

# Finding the Silver Lining

HOW A WATERSHED MOMENT IN HIV PREVENTION RESEARCH LED TO INNOVATIONS IN BEHAVIORAL SCIENCE

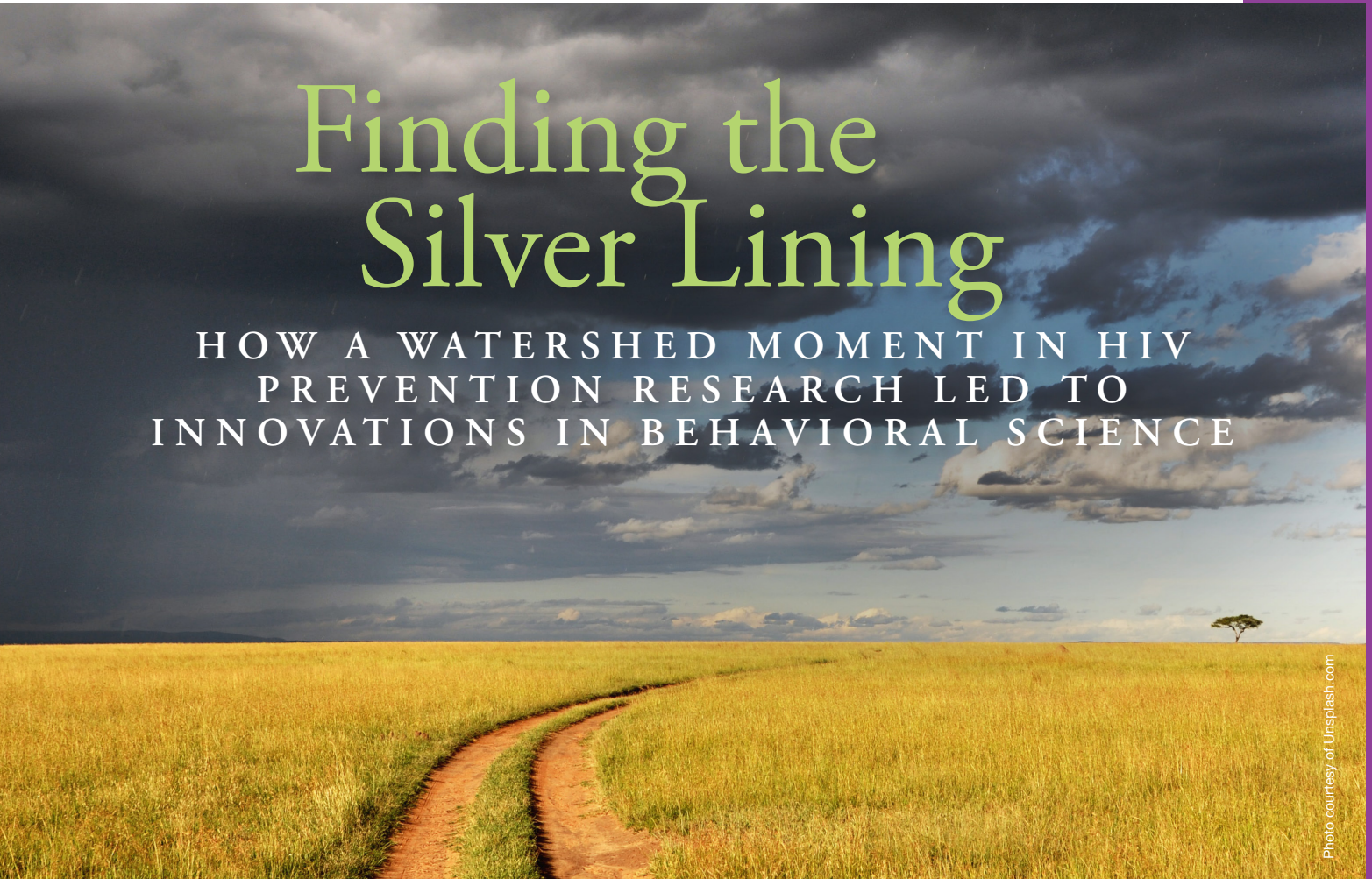


Photo courtesy of Unsplash.com

**B**usi Tshabalala was shocked when she was told a major HIV clinical trial she had worked on as a study administrator since its start had “failed.” The reason was attributable to troubling data disclosed when the study, called VOICE, was completed: Nearly three-quarters of the study’s more than 5,000 participants at 15 sites across South Africa, Uganda and Zimbabwe, including Busi’s – the Wits Reproductive Health and HIV Institute (Wits RHI) in Johannesburg, South Africa – had not regularly used their study products, despite having continuously told site staff the opposite. Consequently, the three-year-long study was unable to provide evidence that the products tested prevented HIV, not for lack of efficacy, but because adherence to their use was so poor.

