Meeting Report

Stakeholders consultation on the MTN-034/IPM 045 (REACH) open-label safety and adherence study of the dapivirine vaginal ring and oral PrEP

29-30 September 2016 – Johannesburg

Meeting the HIV Prevention Needs of Adolescent Girls and Young Women

MTN microbicide trials network

AVAC Global Advocacy for HIV Prevention

Impact Research & Development Organization

Soul City Institute for Social Justice

Pangaea

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To learn more about the REACH study, as well as other studies of the dapivirine ring and oral PrEP conducted by the Microbicide Trials Network, please go to www.mtnstopshiv.org

MTN microbicide trials network

December 2016

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Due to the sensitive and personal nature of some of the subject matter discussed at this consultation, this version of the Meeting Report does not identify young women by name, although affiliations and other identifying information may be provided where appropriate and relevant, and both the List of Meeting Participants and Meeting Agenda have been excluded.

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Acknowledgments

We would like to give special thanks to the presenters, panelists and meeting participants, who collectively contributed to the success of this consultation. In particular, our sincerest thanks to the stellar group of young women who held their own in a meeting with some of HIV prevention's most influential researchers, policy makers and advocates. These brave young women were open, candid, thoughtful and passionate. Above all, they were an inspiration to all of us.

The consultation was planned by Lisa Rossi of the Microbicide Trials Network and Manju Chatani-Gada of AVAC, both based in the U.S., together with Kawango Agot from Impact Research & Development Organization in Kenya; Lebogang Ramfoko and Ntombozuko Kraai from South Africa's Soul City Institute for Social Justice; and Definate Nhamo, Imelda Mahaka and Megan Dunbar representing Pangaea Zimbabwe AIDS Trust. Special thanks to Kawango, Definate and Ntombozuko for identifying and mentoring the young women who attended the consultation, and with Manju, for leading a fruitful and positively charged three-hour preparatory meeting prior to the consultation. Lest we forget, we also want to thank Godfrey Okumu, a 2016 AVAC fellow working with Impact RDO, who helped secure first-time passports and visas for the young delegation who traveled from Kenya.

MTN received funding to convene this meeting, including for travel and lodging of meeting participants. AVAC provided additional travel and hospitality support for the participants. We would like to thank both organizations, and their funders, for their generous support. We would also like to thank and acknowledge Chris Rullo (MTN) for coordinating hotel and flights as well as arrangements for the meeting, and Stevens Masebe, who helped manage logistics on-site. Working behind the scenes at AVAC were Alysha White, Heeyoung Sohn and Jessica Saldzwedel.

This report was prepared by Lisa Rossi based largely on the comprehensive notes provided by Maria Djordjevic and Jo-Anne Collinge (Meropa Communications, Johannesburg) and drafts written by Jo-Anne containing key content.

Executive Summary

It might seem that HIV prevention efforts are turning a corner. Daily use of Truvada® as oral pre-exposure prophylaxis, or PrEP, is making its way into a number of African countries. Within three years, a monthly vaginal ring could also be available in some settings. At the same time, there is growing concern about the fate of girls and young women, a population in sub-Saharan Africa that continues to be among those at greatest risk of acquiring HIV. For all the enthusiasm about oral PrEP and the dapivirine ring, there is still much to learn about the safety of and adherence to these approaches in teen girls and young women.

As a group, younger women did not fare well in the VOICE and FEM-PrEP Phase III trials of oral PrEP nor in the ASPIRE and The Ring Study trials of the dapivirine ring. The efficacy of both approaches is highly dependent on regular and consistent use, and adherence to product use was low for the young women in these trials. There is cause for optimism, however. In the context of open-label demonstration projects, PrEP has been found to be highly effective in all populations, including in younger women, who were able to adhere well to the daily regimen. And recent post-hoc analyses of ASPIRE data show that even for young women, the ring can be highly protective when used consistently.

It is important to understand the challenges that the majority of young women face in using these products, especially in more "real-life" settings, so that strategies to help overcome them can be identified. And without a solid base of evidence about the safety of both PrEP and the dapivirine vaginal ring in younger women, and in particular in girls under age 18, there will be reluctance on the part of national programs and regulators to make these approaches available to this vulnerable population.

MTN-034/IPM 045, or REACH, is a study being developed by the U.S. National Institutes of Health-funded Microbicide Trials Network (MTN) that aims to fill important gaps in understanding about oral PrEP and the vaginal ring in adolescent girls and young women. In REACH, all participants would use the monthly ring and daily oral PrEP, each for six months (there will be no placebo ring or placebo tablet), and then choose the method they would like to use for an additional six months. In this way, the study will be able to evaluate the safety of both oral PrEP and the dapivirine ring and how girls and young women use these products, as well as learn which of these approaches they prefer – and why. Pending all approvals, the REACH study would begin mid-2017, enrolling 300 16-21 year-old young women at sites in Kenya, South Africa and Zimbabwe.

As part of the protocol development process, the MTN held a consultative meeting in Johannesburg, South Africa on 29 and 30 September 2016, to seek input from stakeholders from each of the trial site countries about the study and issues related to the study's approval and implementation. MTN co-hosted the meeting with AVAC in close partnership with Impact Research and Development Organization in Kenya, Soul City Institute for Social Justice in South Africa and Pangaea Zimbabwe AIDS Trust.

The more than 40 stakeholders who attended included civil society and advocates focused on HIV prevention, women's reproductive health and girls empowerment; ethicists and Institutional Review Board/Ethics Committee chairs; national HIV program officers; and importantly, some 15 young women between the ages of 16 and 25, among them, former ASPIRE participants, current and former PrEP demonstration project participants, members of youth community advisory boards and youth ambassadors for HIV programs.

Stakeholders expressed overall support of the study, acknowledging especially the importance of choice when neither the ring nor oral PrEP (or other methods) could be expected to right for or appeal to everyone. Young women in particular viewed choice as empowering while also recognizing the complex personal and social barriers they face. They saw the REACH study as an opportunity to explore – and perhaps overcome – many of these.

Young women believed that providing participants individual adherence feedback would be very helpful and they liked the idea of an "adherence support menu." With the ring, they thought women will need more support initially, until they were confident in inserting and removing it and using it during sex and their periods. Whereas, with PrEP, adherence support might need to be sustained given the difficulty young people may have in following daily regimens and the spontaneity of their daily lives. The size of the pills, side effects and the stigma associated with use of antiretroviral (ARV) medications were significant drawbacks. They argued that sites should employ counselors who won't be judgmental and a younger staff, who they would be more inclined to open up to. Young women also spoke emphatically about the need to introduce elements of youth culture into the conduct of the study, both at the trial site and by tapping into social media and youth influencers.

They understood that being part of a trial was a service to society. They stressed the need for REACH

to enroll motivated participants who would be committed to the trial. They also acknowledged how male partners could influence whether or not they would use the ring or PrEP. Some believed involving male partners in the study would be important, while others felt it was about time that young women felt empowered to place their own health above the preferences of their partners.

Similarly, there was much discussion about the role that parents should or should not play as meeting participants grappled with ethical and regulatory questions.

For girls under age 18, parental consent and the assent (agreement) of the minor is required. This will be challenging, given widely held cultural beliefs disdaining sexual activity in young women, making it all the more difficult for youth to broach the subject with parents. Because there was obvious benefit to taking part in the study, stakeholders strongly supported having the research team seek a waiver for parental consent. Recognizing also the consequences should parents discover the ARV tablets or vaginal ring or hear about their participation in the study, it was also recommended the study look for ways for parents or other trusted adults to be involved. Combined with community sensitization, this could help mitigate potential misunderstandings about the study and the risk of young women being stigmatized, chastised or harmed.

Communications and community engagement activities should serve to create a social environment conducive to and supportive of the conduct of the study. Communications should be strategically directed at groups whose support was critical – parents generally, conservative religious organizations, and peer groups, with media being an important ally. In addition, it was recommended that trial sites partner with organizations that could offer young women comprehensive social support, and help address social and structural factors that could undermine their ability to use HIV prevention products successfully.

