy and postpartum, specifically in adolescent and young women. This is important because the drug may be metabolized differently during pregnancy, and hormonal differences associated with age may be also be a factor. Two groups will be enrolled, each with approximately 20 women – one consisting women who are 14-24 weeks pregnant and a second group who will be enrolled six to 12 weeks following delivery. Each group will use daily oral PrEP under direct observation for 12 weeks, and blood samples will be taken to determine drug concentrations. If it is determined that drug levels are adequate for providing protection against HIV, researchers will proceed with the second part of the study.

The aim of the second part of the study is to understand adherence, i.e., how well pregnant girls and young women are able to use daily PrEP, as well as to learn about the safety of PrEP for both mothers and babies. Researchers will enroll 300 young women who are approximately 32 weeks pregnant. All participants will be offered the chance to use PrEP for the remainder of their pregnancies (about 10 weeks) and for six months after delivery while breastfeeding. About 200 women who accept the offer to use PrEP will be enrolled, and to allow for comparison of outcomes, about 100 women who choose not to use PrEP will also be enrolled. Both groups will receive behavioral HIV risk reduction counseling, and those in the PrEP group will receive adherence counseling, and support throughout follow-up.

The IMPAACT 2009 study differs from MTN-042 in a number of ways, as can be seen in the comparison below:

Comparisons are based on the version of the MTN-042 protocol at the time of the consultation

	Two Studies Involving Pregnant Women	
	IMPAACT 2009	**MTN-042**
Population	340 young women ages 16-24 Component 1: 40 women (4-24 weeks pregnant or 6-12 weeks post- delivery) Component 2: 300 women about 32 weeks pregnant	750 women ages 18-40 Cohort 1: 150 women 36+ weeks pregnant Cohort 2: 150 women 30-35 weeks pregnant Cohort 3: 150 women 20-29 weeks pregnant Cohort 4: 300 women 12-19 weeks pregnant
Product	Oral PrEP (40 in Cohort 1; 200 women in Cohort 2)	Oral PrEP (250 women) Dapivirine ring (500 women)
Key design features	• Pharmacokinetic (PK) lead-in -- to learn drug levels associated with daily PrEP. Will proceed to PrEP comparison if levels are considered protective • PrEP comparison – Pregnant women who choose to use PrEP (200) versus those who decline (100)	• Backwards, stepwise enrollment beginning with women closest to delivery • Women randomized (2:1) to use either the ring or PrEP until delivery. • Interim reviews conducted after each cohort before determining to proceed enrolling the next group.
Product use duration	*Component 1* – 12 weeks *Component 2* – Until delivery (about 10 wks) plus 6 months after delivery	Each group uses assigned product for progressively longer - up to 30 weeks for cohort 4
Primary objectives	*Component 1* – • Drug levels (PK) *Component 2* – • Adherence • Safety - mothers and infants	• Safety –mother and infants
Secondary and Exploratory objectives	• Adherence barriers and facilitators • Risk behaviors, HIV and other STIs • Drug resistance (among women who acquire HIV) • Bone density in women and infants	• Pregnancy outcomes • How the body takes up active drug in PrEP and ring (PK) • Product adherence and acceptability
	• Changes in microbiome of the gut in mothers and babies	• Changes in vaginal microbiome
Follow-up after delivery	6 months for both mothers and babies	6 weeks for both mothers and babies (Follow-up for up to 1 year in MTN-016 registry study)

Considerations for MTN-042: Questions and Comments

Information about the use of Truvada for HIV prevention during pregnancy has been limited to observational and retrospective studies that, while informative, are not able to answer key questions about safety and outcomes. Stakeholders agreed that obtaining safety data from controlled studies, such as MTN-042 and IMPAACT 2009, will be important. There was particular interest in the fact that IMPAACT 2009 will be enrolling adolescents, a group often excluded in clinical research.

It was also noted that the IMPACCT 2009 study includes a comparison (control) group, and that this needs to be an important consideration for MTN-042. Otherwise, it will be difficult to ascertain whether the type and frequency of certain adverse events and pregnancy outcomes are due to use of the product or complications of pregnancy that could have occurred anyway. Similarly, it was recommended that the two studies try to harmonize clinical and laboratory definitions and criteria for medical conditions and assessments so that the findings from each study are able to be compared and possibly corroborate the other.

In the IMPAACT 2009 study, women and their babies will be followed for six months after delivery, whereas in MTN-042 the length of follow-up is only six weeks, which stakeholders felt was too short. At the same time, they suggested that both studies should extend follow-up to one year to better capture information about the long-term effects, if any, to infants having been exposed to Truvada during fetal development.

How many women would actually consider using PrEP during pregnancy or take interest in either the IMPAACT 2009 or MTN-042 studies was debated. Dr. Heffron reported that in the Partners Demonstration Project, women who learned they were pregnant were offered the choice to continue taking PrEP, and 88 percent opted to do so. But, clearly, the decision is a personal one, and there will be women who may be concerned about the possible risks or have other reasons for not wanting to use PrEP while they are pregnant. One of the attendees at the consultation was a young woman pregnant with her first child. She had been taking PrEP as part of a safer conception clinic but stopped once she learned she was pregnant. When asked how she would have responded if given the option to continue using PrEP, or even if a study like MTN-042 or IMPAACT 2009 appealed to her, she was honest about her feelings. She was not comfortable with the idea of using PrEP. If there were more information about its benefits she might be convinced, but until then, she was not willing to risk the safety of her baby.

(*See* **Seeking Feedback from Stakeholders** *for more discussion about MTN-042 in the context of PrEP and IMPAACT 2009*.)

The Dapivirine Vaginal Ring: A Different Option for Women

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About the Ring

The dapivirine vaginal ring is the first biomedical HIV prevention product designed specifically for women that has been shown to be well-tolerated and to reduce the risk of acquiring HIV in two independently conducted Phase III trials. ASPIRE (MTN-020) was conducted by the MTN, while its sister study, The Ring Study (IPM 027), was conducted by the International Partnership for Microbicides (IPM), a non-profit organization that also developed the dapivirine ring and is seeking its regulatory approval. Together, ASPIRE and The Ring Study involved 4, 588 women in Malawi, Uganda, South Africa and Zimbabwe.

The ring, which women can insert and replace themselves, is made of a flexible silicone material containing an ARV called dapivirine that is slowly released into the vagina during the month that it is worn. Dapivirine is a non-nucleoside reverse transcriptase inhibitor that binds to and disables a key protein that HIV needs to make copies of itself. It was originally developed to be used in the treatment of HIV but was deemed more suitable for use in prevention. IPM holds an exclusive worldwide license for dapivirine from Janssen Sciences Ireland UC, one of the Janssen Pharmaceutical Companies of Johnson & Johnson (Janssen), which is designed to ensure that women in low-resource settings have affordable access to any dapivirine-based prevention product.

The results of both ASPIRE and The Ring Study were reported in February 2016. Overall, the two studies found the ring reduced women's risk of acquiring HIV by about 30 percent overall (by 27 percent in ASPIRE and by 31 percent in The Ring Study). Higher levels of protection were seen in women who used the ring most consistently, and the ring was not effective among younger women ages 18-21, who used the ring least regularly. Results of an exploratory analysis of ASPIRE data reported later the same year found the level of HIV protection for those who appeared to use the ring most consistently was at least 56 percent and as high as 75 percent or more with near perfect use.

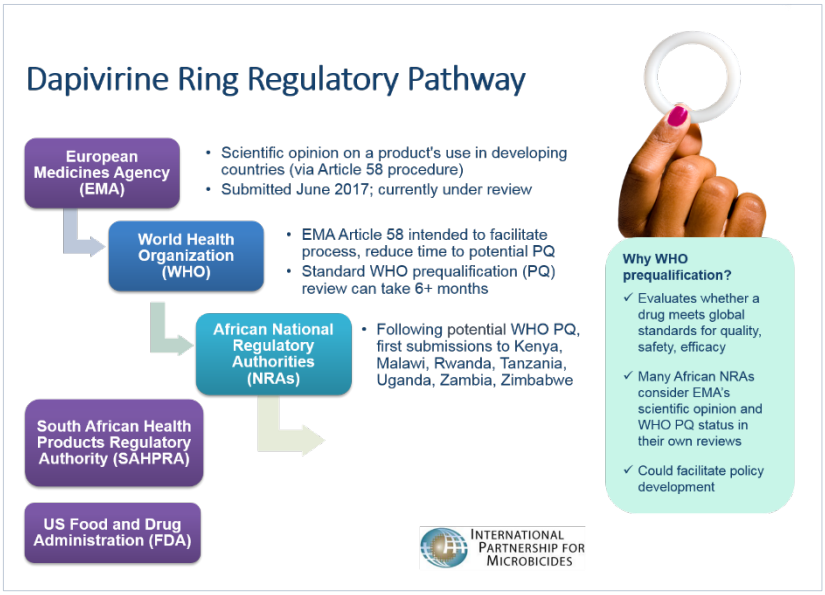
Two open-label extension studies — HOPE for former ASPIRE participants and DREAM for women who participated in The Ring Study — have been ongoing since mid-2016 and will be completing follow-up later in 2018. In HOPE and DREAM, women are provided the opportunity to use the ring in the context of knowing that it has been shown to protect against HIV infection. Interim results, reported in March 2018, found HIV risk was reduced by more than half (54 percent). suggesting that women are using the ring better than they did in the Phase III trials. and Final results of both studies are expected in 2019.

Studies to date have found the dapivirine ring to be well-tolerated with no safety concerns. These include Phase I and Phase II studies that were conducted in the United States: MTN-023/IPM 030, a Phase IIa safety study of the ring in adolescent girls; MTN-024/IPM 031, a Phase IIa safety study of the ring in post-menopausal women; and MTN-029/ IPM 039 in lactating women.

In addition to MTN-042, the MTN is planning additional studies of the dapivirine ring. REACH (MTN-034), will evaluate both the ring and oral PrEP among adolescent girls and young women in Kenya, Uganda, South Africa and Zimbabwe. MTN-043, which is still being drafted, will involve breastfeeding women and their infants and be conducted at the same trial sites as MTN-042.

