

A look back ...

The Pleasure Principle: AN EVOLUTION IN RECTAL MICROBICIDE RESEARCH



*Love me, hey yeah, love me yeah.
It's the pleasure principle.*
-From the Janet Jackson song,
[The Pleasure Principle](#)

Pop star Janet Jackson cooed about it in the 1980s. Sigmund Freud wrote about it much earlier as a driving force within our personalities. Pleasure, undeniably, has long played an essential role in our lives.

Yet, in the field of HIV prevention, there has been a reluctance to talk openly about pleasure and sex. For most of the past 40 years, our efforts focused on the prevention of HIV (a virus that is predominantly transmitted sexually) have largely dismissed the role of pleasure, or the act of sex itself. Especially in the context of anal sex.

Little to no consideration has been given to what people who engage in anal sex want or even desire in an HIV prevention product. It's been generally assumed that if a product is safe and protects against HIV, then surely people will use it.

This is troublesome and wrong-headed, says Jim Pickett, senior director of prevention advocacy and gay men's health at AIDS Foundation Chicago. "Sexual health is not just about avoiding disease, the same way pleasure is not some dirty word or a crime," he asserts. "As someone living with HIV, I have always been more animated by prevention because it's so fraught with shame, stigma and sex—all the things people don't want to talk about."

Jim began pondering these concepts in the late 1990s and early 2000s, but it wasn't until much later that the importance of pleasure would be considered as a key issue in the HIV prevention research agenda.

Around 2003, Jim began hearing about researchers who were exploring the feasibility of developing and testing a lubricant-like product for HIV prevention from anal sex. It was the first he learned of a product called a rectal microbicide that was intended to provide a non-systemic, or localized, option for the prevention of HIV from anal sex which researchers hoped could help address the especially high rates of HIV among people engaging in anal sex.

Vaginal microbicides, in the form of gels, were already in clinical trials at the time—a rectal microbicide was only a concept then, but a movement was beginning to take shape.

In 2005, the National Institute of Allergy and Infectious Diseases (NIAID) decided it would establish a research network focused specifically on the development and evaluation of microbicides—both vaginal and rectal—and the following year, the Microbicide Trials Network (MTN) came to be.

The fact that rectal microbicides would share equal billing with vaginal products was a significant development, and the MTN would in the ensuing years contribute substantially to our understanding of pharmacokinetics

(the way drugs are absorbed, distributed and removed by the body), pharmacodynamics (what drugs do in the body), and the safety and acceptability of rectal products.

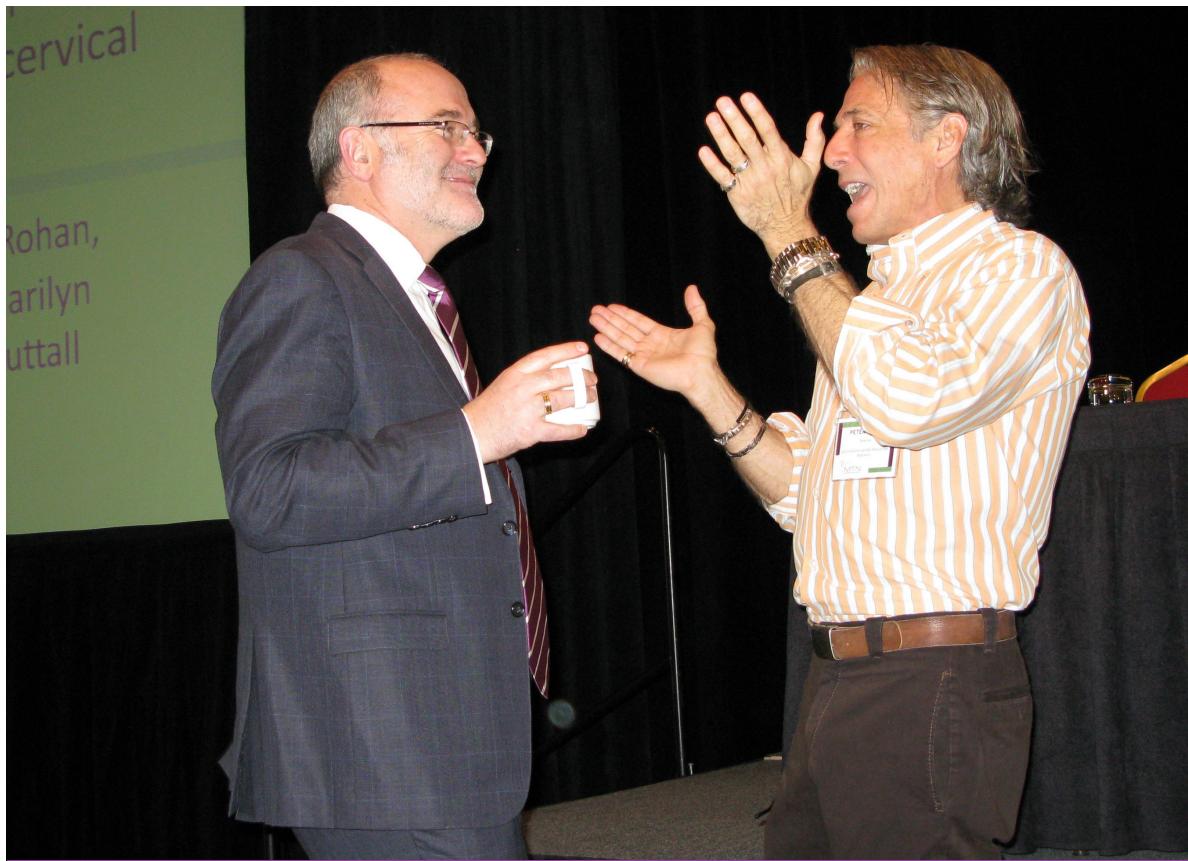
Perhaps even more notably, the discourse about anal sex in the context of HIV prevention would change from one that was both impersonal and stigmatizing to one of acceptance and genuine concern for ensuring the safety and well-being of those who chose to engage (and seek pleasure) in anal sex.