Acronyms and Abbreviations

ARS	Automated Response System
ART	antiretroviral treatment
ARV	antiretroviral medicine
ASPIRE	A Study to Prevent Infection with a Ring for Extended use
CAB	community advisory board
DREAM	Dapivirine Ring Extended Access and Monitoring (open-label extension study for former Ring Study participants)
DREAMS	Determined, Resilient, Empowered, AIDS-free, Mentored, and Safe women (PEPFAR initiative)
DTHF	Desmond Tutu HIV Foundation
EC	Ethics Committee
EMA	European Medicines Authority
FDA	US Food and Drug Administration
HAVEG	HIV AIDS Vaccines Ethics Group
HOPE	HIV Open-label Prevention Extension (open-label extension study for former ASPIRE participants)
Impact-RDO	Impact Research and Development Organization
IPCP	Introducing PrEP Into HIV Combination Prevention -Kenya demonstration project
IPM	International Partnership for Microbicides
IRB	Institutional Review Board
KEMRI	Kenya Medical Research Institute
MCC	Medicines Control Council of South Africa
MRC	Medical Research Council (of South Africa)
MRCZ	Medical Research Council in Zimbabwe
MTN	Microbicide Trials Network
NGO	nongovernmental organization
NIGEE	Nyanza Initiative for Girls Education and Empowerment
OLE	open-label extension
PEPFAR	U.S. President's Emergency Plan for AIDS Relief
PrEP	pre-exposure prophylaxis
REACH	Reversing the Epidemic in Africa with Choices in HIV prevention (also known as MTN-034/IPM 045)
SayWhat	Students And Youths Working on Reproductive Health Action Team
SMS	short message service, or, more commonly, instant messaging
STI	sexually transmitted infection
UZ-UCSF	University of Zimbabwe-University of California San Francisco
VOICE	Vaginal and Oral Interventions to Control the Epidemic (study)
WHO	World Health Organization
Wits RHI	Wits Reproductive Health and HIV Institute



“At school I told my friends that I am coming to South Africa to talk about some medicine that can prevent HIV. The boys asked me if they can have some, and I told them that if there is a ring for boys I will ask …!”

– A 17-year-old meeting participant from Kenya, whose trip to South Africa was her first time being outside her country, as was also the case for several other meeting participants.

Information and Background

The Need

Adolescent girls and young women are among those at highest risk of HIV in sub-Saharan Africa. Oral pre-exposure prophylaxis (PrEP) and the dapivirine ring, should it eventually receive regulatory approval, could help curtail the rate of new infections, yet neither can be effective if not used with sufficient adherence. Studies have shown adherence to be particularly challenging for younger women.

- In VOICE, neither daily oral PrEP (Truvada) nor a vaginal gel (tenofovir) was effective in preventing HIV, with women younger than 25 least likely to use their assigned products and most likely to have acquired HIV.

- In ASPIRE and The Ring Study, the dapivirine ring was shown to reduce the risk of HIV by about 30 percent across both studies. Among women 22 and older, HIV risk was reduced by 56 percent; the ring was not effective in women aged 18-21, who also used the ring least consistently.

As these were Phase III double-blind placebo-controlled trials, participants did not know whether they were using a placebo or the active product, or if the study product was safe or effective. Open-label studies of the dapivirine ring – HOPE for former ASPIRE participants and DREAM for former participants of The Ring Study – are currently ongoing. Researchers are hopeful that in knowing the results of both ASPIRE and The Ring Study, women will feel more at ease about the ring and motivated to use it as consistently as possible. This has been seen in open-label studies of PrEP, with adherence – and efficacy – proving better than in the original Phase III trials.

In 2016, the World Health Organization (WHO) recommended oral PrEP for all persons at substantial HIV risk, and a number of countries, including South Africa and Kenya, have approved Truvada as PrEP for adults 18 years of age and older, and are making plans for its introduction in different populations. (For those with the ability to pay, PrEP is available in the private sector.) South Africa has begun implementing PrEP rollout to female sex workers, with men who have sex with men the next targeted population. Adolescent girls and young women are expected to follow, but several questions remain about delivery channels for reaching those who would benefit most. In the meantime, access to PrEP will be available to this population in South Africa, Kenya and Zimbabwe (as well as in other countries) through ongoing or planned demonstration projects, including the U.S. President's Emergency Plan for AIDS Relief (PEPFAR)-funded DREAMS initiative. The South Africa Department of Health has also launched a three-year national Girls and Young Women Campaign (She Conquers) aiming to decrease new HIV infections, teenage pregnancies and gender-based violence among young women and adolescent girls.

Reducing HIV incidence in this vulnerable population is clearly a global priority. For its part, the Microbicide Trials Network (MTN) is planning a study that would help answer key questions about the safety in and use of oral PrEP and the dapivirine ring by adolescent girls and young women.

MTN-034/IPM 045 – The REACH Study

MTN-034/IPM 045, or REACH (Reversing the Epidemic in Africa with Choices in HIV prevention), is a Phase IIa study in the late stages of development that will evaluate how adolescent girls and young women use the monthly dapivirine vaginal ring and Truvada as daily PrEP, and their preferences for either or both approaches. The study will also collect much needed information on the safety of these approaches in young women and assess whether biological or physiological factors affect how the active drug in each of these products is taken up in the body or may contribute to HIV susceptibility. This is especially important for the dapivirine ring. Based on the results of The Ring Study and ASPIRE, as well as several smaller studies, the International Partnership for Microbicides (IPM), which developed the dapivirine ring, plans to seek regulatory approval for its use by women ages 18-45 years. However, specific data on the ring's safety and use among women younger than 18 will be required for the ring to be approved for and made available to this population.

The MTN has already completed a study called MTN-023 evaluating the safety and drug absorption qualities of the dapivirine ring in 96 adolescent girls in the United States. The REACH study would contribute important data about the ring in African girls.

Seeking input from stakeholders

As part of the protocol development process, the MTN sought input from key stakeholders through a consultation held in Rosebank, Johannesburg on 29 and 30 September 2016. Looking beyond the design of the study, MTN also sought to engage participants on issues that may affect the study's approval and implementation, including the ethical and regulatory framework for conducting research among adolescents.

MTN and AVAC co-hosted the meeting in close partnership with Pangaea Zimbabwe AIDS Trust, Impact Research and Development Organization (Impact-RDO) in Kenya, and South Africa's Soul City Institute for Social Justice.

In-country partners were largely responsible for identifying the invitation list based on agreed upon criteria. The meeting was attended by 43 stakeholders, and included 15 young women ranging in age from 16 to 25, as well as civil society and advocates focused on HIV prevention (PrEP and/or ring), women's reproductive health and girls empowerment; ethicists, Institutional Review Board/Ethics Committee chairs; national HIV program officers; and NGO representatives with experience working with adolescents. Included among the 15 young women who attended were two former ASPIRE participants, two former participants in the PlusPills PrEP study and a young woman from Kisumu, Kenya, who is taking part in the IPCP (Introducing PrEP Into HIV Combination Prevention)-Kenya demonstration project at LVCT Health. For many of those coming from Kenya and Zimbabwe, it was their first experience being out of the country and the first time they had traveled by airplane.

MTN researchers attending were Sharon Hillier, MTN principal investigator (University of Pittsburgh); REACH Protocol Chair Gonasagrie (Lulu) Nair of the Desmond Tutu HIV Foundation (DTHF) in Cape Town; and REACH protocol co-chairs, Kenneth Ngure (Jomo Kenyatta University of Agriculture and Technology, Nairobi) and Connie Celum (University of Washington). Felix Mhualanga, Investigator of Record for REACH at the Spilhaus Clinical Research Site, University of Zimbabwe-University of California San Francisco (UZ-UCSF), and Mumbi Makanga, Investigator of Record for REACH at the Kenya Medical Research Institute (KEMRI), KEMRI/CDC Kisumu Clinical Research Site, also attended.

Objectives of the consultation

- To provide an overview of the evidence available for the dapivirine vaginal ring and oral PrEP in women and the need for additional data on use, adherence, safety and acceptability of both oral PrEP and the vaginal ring among adolescent girls and young women.
- To solicit stakeholders' views of MTN-034/IPM 045 – the REACH study – generally, and feedback on specific aspects of the study's design and implementation.
- To consider how REACH fits into sub-Saharan Africa's broader HIV prevention landscape and socio-cultural contexts, identify where potential communication challenges and/or synergies may exist, and where coordination and information sharing may be especially important in each trial site country.
- To identify key concerns and challenges, including legal and ethical, for engaging adolescents in HIV prevention research generally and REACH in particular, and possible ways of overcoming these.
- To establish new ties and strengthen existing relationships between researchers and key in-country stakeholders concerned with HIV prevention in adolescent girls and young women and create a framework for continued engagement on issues of particular relevance in each country.

Agenda Overview

The meeting began Thursday evening 29 September. MTN Principal Investigator Sharon Hillier and Manju Chatani-Gada, Senior Program Manager at AVAC, welcomed everyone. Each attendee then introduced themselves adding also something personal about themselves. This set the tone for the entire meeting, creating a space in which participants felt comfortable being open and expressing their thoughts and views.

The presentations that followed intended to set the stage for Friday's full-day agenda. Dr. Hillier provided an overview of the results of the ASPIRE and Ring Study Phase III trials of the dapivirine vaginal ring. Leonard Solai, Senior Director of External Affairs and Community Engagement at IPM, then explained IPM's plans and timelines for seeking licensure of the dapivirine ring. Dr. Connie Celum, protocol co-chair of the REACH study (MTN-034/IPM 045), provided an overview of oral PrEP in women and an update on regulatory approvals of Truvada as PrEP and on PrEP demonstration projects.