Regulatory Pathways and Timelines

IPM, the ring's developer, is pursuing approvals from global and national regulatory authorities to license the product in countries where women face the highest risk. Its first application was to the European Medicines Agency (EMA) in June 2017, under a procedure called Article 58 in which the EMA, in cooperation with WHO, is asked to provide a scientific opinion on the safety,



efficacy and quality of the dapivirine ring for use specifically in low- and middle-income countries. The application, or dossier, includes data from more than 250 laboratory and clinical studies, detailing nearly 15 years of research into 260,000 pages.

Should the EMA grant a favorable opinion, IPM will then seek WHO pre-qualification, which regulatory authorities in many developing countries often rely on to determine which new products or drugs to consider for approval. If WHO pre-qualification is granted, IPM will proceed with applications to drug authorities in several African countries, namely, Kenya, Malawi, Rwanda, Tanzania, Uganda, Zambia and Zimbabwe.

In the meantime, IPM plans to submit separate applications to the South African Health Products Regulatory Authority (SAHPRA) (formerly the Medicines Control Council) late 2018, and to the FDA the following year.

If approved, the monthly dapivirine ring would be the first biomedical HIV prevention product developed specifically for women — and the first long-acting product. Importantly, it would represent another option from which they may choose.

Pregnancy and Safety of Dapivirine

Before a drug can be tested in people, researchers must first conduct extensive laboratory and animal studies to be sure that it does not have the potential to cause serious harm. Among the studies conducted are those that evaluate developmental and reproductive toxicity, whereby the drug is tested in pregnant animals, often at doses considerably higher than intended for humans, to assess effects on fertility, embryo-fetal development, infant growth and development, and maternal function. Pre-clinical studies of dapivirine, in which drug was delivered orally or as a vaginal gel, showed no effects on embryo-fetal development, post-natal development or maternal toxicity. In the studies of oral delivery, animals were exposed to systemic levels of drug 1,000 times greater than what women using the vaginal ring are exposed to. A ring contains about 25 mg of drug of which about 4 mg is released into the vagina over 28 days, and with minimal amounts getting systemically absorbed.

Data about dapivirine in pregnant women is quite limited, but thus far are reassuring. With about 250 women across both ASPIRE and The Ring Study who became pregnant during trial participation, researchers were able to compare pregnancy and infant outcomes that occurred among women who were assigned to use the dapivirine ring with those who were in the placebo group and found there were no significant differences between the two groups. Because women stopped using the ring as soon as they learned they were pregnant, however, the information is useful for understanding outcomes associated with exposure during conception and early development only.

The dapivirine ring

Considerations for MTN-042: Questions and Comments

Meeting participants agreed that the monthly dapivirine ring could be an alternative method of HIV prevention for women not wanting or able to follow the daily pill-taking regimen of PrEP and that it should therefore be studied to determine its safety for women during pregnancy. While what has been observed so far in the Phase III and open-label studies in women who became pregnant while using the ring is reassuring, the data are clearly not sufficient and a study like MTN-042 is needed. Because MTN-042 will be conducted in parallel with the regulatory approval process for the dapivirine ring, a hypothetical question was raised about whether the study would continue if the EMA did not render a positive opinion, to which there was no easy answer.

Since the ring was unfamiliar to many of the stakeholders, there were several questions about the product itself, including what happens to the ring during sex (does it come out?), and thinking about MTN-042, whether the ring will stay in during pregnancy and labor. Women who participated in the ASPIRE and The Ring Study reported that their partners seldom felt the ring during sex. In addressing whether the ring can come out during sex, Sharon Hillier said that MTN researchers had estimated this could happen in about one in 3,000 sex acts, based on their analysis ASPIRE participants' responses to questions of this nature. As for whether pregnancy and labor would cause the ring to get expelled, investigators doubted this would be too much of an issue. The ring, which is 56mm in diameter, sits high up in the vagina, just under the cervix. No matter a woman's size, the vaginal wall naturally caresses the ring for a snug fit. They also described another device called a pessary, which is of similar size and shape to the dapivirine ring, that women with a shortened cervical length use during pregnancy to prevent preterm delivery. No instances of the pessary being expelled were reported in any of three clinical trials. Still, some meeting participants noted that the cervix thins during pregnancy, and especially during labor. The team said they will be instructing women to remove the ring as soon as they go into labor.

Helen Rees, a professor from Wits RHI and also chairperson of the SAHPRA board, was concerned about the inclusion of young women, ages 18-21, for whom the ring was not effective in ASPIRE and Ring Study due to poor adherence. She felt that it would be important that the protocol clearly explains the rationale for this and be forthcoming about what the data shows to address an issue that could be a concern to regulators.

Pregnancy in Context: Socio-Cultural Concerns

Pregnancy in Context: Socio-Cultural Concerns

Understanding Cultural and Community Context

Researchers who will be conducting the MTN-042 study realize the challenges will be many and complex, including at the community level. Understanding cultural beliefs, societal norms and roles within the community will be especially important for a study of this kind – one that involves pregnant women. To this end, and in preparation for MTN-042, the researchers are conducting another study called MTN-041. As a qualitative study, MTN-041 is designed to identify specific factors, belief systems and attitudes that may affect pregnant women's perceptions of the MTN-042 study and potential interest in using a vaginal ring or PrEP during pregnancy and/or breastfeeding, and who within a woman's sphere of influence is most likely to support or discourage use of either or both products.

The study will involve focus group discussions with women currently or recently pregnant and breastfeeding; men whose partners are or were recently pregnant or breastfeeding; and mothers and mothers-in-law of pregnant and breastfeeding women. In-depth interviews will be conducted with community and traditional leaders, healthcare providers, midwives and traditional birth attendants, whose perceptions and attitudes about what is and is not acceptable to do during pregnancy and breastfeeding can have significant impact on the study's implementation and provision of HIV prevention and maternal health services.

In addition to seeking to understand perceptions about the use of a vaginal ring and/or oral PrEP by pregnant and breastfeeding women, the focus group discussions and individual interviews will explore perceptions about HIV risk during pregnancy and breastfeeding; sexual activity and vaginal practices among pregnant and breastfeeding women; as well as community beliefs and practices considered taboo or encouraged during pregnancy and breastfeeding.

MTN-041 is taking place at the same trial sites in Malawi, Uganda, South Africa, and Zimbabwe that will be conducting MTN-042 (as well as the MTN-043 study of the vaginal ring in breastfeeding women). MTN-041 will help to understand community and individual perspectives, socio-cultural beliefs and practices about pregnancy and the use of the ring or PrEP during pregnancy and breastfeeding and the potential impact these may have on pregnant and breastfeeding women's opinions about and willingness to use the dapivirine vaginal ring and PrEP. Support from key stakeholders and leaders, health care providers and family members will be essential. The MTN-041 study will be completed before MTN-042 is set to launch. What is learned will help inform community and stakeholder engagement programs, participant recruitment and the informed consent process for both the MTN-042 and MTN-043 studies.

Speaking as Women: Community and Civil Society Perspectives on MTN-042

Many of the same issues that will be explored in the MTN-041 study were echoed by a panel comprised of HIV prevention advocates, women's health activists and civil society representatives from each of the trial site countries.

All agreed that immediate family members —mothers and mothers-in-law, in particular — play important roles and are closely involved in caring for and protecting the pregnant mother and her baby. In many countries, they play a particularly important role with a first pregnancy. Decisions about what the pregnant woman eats, which activities she engages in, and about her health and wellbeing become those of others. In fact, very often women having their first child are expected to return to the home of her mother or mother-in law — often in rural settings — where they are watched over and cared for in the final months and where they will give birth.

In many countries, men are conferred the power to make health-related decisions for the family, including HIV-related prevention and treatment services. This extends to decisions in pregnancy as well. Women must also heed the advice of elder women regarding practices that are said to ensure the baby's safe and healthy delivery, and will do so even if in disagreement

for fear of being blamed if there are complications during pregnancy or delivery. Panelists thought it likely that various superstitions could scare some into not using the ring or PrEP in the MTN-042 study. Herbal mixtures are known to be used for douching, and some in instances, someone else (usually a trusted member of the family) inserts the mixtures inside the woman's vagina with their fingers. Whether or not this practice would affect the ring was less worrisome than the possibility that the woman's husband, mother or

mother-in-law would discover the ring. This led to discussion about concerns that women in the study could be subject to social harms and that it would be important that trial sites had protective and supportive measures in place. Discussion also touched on the mental health needs of pregnant women in the study. Clinicians have reported a rise in mental health issues in pregnant women and MTN-042 may offer further insight.

The panel agreed that engaging with traditional birth attendants will be essential so that they are more likely to support rather than hinder the study's conduct. Targeted messaging and materials for other key stakeholders will be important as well, but most critical will be what and how the MTN-042 study is communicated to potential participants. Why the study is being conducted and the potential risks and benefits of participation must be explained clearly, so that women can make informed decisions about whether to participate. Panelists also believed there was something valuable to learn from prevention of mother-to-child transmission (PMTCT) programs. What motivates women to join a PMTCT program or study is the prospect of having a healthy, HIV-negative baby, and this is a message that needs to get across about the MTN-042 study as well.

Community and Civil Society Perspectives

Considerations for MTN-042: Key Audiences and Key Messages

Meeting participants agreed that the MTN-041 qualitative study will provide insight that will help guide implementation of the MTN-042 study, including recruitment efforts, informed consent, messaging and ways to support product use. Communicating with and involving family members (if a participant allows) and traditional birth attendants will be important for ensuring adherence to study visits, procedures and product use – using the ring for a month at a time or taking daily PrEP. Communication with other health facilities and providers will be equally important so they understand the purpose of the study and therefore refrain from advising women not to use study products.

Researchers should ensure women in the study understand that they will be closely monitored and be provided with any support they may need, and that if they experience problems or have questions they should contact study staff as their first course, before taking advice from others. Some women may find it difficult to assert themselves due to socio-cultural norms, but others may come to realize that pregnancy is an important and special time for them as well — that they are more than just a vessel for an unborn child.