The gut of the problem

When Peter Anton, M.D., began attending national HIV conferences in the late 1990s, people wondered why he—a gastroenterologist—was there, he recalls.

"When I first started working in HIV, people weren't really thinking about the gut," says Peter, professor of digestive diseases at the David Geffen School of Medicine at University of California Los Angeles (UCLA). "They didn't recognize its mucosa [lining] as particularly vulnerable to HIV. Now, we simply don't conduct a big vaccine trial or any other trial without considering the mucosal compartment. It's very clear this is where the action is taking place."

Seventy to 80 percent of our immune cells are located in the gastrointestinal tract, which are shielded by a mucosa that's only a single-cell thick and can easily



Peter Anton (right) and Ian McGowan during MTN's 2012 Annual Meeting in North Bethesda, Maryland.



Alex Carballo-Diequez (left) with José Bauermeister, who in 2007 was a post-doctoral fellow at Columbia University working with Alex. It was then that the two began writing articles together about rectal microbicides and behaviors.

Photo courtesy of Alex Carballo-Diequez.

be torn, providing HIV, and other viruses, free access to billions of target cells to infect. This is an important reason why condomless anal sex is particularly vulnerable to HIV infection, explains Peter.

One of the first publications in this area of research was written by Ian McGowan, M.D., Ph.D., now chief medical officer of AELIX Therapeutics in Barcelona, Spain, who, with Sharon Hillier, Ph.D., was a principal investigator of the MTN from its start in 2006 until his departure in 2016. In the paper, Ian and colleagues documented the presence of HIV in the gastrointestinal tract among people with AIDS.

In the early 2000s, with funding available from the National Institutes of Health (NIH) to support multi-institutional programs focused on drug development, Ian, who had been recruited to UCLA, and Peter structured an ambitious program to develop drugs to prevent HIV through anal sex. As they moved from laboratory research to animal studies, it was very clear to both that should their work advance to clinical trials in humans, sexual practices and acceptability would be crucial. “We knew that while we were going to target the virus and protect the cells, we also had to be aware of—and not change—the behaviors behind the use,” says Peter.

Meanwhile, some 3,000 miles away, Alex Carballo-Diequez, Ph.D., a clinical psychologist and behavioral scientist at Columbia University’s HIV Center for Clinical and Behavioral Studies, began pondering whether microbicides—which had mainly been thought about in the context of vaginal use as products women could control themselves, as opposed to, say, the male condom—could also be applicable to anal sex for the receptive partner’s use. Their common interests soon became known to one another, and in 2005, Alex, Ian and Peter started talking in earnest.

“We started thinking about the idea that lubricants were being used for anal sex, and hypothetically, a rectal microbicide could have great acceptability,” explains Alex, now retired. Still, he admits, there were a lot of questions that needed to be answered. How much gel would be needed? Would the amount of gel needed for protection be acceptable? Would it even feel like a lube to those using it?