As much as possible, the agenda was structured to provide young women the opportunity to speak. One such opportunity, "Voices that Matter," was scheduled for Thursday evening's program, and took place Friday morning instead, with a DREAMS program champion from Kenya and youth community advisory board (CAB) member from the Desmond Tutu HIV Foundation in Cape Town, each explaining why attending this meeting was important to them. This was followed by a broad-ranging discussion and question and answer session about the dapivirine ring and oral PrEP, as well as a panel discussion, "Making it Real: Women's Reactions and Responses," moderated by Definate Nhamo, Senior Program Manager, Pangaea Zimbabwe AIDS Trust. Panelists included a former ASPIRE participant who was 21 when she enrolled; an advocate at SHAZ! HUB and member of the UZ-UCSF youth CAB in Zimbabwe; and an advocate working on girl empowerment for Young County Changemakers in Kenya.

Dr. Lulu Nair, REACH study protocol chair, led the presentation describing the study, and she and Drs. Hillier, Celum and Kenneth Ngure (protocol co-chair) addressed numerous questions, with Kawango Agot, Director of Impact-RDO, moderating.

What followed were three brief presentations outlining the legal and ethical framework for conducting trials involving adolescent girls and young women in each trial site country, given by Ambrose Rachier, chairman of the Ethical Review Committee at the KEMRI (Kenya); Paul Ndebele, Director of the Medical Research Council of Zimbabwe; and Cathy Slack, Project Manager of the HIV AIDS Vaccines Ethics Group at the University of KwaZulu-Natal. Imelda Mahaka, Country Director of Pangaea in Zimbabwe, moderated. As part of this session, MTN researchers presented different hypothetical scenarios on issues related to parental waivers, parental involvement and informed consent. Meeting participants registered their feedback in real-time using handheld remote devices.

Much of the discussion continued into the next session, "MTN in Context: What do young women think," which was moderated by Megan Dunbar, Vice President, Research and Programs, Pangaea Global AIDS. The panel included a 16-year-old who is secretary of a Rise Young Women's Club affiliated with the Soul City Institute for Social Justice (South Africa); a University of Zimbabwe student who co-chairs SayWhat Club; a 22-yer-old Girls' Steering Committee Member and Peer Educator with Nyanza Initiative for Girls Education and Empowerment (NIGEE) in Kenya; 21-year-old twins who had both participated in the Pluspills Study; a former ASPIRE study participant, now age 21; and a 20-year-old participant in the IPCP-KENYA PrEP demonstration study. Many others also contributed to the discussion, which focused primarily on questions about adherence, product use and adherence monitoring and support.

Due to time constraints, "Complicated Issues and Sensitive Topics: What are your views?" was not included. Topics that were to be covered (sexual activity as a requirement for enrollment, social harms risk and reimbursement for study participation) had been addressed previously.

Mitchell Warren, AVAC Executive Director, began the next session, "MTN-034 in Context: PrEP access and in-country considerations within a rapidly evolving landscape," with a brief overview of current, ongoing and planned clinical trials in each trial site country. Saiqa Mullick, Director, Implementation Science, Wits Reproductive Health and HIV Institute (Wits RHI), outlined activities related to PrEP access.

In the time remaining, unanswered questions were addressed, and Drs. Hillier and Nair discussed study timelines and next steps. The meeting ended with one of the young meeting participants performing a dance number, and others joining in.

Please see the appendix for the full agenda.

Special Preparatory Meeting

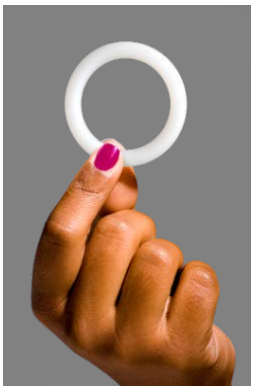
Prior to the consultation, a special preparatory meeting was organized for the young women who would be attending to help them achieve greater understanding of the clinical research process and specific topic areas on the agenda and better anticipate what to expect of the consultation experience. The three-hour meeting was facilitated by Manju Chatani-Gada (AVAC), Definate Nhamo (Pangaea Zimbabwe AIDS Trust), Kawango Agot (Impact-RDO) and Ntombozuko Kraai (Soul City Institute for Social Justice).

A series of informal and interactive exercises were used to introduce and/or enhance understanding of key terms and basic concepts that were expected to figure in discussions during the consultation; outline expectations for the consultation; clarify any questions from reading materials; and, most importantly, to make them feel comfortable and confident in this setting. The young women were enthusiastic to learn and engage, and they asked many pointed questions about the research process. Several participants commented that this pre-meeting made them feel much less nervous and more comfortable in "this new sisterhood" and they were delighted to create alliances with 'safe' people before entering the consultation.

Setting the Stage: About PrEP and the Dapivirine Ring

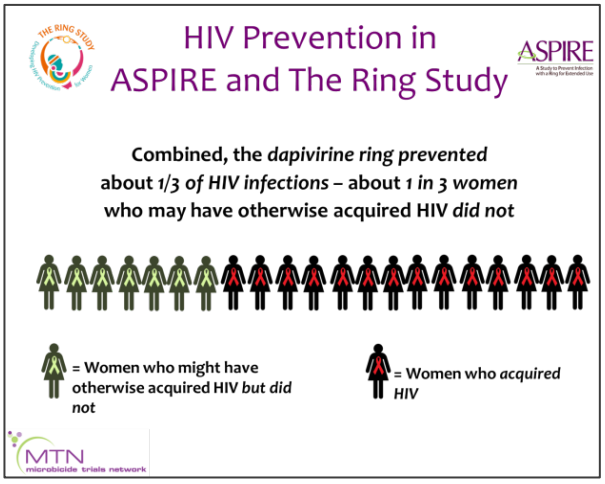
Overview and status of the dapivirine ring

The dapivirine vaginal ring is the first HIV prevention product developed specifically for women that was found to be safe and to help protect against HIV in two independently conducted large-scale trials. ASPIRE, also known as MTN-020, was conducted by the MTN. The Ring Study was conducted by IPM, a non-profit organization based in South Africa and the United States, which also developed the dapivirine ring.



Vaginal rings are flexible products that fit high up inside the vagina where they release a medication slowly over time. The ring tested in these two trials contains an antiretroviral (ARV) drug called dapivirine. The ring is used for a month at a time, and women can insert and remove the ring themselves.

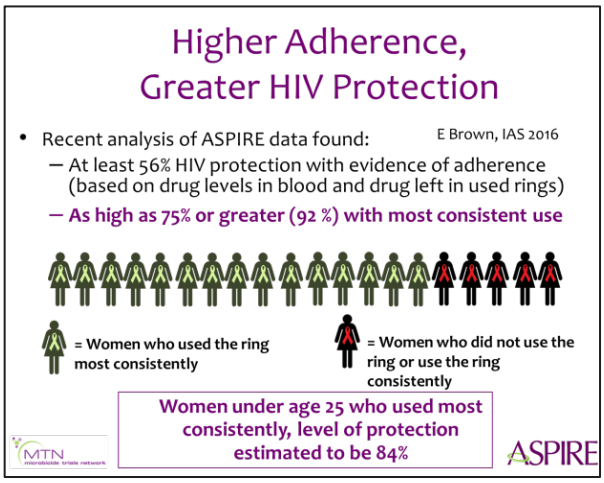
Across both studies, which collectively involved 4,588 women ages 18-45 in four African countries, HIV risk was reduced by about one-third, meaning that one in three women who might have acquired HIV did not. The primary results of both studies were reported in February 2016.



ASPIRE found HIV risk was cut by more than half (56 percent) in women older than 21; for women ages 18-21, who as a group appeared to use the ring least consistently, the ring was not effective. Similar results were seen in The Ring Study.

Dr. Sharon Hillier explained that results of additional analyses reported at the International Conference on AIDS (AIDS 2016) showed higher levels of protection were associated with regular and consistent use of the ring. Researchers determined adherence by measuring drug levels in blood and the amount of drug leftover in used rings. These analyses found that when the ring was used regularly, HIV incidence was reduced by 56-65 percent, and by as much as 75-92 percent with near perfect use. Age was not necessarily a factor. In fact, researchers found that for women under age 25 who used the ring most consistently, HIV risk was reduced by about 84 percent.

What all these results tell us, Dr. Hillier said, is that, "*If you **do** use the dapivirine ring it can work very well – even if you are a young woman*."



Both ASPIRE and The Ring Study found the ring was very safe, with minimal side effects. That may be because the ring releases a relatively small amount of drug into the vagina, of which an even smaller amount gets into the rest of the body.

The ring releases enough drug to offer protection within six to eight hours after insertion. But once the ring is removed, drug will dissipate quickly, with virtually none remaining after 24 hours. Though reassuring from a safety point of view, this is why the ring must be worn continuously for a month at a time. In contrast, women must take PrEP daily for about a week to reach protective levels of drug. Drug also stays around in the body longer. Compared to PrEP, "*The ring is faster on and faster off,*" Dr. Hillier said.

Women who took part in ASPIRE and The Ring Study are now being given the opportunity to use the dapivirine ring in the context of open-label extension (OLE) studies – HOPE for former ASPIRE participants and DREAM for former participants of The Ring Study. Dr. Hillier said she was hopeful that women will feel more at ease about the ring than they may have been during the Phase III trials, and will be more motivated to use it as consistently as possible now that they

know it is safe and can help prevent HIV. In other OLEs that followed Phase III trials of oral PrEP, adherence to product use increased, and as a result, those studies were able to demonstrate the approach was more effective than the original trials had found.