Although audience-specific messaging and materials will need to be developed, it was recommended that in all communications across all groups and stakeholders, including potential participants, these top-line messages be incorporated:

- PrEP and the dapivirine ring are products being studied for use in pregnant women, but they have already been shown to be safe and to protect women against HIV in studies involving women who were not pregnant.
- Women are at greater risk of HIV during pregnancy than when they are not, and they deserve and have a right to be protected.
- Protecting yourselves means delivering an HIV-negative baby.
- Women need choices — it will be good to have choices like PrEP and the ring in the "HIV prevention basket for women."

Pregnant Women as Trial Participants: Ethical and Legal Framework

Pregnant Women as Trial Participants: Ethical and Legal Framework

International Guidelines: Moving Toward Inclusion of Pregnant Women

Research Ethics Committees, sometimes referred to as Institutional Review Boards or Independent Ethics Committees (IRB/IECs), are responsible for safeguarding the rights, safety and welfare of research participants. As such, in evaluating a research protocol, they must judge the scientific merits of the study, including all proposed methods and procedures, against the potential risks and benefits to participants, to determine whether, ethically, the end justifies the means. Through ongoing monitoring and oversight of the study, IRB/IECs must ensure that it remains in compliance with the protocol as well as international research requirements for Good Clinical Practice.

The work of IRB/IECs is guided by basic principles of research ethics that stem in part from the Belmont Report produced by the (U.S.) National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in 1979. The Belmont Report describes three ethical principles regarding research involving humans:

1. **Respect for persons** - Recognizing and protecting individual autonomy, and providing for informed consent
2. **Beneficence**: To do good, and do no harm, ensuring the wellbeing of participants and maximizing the benefits to participants and minimizing their risks
3. **Justice:** ensuring equal distributions of benefits and burdens of research

IRB/IECs are also guided by principles outlined in the World Medical Association's Declaration of Helsinki and by the Council for International Organizations of Medical Sciences (CIOMS). Recommendations and guidance on the ethical conduct of clinical research may also be provided by WHO and/or the Joint United Nations Programme on HIV/AIDS (UNAIDS).

IRBs/IECs must adhere to national regulations, and in the case of research funded by foreign institutions, all relevant regulations that are required of that country. Because MTN-042 is funded by the U.S. National Institutes of Health, U.S. regulations would apply in the conduct of the study in each trial site country.

The research community has for decades taken a protectionist view when it comes to research involving pregnant and breastfeeding women, mostly due to concerns about potential harm to the fetus and child. Many studies have excluded women of childbearing potential from participation, while others require women be on contraception and to stop the study drug if they become pregnant. Therefore, drugs that are approved often lack information about their safety during pregnancy and breastfeeding yet, in practice, may be used by pregnant and breastfeeding women anyway, without the benefit of knowing this is safe.

Many ethicists now recognize that the pendulum has swung too far, and that the research community has been unnecessarily overly protective of pregnant women, to their detriment.

"Rather than be protected, pregnant and breastfeeding women are actually being treated unjustly," said Paul Ndebele, then the director of the Medical Research Council of Zimbabwe (MRCZ). It can't be assumed that something shown to be safe in a clinical trial of women who were not pregnant will be safe to use by women who are, nor that the drug will work exactly the same way. Pregnant women should have the same rights to safe and effective products as do others, Dr. Ndebele explained. *"*After all, pregnant women become ill and sick women become pregnant.*"*

Part of the problem has been in the classification of pregnant women as a vulnerable population, who, along with minors, prisoners, persons with diminished mental capacity, and people who may be disadvantaged in other ways, are considered to lack the capacity to protect their own interests and provide informed consent. Moreover, pregnant women are listed together with fetuses, making it difficult to separate the circumstances of one from the other. So, although the mental capacity of a woman during pregnancy should be no different than when she is not, a pregnant woman is inextricably linked to her fetus who obviously cannot provide consent.

Many international groups, such as CIOMS, now hold the view that pregnant women should be afforded autonomy to make their own informed decisions for both themselves and their fetus or infant. Now, instead of being called vulnerable, pregnant women are beginning to be referred to as "special," "scientifically complex," or "medically complex" populations. Guidelines seem to be moving toward requiring that researchers provide justification for why pregnant women are *not* included in a study, especially when it is possible that the research may benefit the pregnant woman, the fetus, or her infant.

"Researchers, ethics committees, sponsors and society, have roles to play in correcting the pendulum to include – not exclude – pregnant women from research," said Dr. Ndebele. There is a scientific and ethical imperative to do so.

What do different groups and organizations say about research in pregnant women?

Declaration of Helsinki

First created in 1964, the Declaration of Helsinki was developed by the World Medical Association as a statement of ethical principles for medical research involving humans. While the most recent version, published in 2013, states that as a general principle, "Groups that are underrepresented in medical research should be provided appropriate access to participation in research," the document does not specify which groups are considered underrepresented. With reference to vulnerable groups and individuals, the statement is likewise vague. The Declaration contains no language specifically about women, let alone pregnant and breastfeeding women.

CIOMS

The CIOMS *International Ethical Guidelines for Health-related Research Involving Humans*, which were updated in 2016, include new guidance regarding pregnant women, stating that "pregnant women must not be considered vulnerable simply because they are pregnant," and making it clear that pregnant and breastfeeding women are entitled to provide informed consent.

The new guidance allows for research involving pregnant women provided certain conditions are met, including that pregnant women are informed of all risks and relevant research, including animal models looking at risk of birth defects. CIOMS also asserts that research with pregnant women must be conducted only in settings where these women can be guaranteed access to a safe, legal abortion, although ethics committees "may permit research with compelling social value when this condition cannot be met." And because adverse events associated with research in pregnancy and breastfeeding women may not be immediately apparent, researchers must provide a plan for monitoring the outcome of the pregnancy and providing longer-term follow-up of the health of both women and their babies.

While CIOMS guidelines are not legally binding, they represent a global consensus regarding the ethical conduct of research and serve as a reference in many low- and middle-income countries.

Global Forum on Bioethics in Research

Among the points of consensus coming out of the 2016 Global Forum on Bioethics in Research (GFBR), which focused exclusively on the ethics of research in pregnancy, was that "Pregnant women should not be excluded from research by default," and that the global research community must work toward the ethical inclusion of pregnant women in research. By conducting research, evidence can be collected in an ethical manner and mitigate uncertainty in the clinical setting.

The proceedings of the meeting were published as a special journal supplement, in which in the introduction the authors delineate "a call to action" based on three ethical arguments:

1. Pregnant women deserve access to *effective* treatment and preventives,
2. Pregnant women deserve access to *safe* treatment and preventives, and
3. Pregnant women deserve *equitable* access to trials carrying the prospect of direct benefit.

UNAIDS/WHO

The joint UNAIDS/WHO guidance document, *Ethical Considerations in Biomedical HIV Prevention Trials,* issued in 2012, recommends that women be included in clinical trials, including women who are pregnant and breastfeeding (Guidance Point 9: Women), arguing that "Women throughout the life span, including those who are sexually active and may become pregnant, be pregnant or be breastfeeding, should be recipients of future safe and effective biomedical HIV prevention products and therefore should be eligible for enrolment in biomedical HIV prevention trials."

The guidance also argues that pregnant and breastfeeding women should be given autonomy to make informed choices for both themselves and their fetus or infant. Women should therefore be provided information about all known and potential risks and benefits about the intervention under study.

U.S. Regulations

The United States permits pregnant women's participation in research under conditions specified in U.S. Department of Health and Human Services federal regulations known as Title 45 CFR (Code of Regulations) part 46, or simply 45 CFR 46. The regulation includes four subparts. Subpart A, also known as the Federal Policy or the "Common Rule," outlines the basic provisions for IRBs, informed consent, and Assurances of Compliance. Subpart B specifies additional ethics requirements for research involving pregnant women, fetuses, and neonates, outlining 10 requirements that must be met. These regulations apply to any research conducted by or supported by any U.S. federal department or agency.

Studies involving investigational drugs are subject to additional regulations promulgated by the FDA, as well as in-country drug regulatory authorities. The FDA does not have regulations specific to research with pregnant women, but FDA Draft Guidance for Industry "Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials" published April 2018 recommends that FDA-regulated clinical research heed the requirements outlined in 45 CFR part 46, subpart B.

The Ethical and Legal Framework in Trial-site Countries

Besides international guidance, what are the country-specific regulations and guidelines that must be considered in each of the countries where MTN-042 is being planned? What are the most significant ethical concerns about or barriers to conducting a trial with pregnant women? An ethics representative from each country outlined their views, experience and the specific processes that lie ahead. Key points are described below.

Malawi

Malawi has taken an overly protectionist and paternalistic view regarding pregnant women's involvement in clinical trials. Joseph Mfutso-Bengo, a professor of ethics at the College of Medicine, University of Malawi, and Center of Bioethics for Eastern and Southern Africa, sees the need for reform to allow for more equity, in line with what is happening on a global level. He believes the most significant ethical questions and challenges for MTN-042 will be balancing the interest of the mother and of the unborn child and balancing the right of the mother to give consent and the right of the unborn to be protected (the duty to protect the unborn child). Moreover, communicating about known and potential risks will need to be managed carefully.

The National Commission for Science and Technology (NCST) is the government body responsible for EC oversight, and for promotion and coordination of research in Malawi. There are two government approved ECs: the National Health Sciences Research Committee (NHSRC) and College of Medicine Research and Ethics Committee (COMREC). For MTN-042, which will be conducted at a clinical research site affiliated with the College of Medicine, review will likely be required of both COMREC and the NHSRC, or an ad hoc committee appointed for this purpose. This is because the dapivirine ring is not a registered product. The Pharmacy Medicines and Poisons Board must then approve the study, and additional review may be needed of the Ministry of Health due to the study's involvement of pregnant women.