There was a pervasive “air of disappointment” when the VOICE results were disclosed to participants at the Wits RHI site in March 2013, recalls Krina Reddy, program manager at the site. “It impacted everyone, especially the clinical team because we had put so much effort into the study,” says Sylvia Sibeko, a community health worker at Wits RHI, whose job was to recruit and retain VOICE participants. The women who had used their study products daily, as instructed, also took the news hard.

“They were terribly sad, and you could see the disappointment in their faces,” adds Lizzie Gama, a Wits RHI VOICE community health worker along with Sylvia. “They were asking, ‘What are we going to do now?’” For some who had not used their assigned products as instructed, there was acknowledgment and candor in admitting they hadn’t stuck with it. Whatever their reasons, they confessed they hadn’t been honest because they didn’t want to disappoint the study staff.

VOICE – Vaginal and Oral Interventions to Control the Epidemic – was launched in 2009 by the Microbicide Trials Network (MTN) with the goal of providing cisgender women with daily user-controlled options for HIV prevention. Unlike the male condom, the products tested in VOICE – oral antiretroviral tablets, tenofovir and Truvada®, and tenofovir vaginal gel – were methods women could use to protect themselves against HIV. MTN and the network’s primary funder – the National Institute of Allergy and Infectious Diseases (NIAID) – and co-funders, the National Institute of Mental Health (NIMH) and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, were passionately committed to this goal given HIV’s devastating toll on women and girls in that part of the world.

“VOICE was such a hard lesson for all of us,” says Ariane van der Straten, Ph.D., adjunct professor at the University of California, San Francisco and chair of MTN’s Behavioral Research Working Group (BRWG). The BRWG, which



was conceived prior to the network’s launch in 2006, provides input and ideas for integrating social and behavioral research within MTN’s clinical trials portfolio. “We were

completely committed to women-controlled methods for HIV prevention, but we learned that even when you love a product and know it can save lives, it has to be loved and accepted by women in general and participants too.”

Looking at it another way, adds Ariane, also a behavioral research consultant, “If people truly loved using condoms, the HIV epidemic would have ended a long time ago.”

“People who are not engaged in behavioral research in an in-depth way think, ‘We’ll tell someone to take a pill and they’ll go home to take it and they’ll get better,’” adds Dianne Rausch, Ph.D., director of the Office of AIDS Research at NIMH. “All you have to do is look at the COVID-19 pandemic and the resistance to getting vaccinated or even being asked to wear a mask to know that human behavior is complex and incredibly important to understand.”

Pamina Gorbach, Dr.P.H., a behavioral epidemiologist at the University of California, Los Angeles, and founding chair of the BRWG, agrees. “The VOICE results required us to do things differently and to understand the communities we are working with much better. Once we got the message from VOICE, it opened the flood gates for the recognition that there is a real need for behavioral science in biomedical HIV prevention research.”

As difficult as they were to accept, the results of VOICE compelled MTN to embark on a journey that changed its nature and fabric, and the network embraced a behavioral and social science research agenda “with extreme diligence,” remarks Dianne. “The data that has come from the MTN then and since about acceptability, usability, and attitudes and behaviors has really moved the behavioral science agenda forward, possibly more than any other entity in the field. We really have learned a tremendous amount over the years.”



*Ariane van der Straten, Barbara Mensch and Pamina Gorbach at the 2011 MTN Annual Meeting in Arlington, Virginia.*

## Clearer skies ahead

Shortly after the VOICE results were announced, MTN launched a behavioral sub-study called VOICE D to engage former participants in candid discussions about why they didn’t adhere to using their study products. In VOICE D, a sub-set of VOICE participants were provided with blood test results that indicated their actual patterns of product use during the trial and were asked about the discrepancies in their self-reported use of products. Employing in-depth interviews and focus group discussions with research staff who had not worked on VOICE and conducting them at a neutral location to encourage openness, the VOICE D team learned that there were many factors that had influenced participants’ decisions not to use the study products consistently. Some of these included medical mistrust, community-based rumors, stigma about taking HIV medication, challenges in remembering to take a daily product and simply not liking the way a product tasted or felt.