In addition to looking more closely at the relationship between ring use and HIV protection, both the HOPE and DREAM studies will be able to contribute additional data on the safety of the ring. Moreover, acknowledging that the ring may not be for everyone, HOPE also looks to better understand why it may work well as a prevention strategy for some women but not others. As such, women may enroll in HOPE even if they do not wish to use the ring.

Dr. Hillier made note of the fact that HOPE and DREAM will not be able to yield information about ring use and safety in young women because those who took part in ASPIRE and The Ring Study are now older – the youngest participants would now be 21. This is why the REACH study will be including young women ages 18-21, as well as 16-17 year-olds.

The dapivirine ring is not designed to prevent STIs, nor does it protect against pregnancy. However, a ring has been developed that is in early phase clinical testing that contains both dapivirine and a contraceptive, potentially offering women the means for dual protection. A 90-day ring is also being evaluated.

Regulatory pathways and timelines for the dapivirine ring

IPM, a nonprofit organization, holds an exclusive worldwide license for dapivirine from Janssen Sciences Ireland UC, one of the Janssen Pharmaceutical Companies of Johnson & Johnson (Janssen), that is designed to ensure women in low-resource settings have affordable access to any dapivirine-based microbicide.

IPM's Leonard Solai described the process for seeking approval of the dapivirine ring, including how a comprehensive dossier about the ring is being compiled. The dossier contains data from ASPIRE and The Ring Study and several smaller supporting studies conducted in the U.S. and Europe, as well as results of laboratory and animal studies. In total, there are 13 years of data from nearly 250 studies that will be included. Considering that the average length of a dossier is 500,000 pages, it is a monumental task.

Moreover, because dapivirine is a new drug, the process is more complex than for a drug like Truvada, which was already approved for the treatment of HIV when it was under review for use as prevention.
IPM will be seeking approval from the European Medicines Authority (EMA), the U.S. Food and Drug Administration (FDA), and South Africa's Medicines Control Council (MCC), followed closely by regulators in other African countries where studies of the dapivirine ring have been conducted.

IPM aims to submit applications to the EMA and FDA in mid-2017. The EMA submission would be linked to an application for WHO pre-qualification, a process in which WHO determines a new drug or product meets global standards for quality, safety and efficacy. African regulators require WHO pre-qualification before they will consider a drug for approval (and they will also review FDA and EMA decisions).

A decision from the EMA and/or FDA and an opinion regarding WHO pre-qualification might be possible in 2018. If approved, the dapivirine ring could be available in some countries as early as 2019. Leonard cautioned that efficacy and safety of the ring in ASPIRE and The Ring Study did not guarantee licensure. In addition, the regulatory review process can take considerably longer, even when expedited by regulators.

IPM will be submitting its applications as the open-label studies HOPE and DREAM are ongoing. Data from these studies will not be required of regulators in their review, however, IPM plans to provide this information upon their completion.

The REACH study will also be conducted in parallel with IPM's efforts to license the ring.

IPM's initial application for licensure of the ring will be for women ages 18–45, the demographic represented in the two Phase III trials and in whom there is the most data.

While the FDA's application, at least, will include data from the MTN-023/MTN 030 study involving 96 US girls ages 16-17, additional data in African girls is likely to be needed for African regulators to consider the ring's approval for girls under 18. As such, data on the safety and adherence of the ring collected in REACH will be critically important.

Overview and status of oral PrEP in women

Unlike dapivirine, which is the active drug contained in the vaginal ring, Truvada, the brand name for a tablet containing both tenofovir and emtricitabine, is an approved drug for treating HIV. It was approved by the FDA for prevention in 2012, based largely on the results of two pivotal trials in two different populations – the iPrEx study in men who have sex with men and the Partners PrEP Study involving serodiscordant heterosexual couples in whom one partner is HIV-infected. Truvada is currently licensed for PrEP in several countries, including Kenya and South Africa, and the WHO has recommended PrEP for all individuals at risk of HIV infection.

Dr. Connie Celum, who helped lead the Partners PrEP study, summarized what has been learned about oral PrEP in women.

In Partners PrEP, daily use of Truvada helped reduce HIV risk among women in serodiscordant relationships by 70 percent compared to a placebo, including in both older and younger women. Yet, the VOICE and FEM-PrEP studies, which enrolled mostly single and younger women, were not able to demonstrate efficacy because most study participants did not take the tablets.

Researchers later learned that participants were concerned about the stigma of using ARVs, because they are drugs intended for people with HIV, and about their side effects. Some women may not have perceived themselves as being at risk of HIV. The fact that they didn't know whether they were using a placebo or the active drug was also a deterrent to use.

The main message about PrEP, said Dr. Celum, is that it works when taken, noting that in open label studies the level of protection among women has increased to almost 90 percent.

Moreover, young women can adhere to a daily regimen.

ADAPT (HPTN 067), a small open-label study conducted among women in Cape Town, looked at the suitability of different PrEP dosing strategies. Adherence was high – approximately 80 percent based on blood drug levels 30 weeks into the study, and young women were equally as adherent as older women. Adherence then dropped off, suggesting women needed more support to keep up with the daily regimen.

The experience with PrEP and women has thus far suggested:

- Motivation is the key to successful use of PrEP, and the motivations of young women need to be considered to a much greater extent.
- Social pressures appear to play a role in whether women use PrEP, with stigma associated with taking ARVs and male partners figuring prominently.

Dr. Celum noted "*There are lots of parallels between PrEP and contraception. PrEP gives women control. And women want choices. … We are now on a journey similar to that of the birth control pill.*"

In answer to a question about whether PrEP was really welcomed by women, Dr. Celum advised:

"*We should start with what we have – now it is PrEP, and in a couple of years the ring – if approved – will mean for the first time we can also offer a tool specifically for women. But PrEP should continue to be part of the mix, so that women have choices."*

Making it Real: Women's reactions and responses

Of particular note was young women's reactions to the results of ASPIRE and The Ring Study. Winnie Wadera, a 27-year-old girl child empowerment advocate with Young County Changemakers in Kenya, may have said it best:

"*This is good progress … Compared to zero percent, it's a place to start from. These results are a symbol of independence, women being in charge of their sexuality, making decisions, having choice. But we need to understand why young adolescents were not adhering."*

Upon learning the results of the more recent analyses showing 75 percent protection with consistent ring use, she added,

"I would go for high adherence because it's my life. You want to live long? Adhere!"

A former ASPIRE participant from the Wits Reproductive Health and HIV Institute (Wits RHI) in Johannesburg, who was 21 when she enrolled, admitted she was "*a bit on and off*" in terms of adherence when she started the study because she didn't know if the ring would work and she needed to get better at using it.

"When I first saw it [the ring]. It was like wow! But when I got information it was simple."

Being at the consultation and hearing more about the results, she said:

"*I'm getting more excited. It's not just for me. There is a young generation that is behind us – kids, daughters who'll grow up. They will say my great-granny was part of this and now we're living in an AIDS-free generation!"*

A common theme throughout the consultation was young women's desires to be in control of their health and their lives.

"*Using condoms is not so easy. If you try and negotiate, it's like you're saying you're not being faithful. [The ring and PrEP] would give me ownership. I don't have to tell my partner I'm using them,*" said one of the young women who went on to tell about how at age 19 she was forced to have sex and got pregnant.

"It was a hard time for me. I wanted to do more school, I wanted to have loads of fun as a young girl. But my life was miserable. I realize now that I was lucky - I only got pregnant, I didn't get HIV. What about other girls who were not so lucky? It shouldn't be a question of luck."

Asked whether she would use PrEP or the ring, she replied, *"Yeah, I would say I would use them."*

But there was also the sentiment that neither a vaginal ring nor oral PrEP was ideal. The pills, in particular, were noted as being too large and difficult to swallow. One of the meeting participants quite literally put the researchers to task:

"You researchers need to go back to your big books and figure out how to make the medicines better and easier to use!"

Most everyone acknowledged that women's choices of product would be closely linked to lifestyle, and the nature of their sexual relationships. Different HIV prevention approaches could be used at different stages in life. It would be great to have options to choose from, but in order to make informed decisions about which approaches would work best, women will need to have a good understanding of what is available and the pros and cons of each.

The REACH Study (MTN-034/IPM 045)

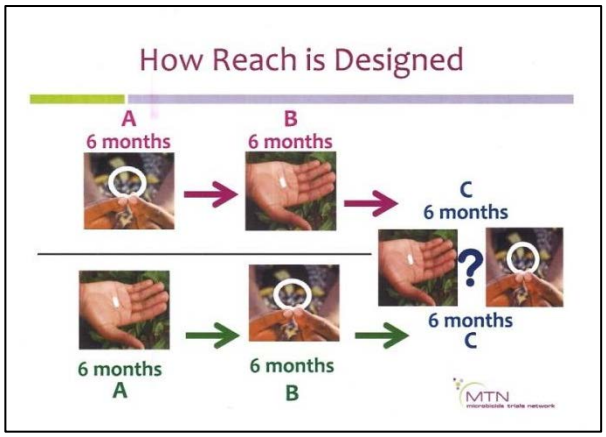
About the REACH Study

MTN-034/IPM 045, or REACH, will evaluate how adolescent girls and young women use the monthly dapivirine vaginal ring and Truvada as daily PrEP, and their preferences for either or both approaches. The study will also collect much needed information on the safety of these approaches in young women and assess whether biological or physiological factors affect how the active drug in each of these products is taken up in the body or may contribute to HIV susceptibility.