Uganda

In Uganda, clinical trials conducted in pregnant women have typically involved pregnancy-related health conditions like post-partum hemorrhage or prevention of mother-to-child infection. In the local context, pregnant women are considered "delicate," and men are the primary decision makers, explained Henry Mugerwa, a board member of the Joint Clinical Research Centre (JCRC) Research Ethics Committee (REC). In fact, national guidelines specify that for research involving pregnant women, informed consent must be obtained from both the mother and father of "the embryos and fetuses." Exceptions apply if the purpose of the research is primarily to meet the health needs of the mother; the father's identity and/or whereabouts are unknown; the pregnancy resulted from rape or incest or the father Is incompetent to give consent.

National guidelines also stipulate that appropriate research in animal models and non-pregnant women should have been completed, and consent should explain all risks, including unforeseeable risks to the participant, the embryo or fetus.

Dr. Mugerwa said that the JCRC REC typically takes about four to eight weeks to review a protocol, and that it would then need to be submitted to the National Drug Authority for approval and to the Uganda National Council for Science and Technology for registration, a process that typically takes an additional 12 weeks.

Zimbabwe

Zimbabwe has been decidedly progressive, having taken on a reform of its guidelines to provide pregnant women more equitable access to clinical research, especially when there is a prospect of a direct benefit. Toward that end, and with a fellowship from the Global Forum for Bioethics in Research, MRCZ's Sithembile Ruzario is working specifically to improve the ethical practice for research in pregnancy, including by reviewing and revising MRCZ's ethics guidelines to allow for inclusion of pregnant women in research.

Ms. Ruzario is senior research compliance officer and National Ethics Committee administrator for the MRCZ, which serves as Zimbabwe's national research ethics committee and would review the MTN-042 after receiving site IRB/IEC approval. Speaking from a justice point of view, she argues that "pregnant women deserve more from clinical research than what they are getting. Justice requires a research agenda that adequately addresses the health needs of pregnant women."

South Africa

Like Zimbabwe, South Africa is paying extra attention to research in pregnant women. Ethics committees are now seeking justification on why research is not being done in pregnant women. Research in pregnant women needs to be prioritized and "we are no longer allowed to bury our heads in the sand," said Francesca Conradie, an HIV clinician and researcher who sits on the Wits University Human Research Ethics Committee (Wits HREC). That being said, it will be important to provide pregnant women with all available information about both the dapivirine ring and Truvada as PrEP, including all possible risks and benefits to both the pregnant woman and fetus.

As with other country guidelines, those of South Africa require that appropriate studies of the drug have already been conducted in animals and non-pregnant women, and the study must ensure the least risk possible. Consent is not required of the father.

Following review and approval by the local IRB/IEC, which in the case of MTN-042 will be the Wits HREC, approval will also be required of the national drug regulatory authority, SAHPRA.

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The Ethical and Legal Framework

Considerations for MTN-042: Questions and Comments

From an ethical point of view, there was support in conducting the study to address the fact that women during pregnancy were especially vulnerable to HIV and that they and their babies could potentially benefit if the mother was indeed protected. The study is not without risks, however, and given the populations involved – mothers, fetuses and newborns – there will need to be great attention paid to safeguarding the safety and minimizing as much as possible the potential risks.

As part of the informed consent process, it will be imperative to provide comprehensive information about the study and the study products, including what is not known or well understood by researchers. With the possible exception of Uganda, where both the mother and father of the fetus may be required to provide consent if the purpose of the research is not deemed primarily to meet the health needs of the mother, the decision will be up to women about whether she finds the risks acceptable to her and her fetus. Women must also be informed that it may be difficult to determine causality in cases of fetal or infant abnormalities — outcomes may or may not be able to be attributed to use of the products — and that even if not participating in a study there is always risk associated with pregnancy.

Although partner consent may not be required, for sociocultural reasons it may be wise to involve male partners in some way. At the same time, researchers will need to be sensitive to the fact that many women may not feel they have autonomy to make decisions if the partner is present.

Participants who enroll in each cohort will need to be informed of results and outcomes from the previous cohort, so informed consent forms and/or materials will need to be revised to include new information, and be approved by IRB/IECs before enrollment into the next cohort can begin. How best to manage this process without adding unnecessary delays to the study's timelines was discussed. There was a suggestion to develop a study information sheet, rather than amending the informed consent form, which would require less time for review and approval.

CIOMS guidelines indicate that pregnant women participating in a study must be guaranteed access to safe and legal abortion if she experiences a complication and wants to terminate the pregnancy. This is not likely something that the protocol or sites can guarantee, as abortion is not legal in most settings (but in some cases may be done when medically indicated). CIOMS does provide for exceptions, however. Nonetheless, it was suggested that inclusion criteria for study participation add that women must have intent to carry their pregnancy through to delivery.

All countries have local Research Ethics Committees and have national procedures for research. As the study includes a new drug, the protocol will need to be submitted to national drug authorities for approval as well. Turnaround time for review of the protocol may be more than four months at some review boards. To harmonize the protocol reviews, regional ethical review committees should be considered. These include the African Vaccine Regulatory Forum (AVAREF).

Asking for Feedback: Stakeholders' Responses to Key Questions

Asking for Feedback: Stakeholders' Responses to Key Questions

To both better understand stakeholders' views about the proposed study and elicit discussion on specific issues of interest to the MTN, stakeholders were asked a series of questions to which they registered their responses anonymously using handheld remote devices called an Automated Response System (ARS). Because the ARS is incorporated into a PowerPoint presentation, responses were compiled immediately and displayed visually on the screen, creating stimulus for further discussion.

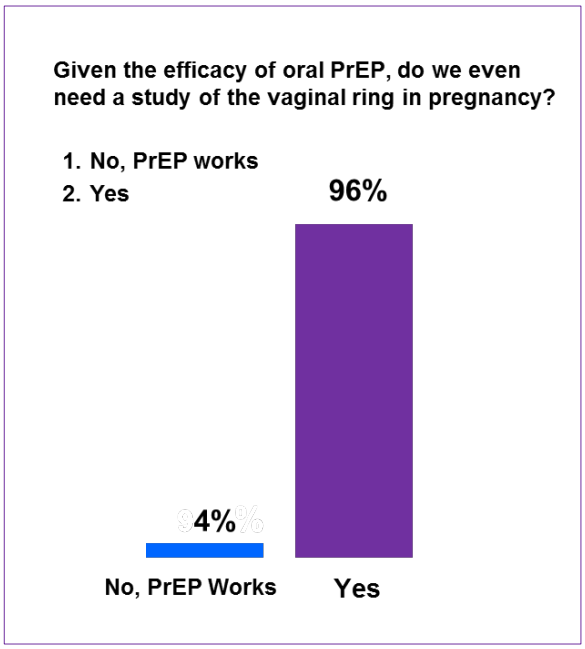
Stakeholders Responses

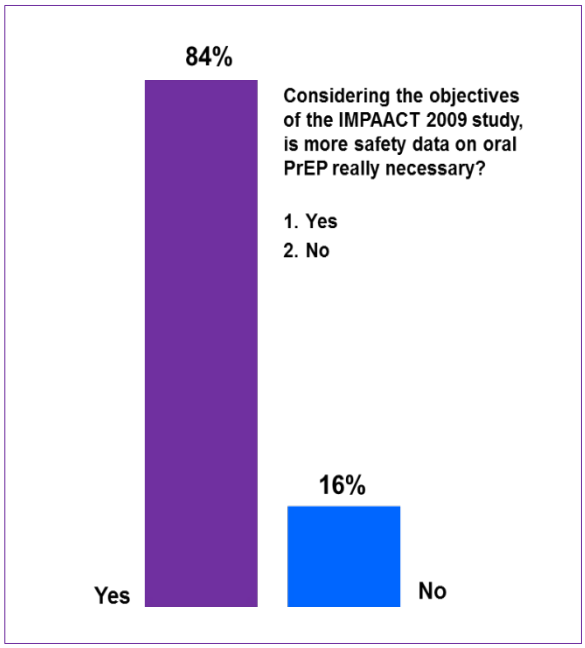
Responses revealed a high level of support for the study. For instance, when asked whether, given the efficacy and approval status of PrEP, a study looking at the vaginal ring in pregnancy was even needed, the vast majority (96 percent) said yes. Participants believed a "one-size fits all" approach alone cannot reduce the HIV burden in women. Moreover, women should be able to choose a method that works best for them. If approved, the ring would provide an additional HIV prevention option, including potentially also for women during pregnancy.

Although the IMPAACT 2009 study will also be evaluating the safety of PrEP during pregnancy, most meeting participants (84 percent) believed additional safety data of PrEP in pregnancy was needed. IMPAACT 2009 will answer questions about women ages 16-24, but it will be important to have information about women of older reproductive age as well. Stakeholders saw the two studies complementing each other, and together, critically important for providing insight about the safety of PrEP during pregnancy.

Before being asked the ARS questions, meeting participants were reminded of the following key points:

- *Women are at very high risk of acquiring HIV during pregnancy.*
- *PrEP is approved in a number of African countries, though guidelines differ with respect to its use during pregnancy.*
- *WHO recommends that women use PrEP during pregnancy. Some countries have guidelines that are in accordance with WHO. Notably, South Africa has been hesitant to recommend PrEP for pregnant women until more data is available.*
- *The dapivirine ring is a new HIV prevention method. Its regulatory approval is being sought, although this would not be for pregnant women.*
- *MTN-042 intends to evaluate both PrEP and the vaginal ring in women during pregnancy, primarily looking at its safety.*
- *Another study – IMPAACT 2009 – will evaluate PrEP among pregnant adolescent girls and young women.*





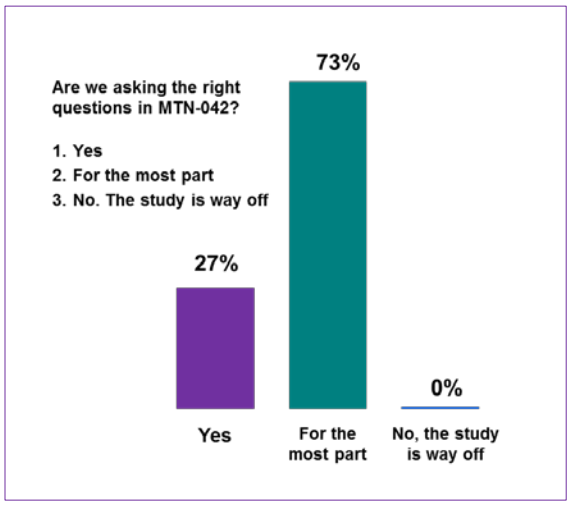
Stakeholders agreed with MTN-042's primary aims but most believed the study could do more — 73 percent thought the study was "for the most part" asking the right questions. It was felt the study should give greater focus to infant safety and to understanding potential long-term effects from drug exposure during fetal development, which could be achieved with longer follow-up, preferably for up to a year. Additional study questions were also proposed, including those that could provide insight into socio-cultural practices, social harms, and motivations for joining the study.