“VOICE D was an eye-opener and a way for us to begin to understand the constraints in people’s lives, their attitudes and the contexts in which they live,” says Barbara Mensch, Ph.D., a consultant at the Population Council, and VOICE D co-investigator. “We asked people what it was about the products they didn’t like and what was going on in their lives that made using a product problematic.”

For Petina Musara, a social scientist and clinical research site coordinator at the University of Zimbabwe Clinical Trials Research Centre, who has been with MTN since its founding, one of the most important lessons learned from both VOICE and VOICE D was the need to engage in behavioral research at the same time – or even before – clinical trial implementation.

“When we received the VOICE results, it was too late,” states Petina. “There was nothing we could do to help participants, to support them, to learn from their experiences or to understand what they didn’t like about the study products. We do this early now so we can address it and do something about it.”





Photo courtesy of Ariane van der Straten.

*Ariane van der Straten and Petina Musara (center, white sweater) are surrounded by other members of the MTN-041/MAMMA study team, including the qualitative interviewers from each of the four study sites. They came together at the 2018 MTN Regional Meeting to take part in a rapid preliminary analysis of the study's data. Also participating was Juliane Etima, second from left.*

A few years later, MTN researchers developed a qualitative study called MTN-041 that exemplified a more proactive approach to exploring community attitudes and perceptions about the use of two HIV prevention products – Truvada as daily oral pre-exposure prophylaxis (PrEP) and the monthly dapivirine vaginal ring – during pregnancy and breastfeeding. The study, fondly called MAMMA – Microbicide/PrEP Acceptability among Mothers and Male Partners in Africa – was designed expressly for the purpose of informing the implementation of the DELIVER (MTN-042) and B-PROTECTED (MTN-043) studies of these products in pregnant and breastfeeding women, respectively. MAMMA, which was co-led by Ariane and Petina, was conducted in 2018, prior to the launch of the two subsequent trials, which are still underway.

An important aspect to MAMMA was understanding the attitudes and perceptions of communities and end users by conducting focus group discussions with pregnant and breastfeeding women, male partners, and mothers and mothers-in-law. Study researchers also interviewed community leaders, health care providers, midwives and traditional birth attendants, among others.

“Through MTN-041, we learned which product attributes fit or didn’t fit with women’s needs and their expectations of HIV prevention, as well as the challenges they may face and concerns they may have,” says Petina. “Including the input of community members who are likely to influence product use has helped us identify the kind of resources and support needed to improve accrual, retention and product adherence in DELIVER and B-PROTECTED.”

Juliane Etima, behavioral scientist at the Makerere University-Johns Hopkins University Research Collaboration in Uganda, and long involved in qualitative research at MTN, co-led another network study called MTN-045. The study enrolled 400 couples in Uganda and Zimbabwe to explore their views about and preferences for dual-purpose products to prevent unintended pregnancy and HIV.

This kind of design, says Juliane, provides participants with a sense of ownership of both the research and the study products. “Through this work, we learned that preferences vary between men and women, and that even younger and older women prefer different things. It has given us invaluable insight into developing future products for different populations and age groups.”



*A panel discussion during the Zimbabwe stakeholders meeting about the DELIVER and B-PROTECTED studies in early 2020 included former participants from MTN-041. Stakeholders meetings in Malawi, Uganda and South Africa featured similar panel discussions.*





*A young woman found a platform to express her views at the regional consultation for the REACH study, which took place in September 2018 in Johannesburg, South Africa, while the study protocol was still in development.*

MTN researchers took a similar thoughtful “step back” when they developed the DESIRE (MTN-035) rectal microbicide study in 2018. In DESIRE – Developing and Evaluating Short-acting Innovations for Rectal Use – participants tried out three methods for the delivery of a rectal microbicide – a douche, suppository and fast-dissolving rectal insert – none of which contained an active drug. The idea was for participants to “try out” the placebo delivery approaches. Only after using them for a month at a time, were they asked to weigh the attributes of each.