REACH will be conducted at four trial sites: the Kenya Medical Research Institute in Kisumu; in South Africa, the Wits RHI in Johannesburg and the Emavundleni site of DTHF in Cape Town; and the Spilhaus clinical research site of UZ-UCSF in Harare, Zimbabwe. (At the time of the consultation there were to be five sites. Since then, the Medical Research Council of South Africa Chatsworth site has opted out of the study.)

Researchers will enroll 300 participants – 100 girls ages 16 and 17 and 200 young women ages 18-21.

Dr. Lulu Nair explained how all participants will use the ring and oral PrEP, each for six months. Random assignment will determine whether PrEP is used for the first six months and then the ring for the following six months, or the ring first and then oral PrEP. After experiencing both approaches, participants will have a choice of using either the ring or PrEP – or neither – for an additional six months.



One meeting participant wondered about the ethics of the design, in that PrEP efficacy is proven and there is much less data on the ring. The researchers explained how with consistent use, the efficacy of the ring could be as high as 92 percent, similar to oral PrEP, the efficacy of which is also highly dependent on adherence. Moreover, there is no placebo – women will be able to use two products that are known to work when used regularly and consistently.

The study will need to enroll girls and young women who have had vaginal sex, and there was discussion concerning how that would be determined – whether by self-report to site staff or via a computer and/or by evidence of a prior STI or pregnancy. Dr. Nair said it was important that young women who are sexually active participate because they are at risk of acquiring HIV and are therefore more likely to benefit from the study. (Participants will be provided contraception through the study.) At the same time, researchers want to be sure to enroll young women who would be sufficiently motivated to keep up with study visits and procedures throughout the duration of the study.

To evaluate the safety of each approach, researchers will conduct medical exams and do laboratory tests of blood, urine and vaginal fluid.

To evaluate adherence to and acceptability of PrEP and the vaginal ring, participants will answer questions about their use and experience with using each product both on a computer and in face-to-face conversations with site staff. In-depth interviews and focus group discussions will also help understand what motivates or is challenging about using each product; whether they experience stigma; how relationships with family, friends and male partners may impact product use, and their preferences for either or both PrEP and the ring.

A main objective of the REACH study is to collect information about adherence, but the study also aims to provide support in helping young women use the products. Participants who took part in both the VOICE and ASPIRE studies told researchers that they would have liked to receive their adherence results during the study (based on drug levels in blood and residual drug in returned rings) to help them with using the study products. Indeed, researchers have seen that sharing individual adherence results can help elicit more open discussion about challenges or difficulties in using the products, as well as help in working through possible solutions. So, in REACH, individual adherence results will be shared with participants.

REACH will evaluate how well participants are using PrEP by measuring drug levels in blood samples taken at each monthly visit. For the ring, they will look at the amount of residual drug left over in rings that are returned each month after having been used.

The study will avoid a one-size-fits-all approach to adherence support. In addition to counseling, which at certain times will include discussion about adherence test results, participants will be offered a menu of support measures – for example, regular instant messages (SMS) or telephone calls. This will enable sites to tailor reminders and support strategies that best suit the participant's desires and needs.

What did young women say about REACH?

Young women and other stakeholders expressed their overall support for the study and study design.

"Trying two products is good, I support it. REACH helps young women to have control over their health, not to depend on her sexual partner, and to be under less risk," said one young woman from Kenya, who is a member of the Girls' Steering Committee and a peer educator at NIGEE in Kisumu. She noted that trying both PrEP and the ring would allow young women to see how their body reacted to both methods and help them choose the better one for them.

Another meeting participant, age 16, who is secretary of a RISE Women's Club in Cape Town, supported the further exploration of PrEP and the ring but highlighted personal reasons women might have for avoiding these products.

"*PrEP and ring are good ideas. The problem will be how many women will do it. We have weird assumptions about what affects our health. Like contraception gives us pimples or we gain weight."*

The most significant barrier for young women would be a boyfriend's disapproval, she said. "*If he says 'don't use it,' I won't. So I think we should first deal with women, empower each other. We don't need other people's opinion about our health – it's our thing."*

Others wondered whether some women would only want to use PrEP. "*When I was talking to peers, they don't want to switch from pill to ring. When you graduate from high school and go to college, you are given the freedom to do what you want. Most people lose virginity that time. We should advocate the pill from high school to college,"* said a university student from Zimbabwe who co-chairs the SayWhat Club (Students And Youths Working on Reproductive Health Action Team).

Paul Ndebele, Director, Medical Research Council of Zimbabwe, countered that "*If someone doesn't want to be switched to the pill – it's interesting to know, it may give us more information about the ring and indicate the person is committed to the ring."*

Moreover, the point was made that PrEP isn't for everyone, and that choice is important. At the same time, it can be expected that many young women will have difficulty using PrEP and the ring, at least at first, said a 21-year-old PlusPills Study participant. She found it difficult taking Truvada regularly: a busy life got in the way and there were the side effects.

"It is going to be a challenge to take the pill. Young women are out there, want to party, go to school… I had side effects of the pill the first few days – stomach aches, headaches, sleeping – and had to stop taking it because I had to study. I started up again and then the side effects came back. The study team and doctor were supportive. They explained it was like teeth brushing – when we wake up we know we need to brush every day. Once the body gets used to the pill it becomes easier. So, it depends on determination and if you feel it will benefit you."

She also added that if offered, she would prefer having an injection. She assumed the ring would be like the female condom, and difficult to insert.

In response, a former ASPIRE participant, jumped up to demonstrate how she positions herself to insert the ring.

"*It was easy to use ring and it was comfortable, I couldn't feel the ring. Even during my periods, it was no problem at all. During sex, I didn't have doubts about it."* Now 21, she was 18 when she enrolled in ASPIRE.

Another former PlusPills participant commented on the potential merits of receiving adherence results, saying it could help in overcoming the challenges with PrEP – starting with the size of the tablets – and be motivating for a participant to hear that the amount of ARV in her blood meant she was protected.

"When you hear the results, you feel embarrassed, because you had flushed the pills and said you took them. Look, the pills are too large, and there are side effects when you start them. But if the nurse were to tell me the results and explain ways to take it well,

that would be good. It would be good to know if I'm protected. That would motivate me to take it every day."

A researcher from one of the study sites asked what the study teams should do to ensure participants feel they can be open with study staff, to ask questions, and discuss challenges they may be having.

"Look at the type of counselors and service providers that communicate with the participant. Age difference matters. A young participant cannot open up to an older counselor. If they ask – how many partners do you have, how many times did you sleep with them? I cannot say 10," said one of the young meeting participants.

A DTHF Youth CAB member ("Future Fighter") from Cape Town, had this to say at the beginning of the meeting:

"When it comes to being with a counselor it's not easy to open up. As a young person, [research] studies are fine, but the sites need to be more welcoming and friendly. When you are a participant, sometimes you feel at home, I see a sister, I see a mother. You're not going to be our mothers, you cannot be all in one. And I don't want to feel pressure. I want to be in control as a young woman."

A number of women said research sites should capture more of the fun of being young and the energy of young people hanging out together, influencing each other and sticking together. In addition to having youthful staff and counselors, meeting participants recommended availability of wifi, sports and entertainment at trial sites, as well as more drop-in centers and young women's support groups, like Zazi in South Africa.

When discussing eligibility for the study, young women at first took issue with researchers who said they needed to enroll the "right" participants. "*You need to choose right women? Who are the right women? We're all at risk!*" But everyone came to agree that it would be important to enroll women who were motivated and saw the value in being in the study.

A number of participants also reflected on how to secure participation of girls and young women at high risk of infection. Among the observations made were:

- The social issues that define "high risk" are complex and it is not always easy to identify those at risk who might be "quite invisible."
- CAB members may be good interpreters of local social dynamics and prove useful in identifying individuals and groups that are "high risk."
- Perception of risk is quite subjective and those who are actually at highest risk might not realize this. Therefore, they might not be easy to recruit and might not be motivated to adhere.
- Communication to potential participants should take into account that their perceptions of their own risk may differ considerably.

It was also suggested that if trials used incentives to attract participants, this could be the real reason for them volunteering. Researchers clarified that participants were reimbursed for travel costs and time and effort in coming to the site. The level of this reimbursement was set by ethics committees and was not intended to be an incentive.

In addition to the several comments about the size of the pills, some expressed concerns about the size of the ring and the implications this might have for use by young women, including virgins. In discussion, it was made clear that the ring is meant for adolescents and young women who are already sexually active. It can be twisted into a figure eight and is generally easy to insert. It was further clarified that ring could be used with tampons (a specific study was done on this) and it could be removed, washed and reinserted. Moreover, provided the ring is inserted correctly, it rarely, if ever, falls out.