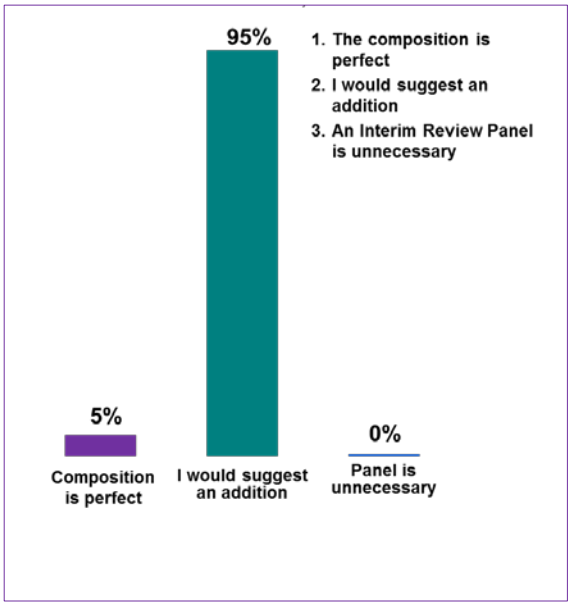
Asked about the level of safety monitoring that the study was planning to provide, 29 percent of the responses indicated it was sufficient, while 25 percent disagreed, and 46 percent selected "It's a start, but more could be done" as their answer. Their biggest concerns were how to manage adverse events that occurred during labor and delivery (which would not be at the trial site), especially in settings that lacked the necessary capacity and expertise. The need for the study to provide longer follow-up of infants was mentioned again as well.

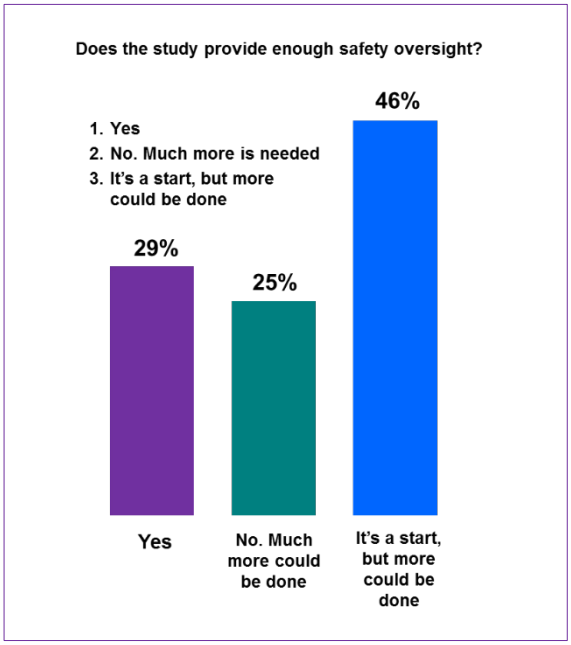
Stakeholders were asked their opinion about the proposed makeup of the Interim Review Panel, which would conduct reviews of safety data between each group of participants and advise whether the study should proceed. Dr. Bunge explained that under consideration was a panel that would be comprised of:

- A community representative
- Two obstetricians – one from sub-Saharan Africa and one from the United States
- A pediatrician from either sub-Saharan Africa or the United States
- An ethicist
- A statistician
- A maternal-child health expert from the public health sector

ARS voting indicated that stakeholders had other ideas. Among the suggestions were that the panel include two community representatives, or alternatively, a community representative plus a civil society representative; that the pediatrician and maternal child health expert both be from sub-Saharan Africa; and that individuals with extensive understanding of regulatory matters and pharmacokinetics and drug interaction be included. Other recommendations were that the panel should be 50 percent women and there be representation of diverse socio-cultural contexts, with at least one person from each of the four trial site countries.





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Summary of Suggestions and Recommendations

Summary of Suggestions and Recommendations

Overall, stakeholders were very supportive of the MTN-042 study but also offered several recommendations and suggestions, some which have been discussed elsewhere in this report. The following pages bring these and other recommendations together in an attempt to summarize the breadth of discussion in short briefs.

The Need for a Comparison Group

As an open-label study, there is no placebo group in MTN-042. Conducting a placebo-controlled trial would be unethical because both PrEP and the ring have been shown to be safe and effective in Phase III trials (and PrEP is already approved for HIV prevention). But this also presents a challenge for investigators. Without some basis for comparison it will be difficult to know with much certainty whether adverse maternal and neonatal outcomes observed in the study are due to the products or complications that might have occurred in pregnancy anyway. At the same time, in communities where certain pregnancy outcomes are more common than in others, use of the product could feasibly contribute to a particular outcome. While the MTN-042 study would allow for comparisons between the PrEP and the ring groups, it is not designed to determine whether the severity or frequency of complications experienced in either group would be different than what might be expected among pregnant women generally — especially in those same communities.

The study would be strengthened, and its results be more meaningful, if there could be a means for comparison, stakeholders argued. Different approaches were discussed. One suggestion was that researchers obtain background rates of pregnancy complications and infant outcomes from publicly available sources such as Department of Health reports. At the same time, it was noted that this data is not always reliable or complete. Comparisons could also be made based on data from MTN's pregnancy registry study (MTN-016, or EMBRACE), though this, too, was felt not to be ideal because the cohort is likely too small and not all outcomes of interest to MTN-042 may have been collected. Alternatively, researchers could collect prospective data on pregnancy and birth outcomes at hospitals within each trial site catchment area prior to the start of the study or as a lead-in phase within the protocol itself. Lastly, researchers could consider the approach being used in the IMPAACT 2009 study and enroll pregnant women who decline being randomized to PrEP or the ring but agree to be followed.

Harmonize and Standardize Study Definitions

The use of differing definitions for maternal and neonatal outcomes within and across both the research community and the public health sector has been a long-standing problem that has made it nearly impossible to compare outcomes, to interpret results or recognize important trends. In response to a call for action by the WHO, the GAIA (Global Alignment of Immunization safety Assessment in pregnancy) was formed and has now developed a globally standardized set of case definitions of key obstetric and neonatal terms with a goal to enhance surveillance and collection of maternal immunization safety data, particularly within low- and middle-income countries. Stakeholders strongly believed that it would be important for the MTN-042 study to conform to these standardized definitions as well. Likewise, the MTN-042 and IMPAACT 2009 studies should try to harmonize clinical and laboratory definitions and criteria for medical conditions and assessments so that findings can be compared to and be used to corroborate one another.

Longer Follow-up of Infants

The design of the study at the time of the consultation included a six-week follow-up visit after delivery for both mothers and infants, at which time women and their infants would be offered enrollment into the MTN-016 observational study to allow for longer follow-up. This was not considered ideal in part because not all women would choose to participate in a second study and identifying or responding to adverse events could also be more difficult in an observational study. It was also noted that IMPAACT 2009 will be following mothers and babies for six months.

As such, stakeholders recommended that researchers incorporate a longer follow-up period directly into the protocol, preferably for one year so that the study could capture any infant adverse events that occur later within the first year of life. Professor Helen Rees proposed that the study could also then include a mechanism for following infants who are being breastfed. *(MTN researchers are already planning a study of the dapivirine ring in breastfeeding women.)*

Informed Consent

Explaining risks and benefits of participation

"What do we tell women on why this is safe?" Priscilla Nyambayo, who heads the Pharmacovigilance and Clinical Trials Division at the Medicines Control Authority of Zimbabwe, asked early into the meeting. Consider that on the one hand, women will hear how everything that is known so far about the ring and PrEP in pregnancy is reassuring — otherwise we would not be conducting the study. Yet, at the same time, a key message will be that the reason for conducting the study is because researchers need to learn more about the safety of these products (particularly about the ring) during pregnancy. Is it safe for women to participate in this study, or not? Are these products safe to use during pregnancy, or not? Indeed, the rationale for the study must be clearly explained to potential participants, and they must be fully informed about what is known and not known about the dapivirine ring and PrEP in both non-pregnant and pregnant populations, and from animal studies as well. For women to make an informed decision about participation in the study they must understand the potential risks to both themselves and their babies, and at the same time understand that they could experience complications of pregnancy or delivery unrelated to the study, or that may be difficult to know either way. Study staff must also explain the potential benefits of being in the study. Along these

lines, a message stakeholders felt should be emphasized was that by women protecting themselves against HIV during pregnancy, they would be protecting their infants as well.

New information

Those enrolling in the second, third and fourth cohort will also need to be informed of the findings from all previous cohorts. Any other new information, such as from other studies, will also be shared and explained to participants. Study information sheets and/or informed consent forms will need to incorporate new information from the prior interim safety review. Revisions made to any study materials must in turn be resubmitted for review by each site's IRB/IEC and be approved before enrollment into the next cohort may proceed. IRB/IEC representatives at the consultation suggested that for expedience, the study teams consider updating only the information sheet.

Consent of the father

Although the consent of the father of the fetus may only be required in Uganda, stakeholders encouraged the study team to engage with partners. Due to the socio-cultural issues around pregnancy, pregnant women may need to consult or inform their partners before joining the study.