“You can’t design products in a vacuum,” says José A. Bauermeister, Ph.D., M.P.H., DESIRE study protocol chair and professor at the University of Pennsylvania. “People need to want to use them. That was the idea behind DESIRE – to have participants’ real-life experiences guide their preferences, and help the science move beyond theoretical concepts.”



*Kenneth Ngure (front right), REACH co-chair, and other protocol team members had some fun before taking a group photo at the 2017 MTN Regional Meeting in Cape Town, South Africa.*

For Kenneth Ngure, Ph.D., M.P.H., associate professor at the Jomo Kenyatta University of Agriculture & Technology in Nairobi, Kenya, and protocol co-chair of REACH – Reversing the Epidemic in Africa with Choices in HIV Prevention – giving participants a voice not only before, but during the study has helped encourage mutual respect among site staff and study participants.

REACH (MTN-034), a study of Truvada as PrEP and the monthly dapivirine vaginal ring among young women and adolescent girls ages 16 to 21, was designed to respect the autonomy of participants and empower them to make decisions. After using each of the two products for six months at a time, participants could choose one or the other, or neither, for the last six months of REACH. They are also able to change their minds as often as they would like, at their discretion, to better represent real-world situations.

Even before launching REACH, in-country site staff and advocacy organizations worked collaboratively with Lisa Rossi, MTN Director of Communications and External Relations, Manju Chatani, Director of Partnerships & Capacity Strengthening at AVAC, and local partners to execute a series of stakeholder consultations in each of the trial site communities where the study was being planned. The purpose of these meetings, which took place in Kenya, South Africa, Uganda and Zimbabwe, was to give stakeholders – a large percentage of whom were young women themselves, as well as civil society representatives, regulators and ethicists – an opportunity to share their thoughts on all aspects of the study’s conduct and implementation.

“Through extensive stakeholder engagement, young women shared what they liked, didn’t like, and wanted to improve in REACH,” says Ngure, also a member of the BRWG. The study team found out, for example, that it was important for the participants to have youth-friendly clinic spaces and short visits. “We went back to look at our data collection instruments and cut some of the questions to make sure they were very focused, so we could reduce their time in the clinic,” remembers Ngure.

Hosting interactive focus group discussions with participants early during the study, Ngure and other team members continued to solicit ideas from participants about changes they’d like to see made in the implementation of REACH, which is expected to complete follow-up in October of 2021. Changes, such as pre-warming the speculum used for pelvic exams to make it more comfortable and limiting the number of clinic staff members present during clinic visits to address participants’ stated need for further privacy, were then incorporated in real-time.

“It’s a true commitment by young women to participate in these studies,” says Ngure. While an ongoing process and not without its challenges, REACH staff learned to be open and give participants an avenue and means to discuss their experiences. “It was important that they felt as though they were partners in the process,” he adds.

## Winds of change

When clinical psychologist Iván C. Balán, Ph.D., a professor at the Florida State University College of Medicine, was introduced to the MTN in 2012, he was involved in a study using motivational interviewing – a collaborative way of working with people that deeply recognizes their own aims and goals – to help engage patients into psychiatric treatment at Columbia Presbyterian in New York City. Iván was invited by a colleague, Alex Carballo-Diéguez, Ph.D., now-retired professor of clinical psychology at the Columbia University Medical Center, to join him in working on a new rectal microbicide study being developed at the MTN.

The study, called MTN-017, was to be the first-ever Phase II study of a rectal microbicide, so the behavioral team for the study, headed by Alex, wanted to make certain the study met its goals in measuring and understanding adherence to a tenofovir-based rectal gel and Truvada as PrEP. Along with utilizing motivational interviewing, Alex and Iván advocated for standardizing the recording of participant counseling sessions to help counselors “draw the motivation out of the participants and highlight it,” says Iván.

“There is a tendency in counseling to convince people to do something you want them to do because we often think, ‘If you just had all the information I have, you would feel just like me,’” explains Iván. “Our inclination is to give people more and more information, but it doesn’t work like that. It’s about making sure the information we are giving is linked to their goals.”

Put another way, says Iván, “You can’t just tell someone to take a pill in the morning by sticking it in a piece of bread. If you ask them, you might find out they don’t even eat breakfast. You need their help in developing an adherence plan that works for them.”