“As a young woman in South Africa, we always talk about the struggles of the past and forget that we have our own struggle. This is our struggle — we want to be free from HIV, both men and women …”

– Youth CAB member (“Future Fighter”) at the Desmond Tutu HIV Foundation, Cape Town

Navigating Informed Consent and Parental Involvement and Disclosure

The ethical and legal framework in trial site countries

Ambrose Rachier, Chair of the Ethical Review Committee for KEMRI; Paul Ndebele, Director of the Medical Research Council in Zimbabwe (MRCZ); and Cathy Slack, Project Manager, HIV AIDS Vaccines Ethics Group (HAVEG) at the University of KwaZulu-Natal School of Applied Human Sciences in Durban, provided overviews of each of their country's ethical and legal framework for conducting HIV prevention research in adolescents.

In all three countries, the legal age at which an individual may provide informed consent to enroll in a research study is 18. For those under age 18, parental consent and the assent (agreement) of the minor is required. The exception applies for mature or emancipated minors, who although under the age of 18, are, for example, already married, a mother or head of a household.

When a parent provides consent for a minor to participate in a study, this does not afford him/her access to information considered confidential by law, which in most cases includes matters of reproductive health and HIV. Ambrose Rachier explained that, ultimately, the overriding responsibility of researchers is to protect the physical, mental and social wellbeing of participants and to minimize risks as much as possible. Ensuring protection of the adolescent is more important than the rights of parents to know the results of medical and screening tests performed as part of the study.

Paul Ndebele highlighted the fact that the consent process occurs within a cultural context in which there is little cross-generational discussion about sex, premarital sex is frowned upon, and virginity testing still occurs in some settings. It is therefore no surprise that adolescents are secretive about their sexual activities, and this can further complicate the consent process.

An option that can be considered is a parental waiver. In fact, he reported that just the day before, the MRCZ had decided that parental consent would be waived for 16-17 year olds in the HPTN-082 study, which will look at uptake and adherence to daily PrEP as a primary prevention strategy for young African women.

"*This is the age at highest risk and those most likely to benefit from findings. A parental consent requirement would have reduced the chance of minors being able to participate,"* he said.

Cathy Slack suggested other approaches that can be taken, including allowing the minor to self-consent but involving the parents with the minor's approval; or asking the participant to name a trusted adult who can receive confidential information, if necessary.

All three panel members indicated that there was a legal obligation for researchers to report instances of sexual abuse of minors.

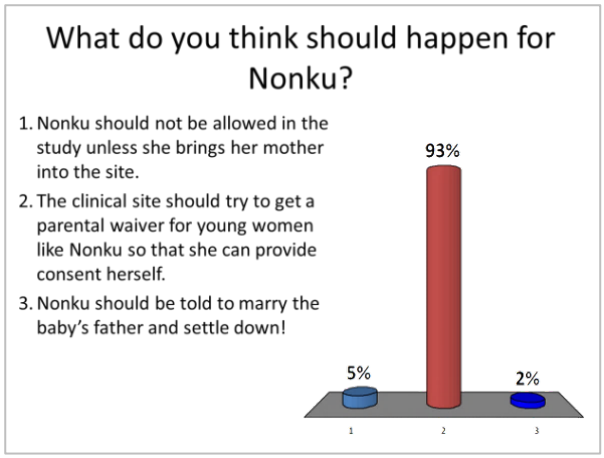
Many of the issues and challenges highlighted in these presentations were brought further to light in a series of scenarios presented by the research team. Meeting participants registered their feedback on each scenario using handheld remote devices called an Automated Response System (ARS). Because the ARS is incorporated into a PowerPoint presentation, responses were compiled immediately and displayed visually on the screen, creating stimulus for further discussion. The outcomes of these scenarios discussions are presented on the following pages.

Parental waivers vs. parental involvement: Discussion and Issues

One of the most salient outcomes of the meeting was stakeholders' firm belief in the merits of a parental waiver for the REACH study. In the ARS scenario below, 93 percent indicated that trial sites should apply for a waiver.

Scenario

Nonku is a 17-year-old *living in Cape Town, South Africa. She is living* with her mother but she already has a 9-month-old baby. She currently has a boyfriend who she has been with for 1 year. She wants to enroll in REACH but she says that she does not want to talk about it with her mother yet. She is under 18 so under South African law she cannot participate in a clinical trial without parental consent.



In discussion, many of the young women reiterated the importance of having control of their lives and actions, and being able to make their own decisions about their health and wellbeing. At the same time, there was recognition that this was not an easy situation. Would allowing parental waivers place young women at risk? What about the consequences of parents later finding out about the study or discovering study product at home?

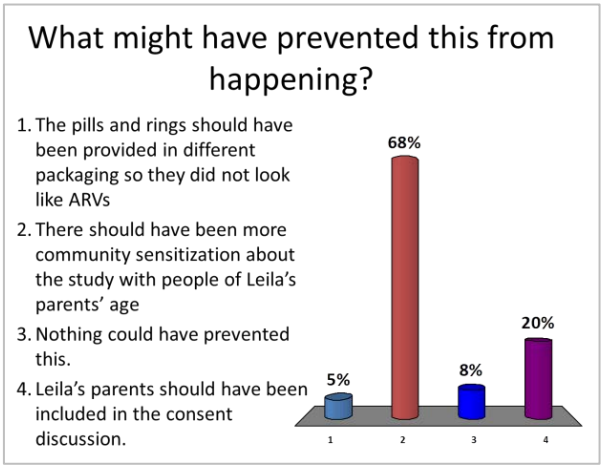
Indeed, as PrEP, Truvada must be taken every day, in the same way that a person with HIV takes it. And the pills are the same color (blue) – *"They will assume I'm positive,"* said one of the girls. Others pointed out how they would have to make up stories about why they weren't coming home from school at the usual time to cover up for when they went to the research clinic.

It was strongly suggested that even with a parental waiver, study staff should explore how to involve parents in some aspects of the study, depending on the adolescent's relationship with her parents. And if not a parent, another sympathetic adult (e.g., an older sister or aunt) could be considered as well. This could help mitigate potential social harms associated with products (e.g., stigma with ARVs, assumptions that girls are infected), and realization that girls are sexually active.

There was also acknowledgment that family dynamics could make this impossible in some instances. The next scenario brought these issues to light.

Scenario

Leila is 18 and has joined the REACH study and her mother does not know about her study participation. Leila's mother is very religious and does not agree with Leila's decision to be sexually active. Leila's mother finds her study product and accuses her in front of the entire family of being HIV positive. She is beaten and has to go to the hospital.



The majority of responses (68 percent) reflected the opinion that there should have been more community sensitization about the study with people of Leila's parents' age, although 20 percent felt this could have been avoided had her parents been included in the consent discussion.

Through broader sensitization, parents would have been made aware of the study and its purpose, and been better positioned to support and understand their daughter's desire to take part – or to champion the cause themselves.

A 20-year-old PrEP demonstration study participant from Kenya explained:

"I knew that if you take PrEP correctly and consistently it will protect you. The pills were too big. But I was motivated since I came from a family with HIV. I disclosed it to my parents, and dad didn't want it. They thought it was antiretroviral therapy but I was open with them, and I explained to them. Mom went to see the doctor and then she discussed it with dad. He then said it's ok to protect your life. I disclosed to my friends. I was motivated."

Another PrEP demonstration study participant had a remarkably similar experience. "*The pill is too big and you must take it every day like a person who's HIV-positive*." She said she had side effects from PrEP – nausea and drowsiness – but continued taking it because she came from a family with HIV. When her family discovered the Truvada they thought she was HIV-positive. She had to go with her mother to the hospital for a doctor to explain about PrEP. "*Then even my sister began to take it*."

A former ASPIRE study participant, who was 18 when she enrolled, said of her mother:

"*I went to the ASPIRE building with my mom, and she said 'You are the first one to do research, do it for young women out there.' So, I had the support from family, mom and boyfriend … You should make your mom your best friend. Mom knows we are at high risk of HIV. I told my mom about my first boyfriend. Mom knows I'm not HIV-positive but that I'm being protected."*

There were divergent views on participants disclosing their participation to their parents. On the one hand it was argued that "making your mother your best friend" for the trial was the surest path to adherence. On the other, it was predicted that confiding in your mother could result in being kicked out of the house. Some explained how it would be difficult to let their parents know they were in a study because, in essence, that would be admitting to being sexually active.

Individual circumstances should be the guide, because not all young women will be able to or want to disclose study participation to their parents.

Some felt strongly the onus should not be on young women.

"Pressure should not be on young women to inform adults. There's work that needs to be done at the community level. It's important to look at tools to work with stakeholders. By the time women want to enroll, the environment should be conducive," commented Lebo Ramafoko from Soul City Institute.