Arrangements with Local Hospitals

Labor and delivery is a time when data and specimen collection will be most critical, yet it will also be the time when study staff will have the least control of the process. If a woman delivers at a remote facility that has not been informed about the study — or at her family's home far from the site — it will be all the more difficult for the researchers to collect the information needed for the study. Trial sites will need to ensure women plan to deliver at nearby hospitals where the site has made special arrangements regarding the study. Study teams will need the cooperation of hospital staff so that they are notified when a participant has been admitted, all information of interest to the study is well documented and they are able to access records and retrieve records, specimens and, when applicable, vaginal rings. Having agreements in place at local hospitals across all trial sites will help ensure more accurate and consistent reporting as well.

Stakeholders also urged teams to establish ties with midwives and traditional birth attendants, especially if they may be present during the time a participant is in labor and delivery.

Enrolling the Right Participants

As mentioned above, stakeholders advised that the study should only enroll women who are planning to deliver at a local facility. They also considered whether the study should exclude women who were pregnant for the first-time, who would more likely be subject to socio-cultural norms and pressures and not follow study procedures or use the ring or PrEP. That being said, it was recommended that the protocol include an explanation for including young women ages 18-21 since there was no clear protection associated with ring use in women of this age in either ASPIRE or The Ring Study.

Social Harms

The prospect of women experiencing social harms due to participation in the study — be they physical, emotional or psychological harms — was raised by stakeholders multiple times. A woman could experience harm if her partner learns that she has been participating in the study without his consent and/or if he has been excluded from decisions affecting their baby. Given that MTN-042 is an HIV prevention study, she could be accused of not having trust in his fidelity or of being unfaithful herself. Family members or others may assume she has HIV if they discover the ARVs she is taking for PrEP, and given the ring's unfamiliarity, there could be concerns about its use — especially during pregnancy. Giving birth to a child with congenital malformations could also be a source of social harms with long-term effects on the mother, her baby and family members. And the blame could easily be placed on her (and the study). Stakeholders emphasized the importance of the study sites providing women with necessary psychosocial support. The study could also consider incorporating specific questions around issues of social harms into behavioral assessments or qualitative interviews, for example.

Male Partners and Family Members

Male partners can play an important role in women's health decisions, and their involvement in HIV prevention trials has been shown to have a positive impact on women's adherence to the study products. As such, stakeholders recommended that, to the extent possible, trial sites seek opportunities to engage with male partners of MTN-042 study participants. Given the context of pregnancy, mothers and mothers in-law, whose first concern will be the baby's wellbeing, should also be invited to become involved. Engaging with both partners and family members could help with women's uptake of the products, reduce the likelihood of some social harms from occurring, as well as help to dispel rumors and misconceptions about the study.

Community and Stakeholder Engagement

Each trial site will need a plan focused on sensitizing the community and stakeholders about the study, targeting especially key influencers, such as community leaders, traditional leaders, healthcare providers, midwives and traditional birth attendants. Of course, communication must also consider potential participants.

Communications and community engagement activities should facilitate understanding of the rationale and need for the study and establish trust in the study teams who will be looking after the safety and wellbeing of both mothers and their babies. While stakeholders agreed that messaging should emphasize that the study is about women staying HIV negative during pregnancy and their babies being born healthy, communications must also be transparent and truthful about the risks and realities of pregnancy, and that serious complications are a possibility — study or no study. Stakeholders must be kept informed throughout the study, including especially updates on interim safety reviews and their outcomes. Site communications plans should anticipate scenarios in which adverse events could be misattributed to products.

Other Suggestions

- The study should facilitate post-mortem (autopsies) in the event of a stillbirth, infant death or maternal death during delivery to help determine any causality with product use and to allay concerns about outcomes that may not be associated with products or the study.

- African experts should be considered for appointment on the Interim Safety Review Panel before Americans with similar credentials and expertise. For instance, the panel's one pediatrician should be African. Stakeholders also suggested there be two, community representatives, not one, and that a person working in civil society be considered to fill this second spot. Additional members to consider include experts on regulatory matters and in pharmacokinetics and drug interaction.

- Per the protocol, participants will stop using their assigned product after delivery. Stakeholders urged that women be provided access to PrEP at least through the six-week follow-up period because of the heightened HIV risk in the weeks that follow delivery.

- The study should explore women's motivations to join the study as they may differ from those of women participating in Prevention of Mother-to-Child Transmission programs. Factors influencing adherence or acceptability may also differ. Other topics researchers should explore are women's intravaginal practices, including the use of herbs; and views about the comfort and convenience of the ring or PrEP, and whether perceptions differ at different times during pregnancy.

- Mental health evaluations of participants should be included in the initial health evaluation, and periodic assessments provided during the study with referrals to appropriate care when indicated. Although it was also viewed unethical to screen for something if appropriate care would not be available.

- The study should provide participants clear guidance about what to do when labor is suspected. For women using the vaginal ring, guidance will need to include information about when to remove the ring, and where to store the ring after removal or should it come out on its own.

- CIOMS guidelines include a stipulation that studies involving pregnant women must provide access to safe and legal abortion. This is not something sites can guarantee, and, indeed, the guidelines indicate that IRB/IECs may allow research to proceed if conditions cannot be met. Stakeholders recommended that sites and their IRB/IECs discuss how circumstances will be managed should a participant request or require (due to medical necessity) an abortion. Stakeholders also recommended that inclusion criteria for study participation provide that women must have intent to carry their pregnancy through to delivery.

- Because MTN-042 will not be enrolling women in their first trimester, researchers should consider if another study could be designed to understand the safety of PrEP, and in particular, the dapivirine ring, in this population.

Study Update and Next Steps: Getting Ready to Deliver

Study Update and Next Steps: Getting Ready to Deliver

The stakeholder's consultation was purposefully scheduled by MTN and AVAC to take place a few days before the MTN-042 protocol development meeting was convened so that stakeholders' comments and suggestions could be considered for inclusion into the next version of the protocol. Indeed, the protocol development meeting agenda was shaped almost entirely around specific issues and recommendations raised at the consultation. In attendance were staff from each of the four trial sites, including study investigators, study coordinators and community educators; MTN physicians specializing in obstetrics/gynecology, infectious diseases and pediatrics; and medical officers from two of the NIH funding institutes, NIAID and NICHD, among others.

Important Modifications

Among the most significant decisions made at the protocol development meeting came about as a direct result of the feedback received from stakeholders about the study, and these were to:

- **Extend follow-up of infants to one-year**. Procedures that were to be part of the MTN-016 pregnancy registry/observational study were folded into the main protocol, with infant follow-up visits to take place one week, six weeks, six months and one year after birth.
- **Identify potential sources of existing background pregnancy outcomes data**, including publicly available data from the local hospitals where study participants would likely be delivering. The protocol team agreed that this would be important for determining whether the type and frequency of pregnancy complications and poor outcomes in the study differ from or are generally similar to trends in pregnancy outcomes within trial-site communities. The specific plan, devised after the stakeholders meeting, is described below.

The team made other refinements to the protocol during the meeting, including to the study's **Primary and Secondary Objectives**. (*See Textbox*.)

- **Assessment of pregnancy outcomes was classified as a primary objective.** In addition to maternal and infant safety, which will be measured by incidence of high grade and serious adverse events, including maternal and neonatal deaths, and congenital anomalies, the protocol also now includes pregnancy outcomes as a primary objective. (Pregnancy outcomes was previously a secondary objective.) Specific outcomes will include whether the pregnancy resulted in a full-term live birth, premature live birth, pregnancy loss after 20 weeks (still birth) or a loss before 20 weeks (miscarriage).
- **Assessment of pregnancy complications was added as a secondary objective**. Pregnancy complications of most interest to the researchers include hypertensive disorders of pregnancy (preeclampsia, eclampsia, gestational hypertension, and chronic hypertension); chorioamnionitis (an intra-amniotic infection); endometritis (an infection involving the uterus); peripartum and postpartum hemorrhage (severe blood loss during or after labor); and preterm premature rupture of membranes (when the "water breaks" before week 37 of pregnancy).

Revised MTN-042 Study Objectives

Primary objectives:

- **Maternal and Infant Safety:** To describe the maternal and infant safety profile associated with use of the dapivirine ring and Truvada as PrEP during pregnancy
- **Pregnancy Outcomes**: To describe the pregnancy outcomes associated with use of the dapivirine ring and Truvada as PrEP during pregnancy

Secondary objectives:

- **Pregnancy Complications**: To describe pregnancy complications associated with use of the dapivirine ring and Truvada as PrEP during pregnancy
- **Infant Drug Levels**: To describe the extent that drug is passed to the infant after product exposure during pregnancy
- **Adherence**: To characterize how well women use the monthly dapivirine ring and daily PrEP during pregnancy and in an open-label study
- **Acceptability**: To characterize whether women find using PrEP and the ring acceptable during pregnancy

Exploratory objectives:

- **Genital Microenvironment**: To describe changes in the genital microenvironment (good and bad bacteria) associated with study product exposure during pregnancy

What is MTN's plan for collecting background rates?

To understand whether the outcomes and complications seen in MTN-042 could be due to women's use of PrEP or the dapivirine ring, researchers will use as a base for comparison estimated background rates derived through two types of approaches. The first involves a comprehensive review of studies containing relevant data from any of the four countries where MTN-042 will be conducted. Despite the inherent limitations with this approach, MTN researchers believe that in combination, the data will provide a frame of reference regarding the nature and frequency of pregnancy and infant outcomes observed in these countries. The analysis is already in progress and will be completed before MTN-042 begins.

The second approach aims to provide estimates of pregnancy outcomes and complications that occur within the general population of women living in the communities served by the MTN-042 study sites. In partnership with providers at local hospitals, research staff will follow a "data abstraction protocol" in which they will review patient charts over a three-month period and record the presence or absence of the specific primary and secondary outcomes that will be monitored in MTN-042. Pending ethic approvals, researchers would aim to complete the review prior to MTN-042's start.

Taken together, researchers believe the two approaches will paint a representative picture of background rates for specific outcomes and complications among pregnant women and infants in the regions where MTN-042 will be conducted, and thus, be a source for making informative comparisons with and helping to interpret the results of MTN-042.

What about other recommendations?