By the time MTN-017 rolled around, the BRWG had already integrated many methods and tools into MTN clinical trials to better assess and understand adherence, such as audio computer-assisted interviewing as a way for participants to privately answer sensitive questions, and adherence biomarkers to get a sense of the level of drug in a participant’s blood. But new innovations were coming



*Iván Balán and Alex Carballo-Diéguez break into a dance at the 2018 HIV Research for Prevention meeting in Madrid, Spain.*

down the pike. Not without skeptics, who thought they might be too intrusive to be approved by the various institutional review boards, these new approaches incorporated into MTN-017 nonetheless set new standards for an ever-evolving field.

The approaches included daily questions about product use sent to participants by text message, referred to as short-message survey (SMS), and real-time adherence reporting in which MTN-017 researchers regularly tested participants’ blood to assess the presence of drug – a determinant of whether they were using their assigned study products. Staff then shared these results with participants as part of their adherence

counseling sessions to clarify discrepancies among the differing adherence measures. The idea was not to confront the participant, but to use a tailored approach to counseling and create an environment in which they felt as though they could speak openly.

Many of these same methods were used in other MTN protocols, including HOPE – HIV Open Label Prevention Extension – an open-label follow-on trial to the ASPIRE – A Study to Prevent Infection with a Ring for Extended Use – trial of the dapivirine vaginal ring. In HOPE, former ASPIRE participants were offered the opportunity to use the dapivirine vaginal ring. They were welcome to accept or reject the ring, to change their minds at any time, and to enroll into the study even if they had no intentions or interest in using the ring. HOPE investigators wanted women to feel empowered to make their own choices, and to be open about the reasons they may or may not want to use the ring.

ASPIRE, HOPE and other studies involving the dapivirine vaginal ring, which the World Health Organization recommended as an additional HIV prevention method for cisgender women in early 2021, have also shown that product dosages and delivery forms matter to participants. “When we started evaluating the dapivirine vaginal ring within the MTN, we heard from participants that a monthly dosage was much more favored than daily dosing,” says Ariane, behavioral lead for ASPIRE and HOPE. “It gave women ‘peace of mind’ as a discreet product that they could insert and then forget about.”

*“You can’t just tell someone to take a pill in the morning by sticking it in a piece of bread. If you ask them, you might find out they don’t even eat breakfast.”*





*Ariane van der Staten listens intently to a panelist at the 2018 MTN Annual Meeting in North Bethesda, Maryland.*

“I think we’ve learned that behavior is not something to overcome with biomedical products,” sums up Iván, the counseling lead on the HOPE study. “We now fully see that participants are actors – they can proactively engage in a clinical trial or they can resist. We’re no longer in that place of ‘Here’s a product, take it, we know it’s good for you, take it.’”

Indeed, through a decade and a half of hard work, creativity and advocacy, MTN – under the auspices of the BRWG – is leaving behind a legacy of critical insights for the HIV prevention field. These behavioral-centered contributions include publication of more than 75 (and counting!) peer-reviewed scientific articles, close to 100 conference posters and presentations, and incorporation of behavioral and social science research into the lion’s share of MTN’s 40-plus protocols. And, perhaps most importantly, affirmation that it is possible

to integrate behavioral research into biomedical science in a manner that genuinely engages and values study participants.

*“We have embraced the idea that behavior is not just a little thing that happens on the side, it’s fundamental and central to any biomedical intervention.”*

“The MTN has been a true trailblazer in recognizing the role of behavioral research by setting-up a nice working family with the BRWG,” says Ngunjiri. “It’s been an incredible experience and we’ve been able to accomplish a great deal of work.”

“VOICE really transformed the MTN and also the field of HIV prevention by showing that we had to be much more user and participant centric,” concurs Ariane. “We have embraced the idea that behavior is not just a little thing that happens on the side, it’s fundamental and central to any biomedical intervention.”

- Clare Collins

Photos: Lisa Rossi (unless otherwise noted)

A catalyst for social and behavioral research, the MTN BRWG has developed a comprehensive compendium, [MTN Behavioral Research Working Group: Progress & Insights 2006-2020](#), outlining their vast accomplishments and lessons learned.

“A Look Back ...” is an occasional series to honor the communities, researchers, staff and study participants who have made countless and meaningful contributions to the work of the MTN since 2006.