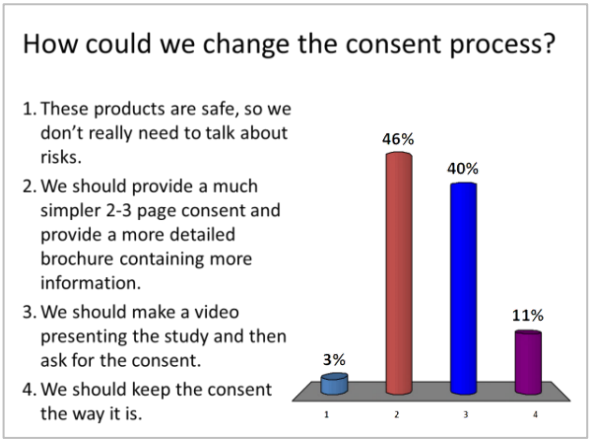
Some of the suggestions that could help inform parents included involving other parents whose children are in HIV prevention studies or demonstration projects to act as community ambassadors or forming parental advisory boards.

Informed consent process and communication: Discussion and Issues

The third scenario revolved around the consent process and the consent form itself. There was agreement on the need for improvements, with 46 percent believing the study should develop a more simple 2-3 page consent with a brochure providing greater detail and additional information; and 40 percent suggesting that a video explaining the study should be used.

Scenario

Pretty is an 18 year old woman from Kisumu who comes to the clinic because she had heard about PrEP in the community and she wants to know more. She is interested in the study when it is described to her, but when she is provided with the consent form she is alarmed because it is 12 pages long and lists many risks with using PrEP, including bone loss and kidney damage. She is also worried about "fat changes"



Most agreed that materials about the study, including the informed consent, should use simple language. There was also a comment about needing to avoid mixed messages, because PrEP and the vaginal ring are not equivalent products. Researchers agreed on the need for properly nuancing messages and in finding more engaging ways to approach informed consent with young people.

Paul Ndebele of the MRCZ mentioned how group information-sharing sessions helped build understanding among female adolescents for a study of sexual and reproductive health in Zimbabwe. Dr. Hillier noted that this approach has also worked in the U.S., with individual consent counseling taking place after group discussions.



“I’m getting more excited. It’s not just for me. There is a young generation that is behind us – kids, daughters who’ll grow up. They will say my great-granny was part of this and now we’re living in an AIDS-free generation!”

– Former ASPIRE Study participant, now age 24

Community Sensitization and Communications: Reaching Key Groups

The importance of engaging with and sensitizing communities about an HIV prevention trial well before the start of the study, and maintaining those lines of communications throughout the life of the trial, cannot be underestimated. Stakeholders felt this would be especially critical for REACH so that the study can be conducted within communities that are both receptive to and supportive of the trial.

Sites should develop advocacy and media education plans as part of their overall communications strategy, also ensuring that key audiences and groups are reached, particularly those that could represent potential barriers or be sources of misunderstanding – parents, generally, religious leaders, community leaders, healthcare workers, other peers, as well as male partners. Journalists were also mentioned as critical allies.

These groups should be informed, and to the extent possible, also be educated about the study to avoid creating a vacuum that might otherwise be filled with misinformation to the detriment of the trial and the young women participating.

For instance, it was felt that engagement with religious leaders was important to counteract the view that PrEP or the ring would encourage promiscuity.

A young woman, who is a student at the University of Zimbabwe, said misconceptions and superstitions about PrEP and the ring were rife – "*Like, they come from Europe, there's the issue of Satansim (Zimbabwe is a Christian country), and the idea that inserting it [the ring] in the vagina is satanic. So, people need to be educated*."

Communications across groups needed to address issues around stigma, emphasizing that people can also use ARVs to be protected from HIV.

Kawango Agot from Impact RDO in Kenya had her own opinion as to why communication targeting men was important, saying that, "*Men are not enemies but when they don't know something, they make it up."*

"Most of us are heterosexual. So, what does the other half say? They are powerful. Reach out to men, get them to buy into this," added Winnie Wadera, the girls empowerment advocate from Kenya.

Messaging in all communications materials (including the informed consent) needs to be clear, simple and sincere. Working with people who have expertise in designing communications programs was advised.

The Youth CAB member from Cape Town said she liked the study videos produced by DTHF and thought other young people were influenced by what they saw on TV.

Youth CABs could help bridge the gap between sites and young people in communities.

Both traditional and social media channels should also be used for reaching potential participants and to gain acceptance of peers. And celebrity endorsements should be considered.

Beyoncé and Bonang (a South African media personality and global ambassador for Revlon Cosmetics) "*would make women **love** these prevention methods*," a 16-year-old meeting participant offered emphatically.

"Get information out there to other women. They listen to media a lot – If Beyoncé or Bonang says something on TV, they will listen and will share it and 'like' the Facebook page. Every woman out there would want to be part of this once it's in the media; and men won't have a say. They won't have the power like now ... Social media has influence. We talk – did you see what happened on Facebook? – and she'll know. It's more effective in our lives. Also, 17-19 year olds are still in high school – so tell them in school, in assembly. They'll be interested and want this, especially when it's working."

There was also a strong plea from Khanyisa Dunjwa, representing the Women's Sector of the South African National AIDS Council, for trial sites to collaborate more closely with organizations that could help participants deal with factors that place them at risk of infection and may also undermine their adherence during a trial.

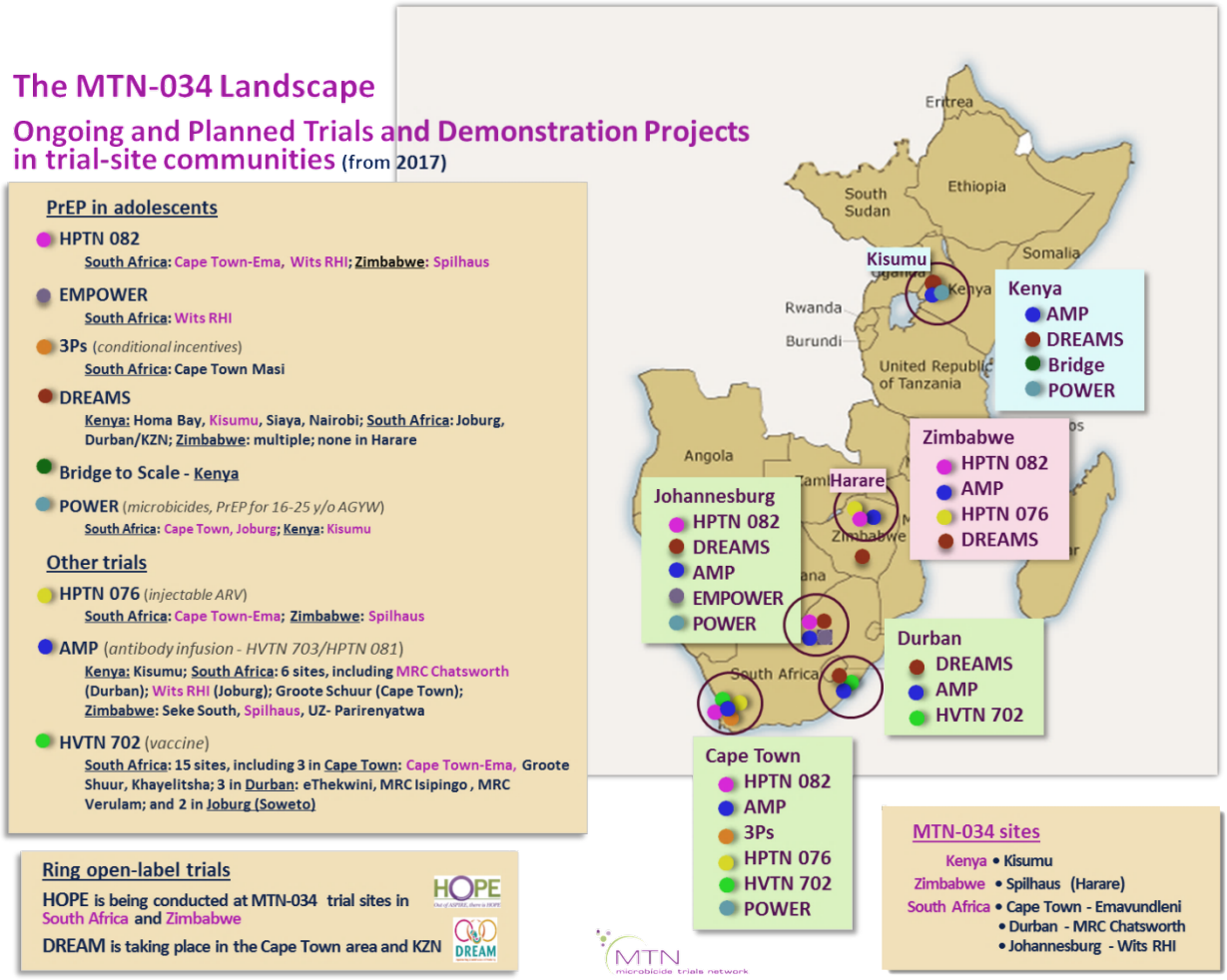
"*Social context is very important. Researchers should partner with stakeholders who are addressing violence and economic empowerment, for example. In communities where participants come from there are other forms of support. When thinking about future research work, we cannot keep highlighting social and structural drivers [of HIV] and not do anything about them,*" she said.