Harmonizing Study Definitions

It was recommended that the study harmonize definitions used in the protocol with those developed by GAIA (Global Alignment of Immunization safety Assessment in pregnancy). Likewise, it was recommended that the MTN-042 and IMPAACT 2009 studies be harmonized so that findings can be compared to and corroborate one another.

Because the IMPAACT 2009 and MTN-042 studies are both NIH-funded studies, the protocols are already aligned in terms of how adverse events are identified and graded. Moreover, the primary objectives of each study are nearly identical, with pregnancy outcomes and adverse events being measured as indications of safety. The leadership of both studies have already engaged in much information sharing and will continue to do so, and opportunities will be sought that could potentially involve the two study teams coming together. The MTN will also be encouraging its trial sites to reach out to and work collaboratively with their IMPAACT 2009 counterparts. This will be especially important in communities – and at trial sites – where both studies are taking places.

As for GAIA, the MTN fully supports this worthwhile endeavor and will do its best to harmonize with GAIA standards where feasible. At the trial sites, maternal and infant safety, as well as pregnancy outcome evaluations, will be based on GAIA criteria to the extent possible. However, several conditions of interest to the MTN-042 study, such as chorioamnionitis, have not yet been classified by GAIA. Moreover, there will be some adverse events or complications that will not be diagnosed by study staff but by clinicians at the hospitals where participants are delivering. Study staff will review and document what is in a participant's medical chart but will have little control over the level of detail in charts. Study teams will try to work closely with hospitals to ensure a common understanding about the study and the outcomes of interest but at the same time will need to respect and trust the providers' clinical judgement. For this reason, all adverse events identified by hospital staff, regardless of whether the diagnoses meet GAIA standards, will be captured.

Social Harms

Stakeholders wanted to be sure there was a means for identifying women experiencing social harms and ensuring provision of psychosocial support. The protocol already specifies that social harms (and benefits) are to be assessed during the study. Sites will be required to have plans for addressing social harms, including having referral organizations in place should a participant experience social harm. Site teams will also discuss potential scenarios, and mechanisms to address these, prior to beginning the study.

Topics for Qualitative Interviews

Stakeholders suggested that, among other things, the study team should explore women's motivations to join the study, intravaginal practices, and views about the comfort and convenience of the ring or PrEP, and whether views differ by cohort. Of note, many of these same topics are currently being explored in the MTN-041 study and will help inform how the MTN-042 will be conducted. Hence, the study team will be giving these and other stakeholders' suggestions their full consideration when developing the qualitative interview questions.

Linkages with Hospitals and other Providers

Stakeholders emphasized the importance of establishing relationships with key healthcare providers, and study teams certainly recognize the importance as well. Midwives and traditional birth attendants will also be important to the success of the study. It is anticipated that the results of the MTN-041 qualitative study will provide valuable information and insight about issues of importance to these key groups that will sites in their outreach.

Male Partners and Family Members

MTN-041 will also provide insight on ways that participants' partners, mothers and mothers-in-law should be engaged. The roles that these and other family members will play in the lives of participants – and the decisions women make – cannot be underestimated, and the study team will seek ways to both involve and educate these key groups.

Community Sensitization and Communications Plans

Trial sites will have community and stakeholder plans and for both sensitizing communities and facilitating ongoing engagement and communication throughout the study, especially between cohorts and around Interim Reviews. Communications plans will consider various scenarios, including adverse events that could be misattributed to PrEP or the vaginal ring. Scenarios planning will also consider possible developments external to the study – related to IMPAACT 2009 or regulatory decisions or opinions about the dapivirine ring, for example. Regarding stakeholders' recommendations about the composition of the Interim Review Panel, these have been shared with NIAID officials, who, as the study's sponsor, will be responsible for planning and convening the panel.

Autopsies

If a stillbirth, or the death of an infant or mother occurs during the study, grieving families, the community and the study itself would benefit from knowing more specifically what and why this happened. Stakeholders recommended, and the MTN agrees, that sites should facilitate arrangements for post-mortem autopsies so

that more information can be known about causality. As such, site investigators will be asked to identify outside providers whose services could be available on short notice should the need arise and family members have given their consent.

Provision of PrEP

Stakeholders recommended that PrEP be provided to participants after delivery, at least through the six-week follow-up period when they are no longer on study product. However, women will be counselled to avoid sexual intercourse for at least six weeks after giving birth – standard practice in most settings. Women will be exited from the study after six weeks (although their babies will remain in the study for one year), and site staff will emphasize the importance of protection during the postpartum period and see that referrals are made to PrEP and other prevention programs.

What happens now?

All protocols developed by the MTN must be reviewed and approved by the Prevention Sciences Review Committee (PSRC), which assesses and evaluates proposed clinical studies on behalf of the NIAID Division of AIDS (DAIDS) Prevention Sciences Program. The MTN-042 protocol was discussed at the 17 July 2018 meeting of the PSRC, and MTN was notified (via a Consensus Review Memo) on 3 August that the protocol was approved contingent on PSRC review and approval of MTN's responses to its comments and questions.

Some of the comments contained in the Consensus Review Memo sought clarification on the rationale for the study, given that PrEP is already recommended by WHO for pregnant women and PrEP will likely be increasingly more available during the course of the study. There was also concern about the ring not being effective in younger women (ages 18-24 years) in the ASPIRE and Ring Study Phase III trials.

In response, MTN researchers explained that these very same questions were discussed at length by stakeholders and that stakeholders were in fact quite supportive of the study. The study team reminded the PSRC that WHO guidelines are based primarily on studies involving the use of Truvada (or tenofovir) by HIV-infected women during pregnancy, and that with relatively little data about PrEP in HIV-negative pregnant women, some countries, such as South Africa, are waiting for more data before routinely offering PrEP to pregnant women. And while observational and retrospective studies can be informative, they will not be able to answer key questions about safety. MTN researchers explained that these were among the reasons for stakeholders supporting both MTN-042 and the IMPAACT 2009 study. Stakeholders were also hopeful about the ring, because even if PrEP were w widely available, PrEP will not be for everyone. As for the poor efficacy of the ring in younger trial participants, the MTN researchers argued that the same could also be said about younger women in the Phase III trials of oral PrEP. Given that MTN-042 is an open-label study, it is hoped that adherence will be higher, as was seen in open-label studies of PrEP. That being said, pregnant women are a very different population, and a study like MTN-042 would provide insight about women's willingness to use either the ring or PrEP during pregnancy, including whether age is a factor.

Once final PSRC approval is received, the protocol will undergo additional review within NIH and DAIDS, including by the DAIDS Regulatory Affairs Branch, Human Subjects Protection Branch and Safety and Pharmacovigilance Team. The MTN remains hopeful in having the protocol finalized – Version 1.0 – before the end of this year, and pending ethics and in-country approvals, launching the study mid-2019.

A Time to Deliver

MTN leadership and the entire MTN-042 study team are most appreciative of the feedback received from stakeholders during the consultative process. The meeting and the guidance it provided have enabled the team to move this important research agenda forward.

Many of the issues described in this report warrant additional discussion and the involvement of many more stakeholders in these discussions. Other questions and issues are likely to emerge and to vary in importance and relevance from community to community. As such, MTN and AVAC will be working with local and regional partners on planning follow-up stakeholder meetings in each trial site country.

In the meantime, the MTN-041 qualitative study will be completed in time for its results to help inform community and stakeholder engagement programs, participant recruitment and the informed consent process for MTN-042, and later, also for the MTN-043 study in breastfeeding women. Whereas the MTN-043 study was originally conceived to evaluate just the dapivirine ring, plans now are for the study to evaluate both the ring and PrEP, possibly beginning mid- 2019.

Finally, it should be noted that the MTN-042 study, while still officially called MTN-042, has a second name the team believes is especially fitting – DELIVER.

deliver

A Study of PrEP and the Dapivirine Ring in Pregnant Women

Appendices

Appendix I – Final Agenda

Appendix II – Meeting Participants

Appendix III – Additional Reading

Stakeholders Consultation on MTN-042

A Phase 3B, Randomized, Open Label Safety and Pharmacokinetic Trial of the Dapivirine Vaginal Ring and Oral PrEP in Pregnant Women

Thursday 5 April – Friday 6 April Protea Hotel Balalaika –Johannesburg

THURSDAY 5 April 2018	
Time / Session	Title
15:30-16:00h	**Meeting Registration and Tea**
16:00-16:30h	**Welcome and Introductions -** *Sharon Hillier, Manju Chatani-Gada*
Session 1 16:30-16:45h	**HIV Risk During Pregnancy -** *Renee Heffron* (15 mins)
Session 2 16:45-17:30h	**Overview of MTN-042 -** *Katie Bunge, Bonus Makanani, Lee Fairlie* (20 mins) **Questions and Discussion** (25 mins) – Sharon Hillier - *Moderator*
Session 3 17:30-19:00h	**Pregnant Women as Participants in Clinical Trials: Ethical Framework and Perspectives** **International Perspectives and Guidance** - *Paul Ndebele* (5 min) **Malawi** - *Joseph Mfutso-Bengo* (5in) **South Africa** - *Francesca Conradie* (5 min) **Uganda -** *Henry Mugerwa* (5 min) **Zimbabwe** - *Sithembile Ruzario* (5 min) **Panel and Group Discussion** (60 mins) – Manju Chatani-Gada - *Moderator*
Please note that there is a 30-minute break before dinner	
19:30--21:00h	**Dinner and Dialogue**