As they began delving into these questions, Peter recalls visiting various sex shops in West Hollywood curious to see how lubes were being packaged. “I remember noting that the packaging of lubes for women was clear, or light colored, with pink or blue. Whereas the ones for men were dark, with black packaging, even when it was the same lube. It underscored our awareness of issues related to acceptance for whatever product we ended up testing, and how companies marketed to specific populations.”

Don’t mess with sex

When Craig Hendrix, M.D., professor of medicine and pharmacology and molecular sciences at the Johns Hopkins University School of Medicine and current director of rectal microbicides research at the MTN, met Peter Anton for the first time, it was early 2001 at a meeting at the Centers for Disease Control and Prevention that was to be attended by someone else from Craig’s group.

At the time, Craig was working in HIV treatment and designing studies to look for so-called “pharmacologic sanctuaries”—places in the body where viruses hide from drugs in their pursuit. He had done a lot of work in the male genital tract to understand how these sanctuaries led to virus replication and transmission, and it seemed to be a useful way to understand drugs for prevention, too. The colon and female genital tract were complicated places that were understudied in terms of the application and absorption of medication.

“The biomedical hook for me in getting involved in microbicide research was looking for drugs in funny places and their distribution,” says Craig. “In order to do this, we really needed to focus on the nitty gritty of how sex happens.”

One of the ways they did this was by conducting focus groups (not your typical focus groups, mind you) where they had a metronome that clicked every so often and at different rates. The participants, who had their heads down or wore blindfolds, were asked to raise their hand when the metronome matched the rhythm of their usual rate of sex.

“Once I started thinking about rectal microbicide research, it just brought this to a whole new level,” admits Craig. “I had to think about anal sex, behaviorally and physically, in terms of forces, vectors, distribution of fluids and friction, and its impact on the distribution of a drug and the virus itself.”



One of many special sessions on the topic of rectal microbicides the MTN, IRMA and other partners convened over the years was this one, at AIDS 2016 in Durban, South Africa.

Research related to the development of vaginal microbicides was much further along, having been initially proposed in the late 1980s and early 1990s by reproductive health specialists and advocates who recognized the need for HIV prevention methods that cisgender women could control. These early products were meant to strengthen natural defenses in the vagina or create a barrier to protect target cells.

As the researchers started work on the development of a rectal microbicide gel, they started asking how, and if, a product developed for vaginal use could also be used in the rectum. They were keenly aware that any such product—wherever it was used—needed to be more than “tolerated.” It had to be something people would be eager to use, and it had to be safe.

“If you’re going to mess with sex by putting something in a sexual place, you gotta make sure it’s not messing with sex,” insists Craig. “We needed to know that if we were going to put something in a rectum or vagina, it was not going to change people’s experience of sex in one way or another.”

A napkin becomes a (rectal) blueprint

In 2005, while attending the 3rd International AIDS Society Conference on HIV Pathogenesis and Treatment in Rio de Janeiro, Brazil, the researchers met during a break to discuss the way forward. It was then that they mapped out a rough design for what would be the first rectal microbicide clinical study—on a napkin. The study was conducted at UCLA in 2007.

“It’s very exciting when you get together with people who have expertise and knowledge from different perspectives of a topic,” says Alex. “It is like a combustion that takes place. All of a sudden something happens, and everybody gets excited.”

There were many questions related to the first study that the group had to address. One of the main issues was the use of the applicator—developed for the vaginal microbicide studies, and not for use in the rectum.

Other questions were related to how much gel would be needed. “At the time, we knew little to nothing about how to give a drug rectally to prevent a rectally acquired infection,” says Craig.

While mulling these and other significant research questions, the group was also contending with some push back from others in the microbicide field who thought focusing on products for anal sex would detract from the need for a vaginal product specifically for cisgender women.

“What they failed to realize is that women have anal sex, too,” says Jim Pickett, who, also in 2005, had connected with other like-minded advocates and formed a group called the International Rectal Microbicides Working Group, which later became known as International Rectal Microbicide Advocates (IRMA). “People were concerned IRMA was making too much noise, but we connected with these main researchers—Ian, Peter and Alex—and brought them in as part of our project, so they felt good about what we were doing and we could to be supportive and in alliance.”

Jim was also very cognizant of framing rectal microbicides in a sex-positive manner. “Many times, in women’s prevention, talking about pleasure or intimacy



Could that be a napkin?

Craig Hendrix (right) and Alex Carballo-Diequez at the 2012 MTN Annual Meeting in North Bethesda, Maryland.