REACH in Context: The HIV Prevention Landscape

Overview of HIV prevention clinical trials

Mitchell Warren of AVAC remarked how it was an exciting and busy time for HIV prevention. PrEP is being implemented or soon will be in each of the trial site countries. In addition, several HIV prevention trials are underway or being planned. These include the AMP (antibody-mediated prevention) study in all three trial-site countries, HVTN 702, a large vaccine trial in South Africa, and a large efficacy trial of injectable PrEP that is on the horizon.

He also emphasized that it was important to remember that products just beginning efficacy trials in 2016 or 2017 would not yield results until 2023 at the earliest. But the fact that they are being conducted in the same countries, cities and even the same communities as the REACH study must be taken into account. Planning for and implementation of REACH will need to consider these contexts, he said.



At the time of the consultation there were to be five clinical trial sites for the REACH study (MTN-034). Since then, the MRC Chatsworth site in Durban has elected not to take part in the study.

Overview of PrEP access and implementation

Saiqa Mullick, Director, Implementation Science at Wits RHI in Johannesburg, provided an outline of where PrEP is currently available in southern Africa and listed studies and projects that would expand access to PrEP in the near future.

- Kenya: July 2016 national guidelines on use the of ARVs for treating and preventing HIV include Truvada for PrEP for sex workers, adolescent girls and young women, serodiscordant couples and men who have sex with men. PrEP is also slated to be rolled out at DREAMS sites beginning September 2016.
- South Africa: June 2016 national guidelines include PrEP as part of combination prevention. PrEP is registered for ages 18 and older, and is being rolled out across 11 sites to provide access to sex workers, clients, truck drivers and anyone who requests PrEP. WHO is monitoring and evaluating and looking at plans for additional roll-out to high-risk populations (adolescent girls and young women and men who have sex with men).
- Zimbabwe: National guidelines are scheduled to be launched at the end of October 2016. Currently, Truvada is licensed for treatment only, but a submission for PrEP is anticipated soon.

Studies and demonstration projects aimed at adolescent girls and young women are taking place in all three countries where REACH will be conducted. Several large-scale implementation projects on PrEP for adolescent girls and young women are being planned.

Dr. Mullick pointed out that expansion of PrEP was restricted by financing and a competing priority to provide better access to ARV treatment (ART). She also said that in South Africa the prevailing view was that rolling out PrEP to all adolescent girls and young women would not be cost-effective, and decision makers were keen on having more data on high-risk subpopulations.

Kenya, in contrast, was reported to be planning to make PrEP generally available to all citizens in all 47 counties.

Conclusion and Next Steps

There was overall support for the REACH study, including by the young women who participated in the consultation. A common theme throughout the meeting was their desire for empowerment – to have control of both their health and lives, and the products being studied in REACH represented these values.

Those who had previously used the ring spoke of initial trepidation but subsequent ease of use, including during menstruation and sex. Daily Truvada was positively viewed but participants had trouble maintaining consistent use, experienced side effects initially, and often needed to counter stigma. One young woman's parents had jumped to the conclusion that she was HIV-positive when they found her ARVs.

Targeted communication should prioritize the parent demographic and organizations and groups that could potentially be in opposition to the study. Moreover, work should commence well before the study's start.

The trial should seek a waiver of parental consent, but also look to ways to incorporate involving parents and/or disclosure to parents or other trusted adults as a participant's individual circumstances may allow. Together with broad community sensitization, these approaches would help facilitate participation of young women, while also providing for their protection against the potential social harms.

The adherence counseling that REACH would provide, including the sharing of individual adherence results, was seen as both important and helpful, provided that counselors are supportive and nonjudgmental of young women.

Young women argued that trial sites needed to include more youthful staff, as they would be more inclined to open up to someone closer in age. The site itself should also be fashioned as a place where they would want to go.

Continued involvement of youth in various phases of the study is essential. Male partner involvement in the trial should also be given consideration.

Drs. Hillier and Nair explained that the research team was hoping to complete the next version of the protocol and submit it to MTN's funders – the Division of AIDS of the National Institute of Allergy and Infectious Diseases (NIAID) and the *Eunice Kennedy Shriver* National Institute for Child Health and Human Development (NICHD) – for review by the end of November. Drs. Hillier and Nair, and other members of the study team, said they would be taking to heart the invaluable feedback received during the consultation.

MTN expects to receive feedback from NIAID and NICHD by mid-December, and depending on whether there is the need for additional review, the protocol would be finalized in January or February 2017. Research sites would then submit the final protocol to in-country regulatory and ethics committees for their review and approval. Given these requirements, the study could begin at some sites in June or July 2017.

The researchers pledged to hold additional stakeholder meetings – at least one in each country – prior to the launch of the study. In addition, trial sites would be developing comprehensive plans for community and stakeholder outreach and communications.

Manju Chatani-Gada thanked everyone for taking part in the consultation – researchers, regulators, policy makers, advocates and, above all, the young women who had contributed with such passion and honesty. She remarked on their joint commitment to undertaking difficult research in order to find HIV prevention products that fit into the lives of young women. The researchers echoed the value of the meeting and the guidance it provided.

Appendix: Meeting Evaluation Summary

Meeting evaluations were sent to all meeting participants; 13 responses were received (28% response rate). The following summarize some of the open-ended questions.

When asked which part of the meeting participants liked best, the most frequent response given was young women's involvement in the consultation, as reflected in these examples:

- *Hearing young women's views which are normally missing in these kinds of consultations*
- *When we as young women were given a chance to speak*
- *When we were able to hear from the young women themselves and have the researchers listen and really take the young women's views seriously.*
- *Hearing the voices of the young women and the diversity of their opinions at the same time as hearing from the experts in science, ethics and programs*
- *Hearing the testimonies of research participants and listening as they shared their experiences. It was quite eye opening.*
- *Listening to the young women's concerns on their study participation and their involvement*
- *The views of the young women who are users of PrEP and microbicides*

One respondent said:

- *To be honest I don't have a best part, all the sessions were intertwined in ways that brought me great insights, in as much as I had something to give as a panelist, I took more home from the entire room and the two days, I am more careful with my personal lifestyle choices and even more driven to impart my immediate associates and teens I speak with on a daily basis. All things in my opinion were adding up to getting me more inspired to be more alive in my pursuit of an HIV free world.*

Some meeting participants felt more time was needed for both discussion and the meeting overall; others felt the time was sufficient despite the tight agenda. Some respondents wanted to hear more from young women and also from young women with different perspectives on product use, especially for the dapivirine ring. At least one respondent wanted to hear more from scientists.

Asked about other topics or issues that would have been helpful to cover, some of the comments were:

- *While I feel that we covered all the necessary topics, there was not much time devoted to the discussion especially with young women ... to have the young women speak about their concerns in-depth. For this to be really meaningful, young women could have had more time allocated to them.*
- *Getting to hear how the young people want to organize themselves for broader HIV prevention work.*
- *It would have been a good idea to bring young women from ASPIRE who were not adherent to the ring and hear their reasons for nonuse … hearing from the ones who did not use the product would really give insight moving into MTN-034.*

All respondents agreed on the need for similar in-country consultations. Opinions varied on who should be targeted. Responses included parents and guardians, teachers and students, community-based and faith-based organizations, particularly those working directly with young women; young women themselves, including sex workers and young disabled people, as well "gatekeepers" such as young men, religious leaders and media." A few responses are highlighted below:

- *I feel it will be important to hold similar in-country consultations and involve more young women who will be potential research participants and potential end-users of the products.*
- *…the kind of audience should be old and young. Old so that they could understand the importance of letting their children get involved. Youngsters so they should know what to do for their future, and have a choice.*
- *I feel particularly that bigger meetings with in country adolescent girls from different walks of life will ultimately increase awareness of the ring and of Prep- which in turns aids acceptability of these products should they become available. I also feel media should be part of the audience*
- *From Kenyan perspective, involving religious leaders and key county health officials would be important as they are key community gatekeepers. I would also involve parents of young girls at risk, e.g. parents to adolescents who are in fishing community, mature minors, school going girls to understand their perspectives. Healthcare workers, especially family planning providers, to sensitize them on advocacy for PrEP, young girls seeking family planning from their clinics.*

Lastly, when asked whether they would like to stay engaged and updated on the study, some meeting participants said they wanted to help with country and regional consultations and in mobilizing young women. The following comments are of especially noteworthy:

- *Yes please I'm not only doing this for myself but for my fellow sisters, and generations to come.*
- *Yes I am interested in being part of this to the very end. I left more passionate and wanting to not just be part of the statistic of stakeholders. But I want to give back, I want to step in and push adherence advocacy, be available for consultations and every other way I can be an active player, via whatever means of staying engaged.*

“Thank you for engaging the young people and the community of HIV Activists in the MTN planning and review processes. I feel like I am part of a special African family that is all about finding solutions that work for women!”

– Stakeholder from Zimbabwe

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.


MTN
microbicide trials network


REACH