FRIDAY 6 April 2018	
07:45 – 08:30h	**Light Breakfast and Tea**
Session 1 08:30-08:45h	**Day One Recap -** *Sharon Hillier, Manju Chatani-Gada*
Session 2 08:45-10:00h	**Oral PrEP in Pregnant Women: What We Know and Don't Know** **Current data, current experience and differing guidelines –** *Renee Heffron* (15 mins) **What we will learn from the IMPAACT 2009 Study -** *Frank Taulo* (20 mins) **What are the implications for MTN-042? Facilitated Group Discussion-** *Lee Fairlie* (40 mins)
Session 3 10:00-11:15h	**The Dapivirine Vaginal Ring: A New HIV Prevention Method for Women** **Overview of the ring and the regulatory pathway -** *John Steytler* (15 mins) **What about the ring in pregnant women? Defining a research agenda one baby step at a time -***Rich Beigi* 15min) **What are the implications for MTN-042? Facilitated Group Discussion:** *Bonus Makanani* (45 mins)
11:15-11:30h	**Tea Break**
Session 4 11:30-12:40h	**Pregnancy in Context: Community Attitudes, Sociocultural Norms and Behavioral Practices** **What we hope to learn in the MTN-041 qualitative study -** *Petina Musara* (10 mins) **Panel Discussion: Perspectives and perceptions about research and pregnancy** (30 mins) *Audrey Tasaranarwo* – Zimbabwe *Lillian Mworeko* – Uganda *Maureen Luba* – Malawi *Thoko Budaza* – South Africa **What are the implications for MTN-042? Facilitated Group Discussion** - *Manju Chatani-Gada* (30 mins)
Session 5 12:40-12:45h	**Food for Thought: Questions to think about -** *Katie Bunge*
12:45h-13:30h	**Lunch**
Session 6 13:30-15:30h	**What do you think? Key Questions about MTN-042 -** *Katie Bunge, Bonus Makanani, Lee Fairlie*
Session 7 15:30-16:00h	**Summary and Next Steps -** *Sharon Hillier, Manju Chatani-Gada*

Stakeholders Consultation on MTN-042

A Phase 3B, Randomized, Open Label Safety and Pharmacokinetic Trial of the Dapivirine Vaginal Ring and Oral PrEP in Pregnant Women

Thursday 5 April – Friday 6 April Protea Hotel Balalaika –Johannesburg, South Africa

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Appendix III -- Additional Reading

Additional information from the consultation, including slide presentations, is available at https://www.avac.org/stakeholders-consultation-mtn042. Information about MTN-042 and related studies is available at https://mtnstopshiv.org/.

HIV Risk in Women and Pregnancy

UNAIDS. Fact sheet - Latest statistics on the status of the AIDS epidemic. 2017
http://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf

Thomson KA, Hughes J, Baeten JM, John-Stewart G, Celum C, Cohen CR, et al. **Increased Risk of HIV Acquisition Among Women Throughout Pregnancy and During the Postpartum Period: A Prospective Per-Coital-Act Analysis Among Women With HIV-Infected Partners**. The Journal of Infectious Diseases. 2018; **218**(1): 16-25.
https://academic.oup.com/jid/article/218/1/16/4915924

Joseph Davey D, Farley E, Towriss C, et al. **Risk perception and sex behaviour in pregnancy and breastfeeding in high HIV prevalence settings: Programmatic implications for PrEP delivery.** Yotebieng M, ed. *PLoS ONE*. 2018;13(5):e0197143.
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0197143

Research Ethics, Guidelines and Regulations

Research Design, Challenges and Opportunities

Proceedings from the Global Forum on Bioethics in Research (GFBR)'s "Ethics of Research in Pregnancy" meeting.
Reproductive Health Volume 14 Supplement 3, 2017:
https://reproductive-health-journal.biomedcentral.com/articles/supplements/volume-14-supplement-3

CB Krubiner, et al**. Advancing HIV Research with Pregnant Women: Navigating Challenges and Opportunities.** .AIDS. 30(15):2261–2265, SEP 2016: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5014683/

Richard H. Beigi, Lisa Noguchi, Gina Brown, Jeanna Piper, D. Heather Watts. **Performing Drug Safety Research During Pregnancy and Lactation: Biomedical HIV Prevention Research as a Template.** J Womens Health (Larchmt) 2016 Jul 1; 25(7): 761–766.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4939378/

PHASES (Pregnancy and HIV/AIDS: Seeling Equitable Study) http://www.hivpregnancyethics.org/

Guidelines and Regulations

Council for International Organizations of Medical Sciences. International Ethical Guidelines for Health-related Research Involving Humans. CIOMS 2016
https://cioms.ch/shop/product/international-ethical-guidelines-for-health-related-research-involving-humans/

UNAIDS. Ethical considerations in biomedical HIV prevention trials. 2012
http://files.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2012/jc1399_ethical_considerations_en.pdf

U.S. Department of Health and Human Services. Protection of Human Subjects: TITLE 45 CODE OF FEDERAL REGULATIONS Part 46 2009 (includes Subpart B - Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research)
https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html

Food and Drug Administration draft guidance for industry ``**Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials**.'' Federal Register Volume 83, Issue 68 (April 9, 2018)
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM603873.pdf

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Belmont Report 1979 https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/read-the-belmont-report/index.html

World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. 2013.
https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

Harmonization of Definitions

Jan Bonhoeffer, Sonali Kochhar, et al. **Global alignment of immunization safety assessment in pregnancy – The GAIA project**
Vaccine. Volume 34, Issue 49, 1 December 2016, Pages 5993-5997.
https://www.sciencedirect.com/science/article/pii/S0264410X16305692?via%3Dihub

Sonali Kochhar, Jan Bonhoeffer, Christine E. Jones, Flor M. Muñoz, et al **Immunization in pregnancy clinical research in low- and middle-income countries – Study design, regulatory and safety considerations**, Vaccine, Volume 35, Issue 48, Part A, 2017, Pages 6575-6581 https://www.sciencedirect.com/science/article/pii/S0264410X17305042?via%3Dihub

Harmonising Immunisation Safety Assessment in Pregnancy. Vaccine. Volume 34, Issue 49, Pages 5991-6110 (1 December 2016) https://www.sciencedirect.com/journal/vaccine/vol/34/issue/49

Harmonising Immunisation Safety Assessment in Pregnancy – Part II. Vaccine. Volume 35, Issue 48, Part A, Pages 6469-6582 (4 December 2017) – https://www.sciencedirect.com/journal/vaccine/vol/35/issue/48/part/PA

PrEP Guidelines and Drug Information

WHO Technical Brief: Preventing HIV during pregnancy and breastfeeding in the context of PREP. July 2017 http://apps.who.int/iris/bitstream/handle/10665/255866/WHO-HIV-2017.09-eng.pdf?sequence=1

World Health Organization Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – 2nd ed. 2016 http://apps.who.int/iris/bitstream/handle/10665/208825/9789241549684_eng.pdf;jsessionid=9FBA18A9631D88CDA5A7152741A5DAC2?sequence=1

Bekker L-G, Rebe K, Venter F. et al. **Southern African guidelines on the safe use of pre-exposure prophylaxis in persons at risk of acquiring HIV-1 infection**. S Afr J HIV Med. 2016;17(1), Art. #455 http://sahivsoc.org/Files/Guidelines%20on%20the%20safe%20use%20of%20PrEP%20(March%202016).pdf

Truvada (emtricitabine / tenofovir disoproxil) – FDA Package Insert https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021752s047lbl.pdf

South African Electronic Package Inserts – Truvada http://home.intekom.com/pharm/aspen-p/truvada.html

The Antiretroviral Pregnancy Registry http://www.apregistry.com/

Matthews LT, Beyeza-Kashesya J, Cooke I, et al. **Consensus statement: Supporting Safer Conception and Pregnancy For Men And Women Living with and Affected by HIV**. *AIDS and Behavior*. 2018;22(6):1713-1724. https://link.springer.com/article/10.1007%2Fs10461-017-1777-7

Studies Involving Pregnant and/or Breastfeeding Women

Marisha N. Wickremsinhe, Margaret O. Little, Alice S. Carter, Kristen A. Sullivan, and Anne D. Lyerly**. Beyond "Vessels and Vectors": A Global Review of Registered HIV-Related Clinical Trials with Pregnant Women.** Journal of Women's Health. http://doi.org/10.1089/jwh.2017.6857 Online Ahead of Print:August 20, 2018

Oral PrEP Studies

IMPAACT 2009 Study: Feasibility, Acceptability and Safety of Oral Pre-Exposure Prophylaxis for Primary HIV Prevention During Pregnancy and Breast Feeding in Adolescents and Young Women. https://impaactnetwork.org/studies/IMPAACT2009.asp#documents

Mofenson LM, Baggaley RC, Mameletzis I. **Tenofovir disoproxil fumarate safety for women and their infants during pregnancy and breastfeeding.** AIDS. 2017; **31**(2): 213-32. https://www.ncbi.nlm.nih.gov/pubmed/27831952

Fowler MG, Qin M, Fiscus SA, Currier JS, Flynn PM, Chipato T, et al. **Benefits and risks of antiretroviral therapy for perinatal HIV prevention**. New England Journal of Medicine. 2016; **375**(18): 1726-37. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5995113/

Siemieniuk RAC, Lytvyn L, Mah Ming J, et al. **Antiretroviral therapy in pregnant women living with HIV: a clinical practice guideline**. *The BMJ*. 2017;358:j3961. https://www.bmj.com/content/358/bmj.j3961

British HIV Association (BHIVA) response to BMJ article "Antiretroviral therapy in pregnant women living with HIV: a clinical practice guideline"1 published 11 September 2017. http://bhiva.org/BHIVA-response-to-BMJ-article.aspx

Comment from PROMISE Team Re: Antiretroviral therapy in pregnant women living with HIV: a clinical practice guideline, 28 September 2017 https://www.bmj.com/content/358/bmj.j3961/rr

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Microbicides (tenofovir gel and dapivirine ring)

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About AVAC

AVAC, founded in 1995, is a nonprofit organization that uses education, policy analysis, advocacy and a network of global partners to accelerate the ethical development and global delivery of new and proven HIV prevention options as part of a comprehensive response to the pandemic. AVAC has built strong institutional and programmatic links with over 50 organizations working in biomedical prevention research and communications, education and advocacy in the U.S. and internationally, and has pioneered efforts with community-based and grassroots organizations to build understanding of and support for evidence-based prevention research. AVAC has been the leading civil society organization engaged in comprehensive ARV-based prevention advocacy, including active leadership in collaborating, translating and engaging with microbicide and PrEP researchers, funders and policy makers. For more information, please visit www.avac.org.

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 www.mtnstopshiv.org.

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Stakeholders Consultation on MTN-042