One of the plenary sessions at the 2020 Annual Meeting, which would be MTN's last, focused on MTN's rectal microbicide studies, including DESIRE. The session was co-moderated by Craig Hendrix (left) and Jim Pickett (to his right). José Bauermeister (far right) is seated next to Ken Ho, who was MTN-033 protocol co-chair.

almost seems verboten," says Jim. "This idea that women only have sex because their partners want them to, instead of making it about their sexual agency. With rectal microbicides, we knew it was important to infuse this message from the very beginning."

Less than a year after the Rio meeting, Ian and Sharon learned they had been awarded funding to lead the MTN. Its base of operations would be at the University of Pittsburgh and Magee-Womens Research Institute, where Ian later served as professor of medicine, and Sharon was, and remains, professor and vice chair of the department of obstetrics, gynecology and reproductive sciences.

The rectal road

The MTN has come a long way since the network conducted its first rectal microbicide clinical trial, a Phase I study of tenofovir gel in 2009 demonstrated a product could suppress HIV in rectal tissue, based

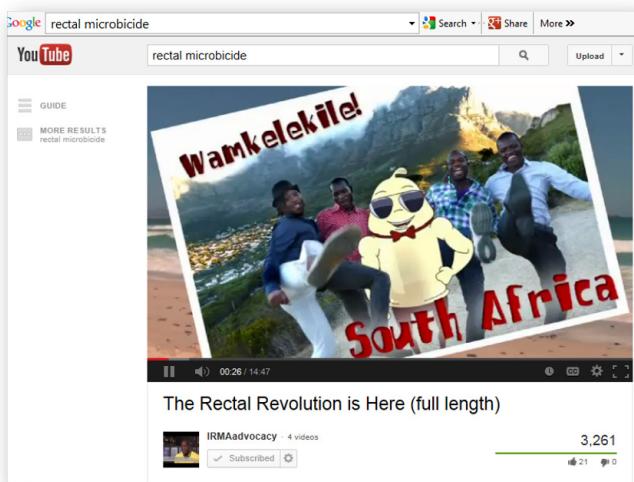
on laboratory studies of biopsies taken from HIV-negative study participants who had used the gel daily for one week.

The network also conducted the first (and to date, only) Phase II study of a rectal microbicide, comparing a reformulated tenofovir gel with Truvada as oral pre-exposure prophylaxis. The global study, MTN-017, found the gel was safe and that participants preferred to use it around the time of sex rather than on a daily basis. Another key finding: participants found the gel's applicator cumbersome and difficult to use, which would make additional studies based on the applicator pointless for a product not likely to be pursued for licensure.

Each subsequent MTN rectal microbicide study (eight in all) represented a progression built on data from the previous study by using different drugs—some that also protected against other sexually transmitted infections—and reformulating others so they were more “rectal-friendly.” The researchers also used advanced behavioral research techniques for understanding which delivery methods people who engage in anal sex would prefer, and took an intentional approach to including both cisgender and transgender men and women in their studies.

“We learned a great deal about four very different kinds of drugs—tenofovir, dapivirine, elvitegravir and PC-1005—and how much of each was needed to suppress HIV and other sexually transmitted infections in the rectum,” says Craig. “These studies taught us a lot about drugs not previously tested in the rectum as well as new delivery methods, providing a firm foundation for advancing products that are safe, effective and also fun to use.”

“Through each successive study, we learned that people need to want to use a particular kind of product,” adds José A. Bauermeister, Ph.D., M.P.H., professor of human relations at the University of Pennsylvania, who has worked with MTN’s behavioral team since 2007. “Early on, we started talking about viscosity [thickness and stickiness] of the gel and about the applicator. Did a vaginal applicator make sense, or did we need to develop a rectal applicator? And then we asked, ‘Do we need an applicator at all? Can we just give it like a lube?’ Then, ‘What if it wasn’t a gel? What if it was an insert or suppository?’”



*A screen shot from the video, *The Rectal Revolution is Here: An introduction to rectal microbicide clinical trials*, which IRMA, the MTN and Population Council produced in 2012. Although not tied to any one specific study, the video was developed for use during MTN-017, the first Phase 2 trial of a rectal microbicide, with versions in English, Spanish and Thai.*

Some of the most important work conducted in the area of safety of personal lubricants related to HIV transmission was led by **Charlene Dezzutti, Ph.D.**, who at the time of her passing in 2018, was associate professor of obstetrics, gynecology and reproductive sciences at the University of Pittsburgh School of Medicine and principal investigator of the MTN Network Laboratory. Charlene's research on the safety of personal lubricants and their effect on epithelial tissue—the layer of mucosal cells that acts as the body's first line of defense against sexually transmitted HIV—helped inform research on the development of a potential rectal microbicide gel. Her research demonstrated that lubricants with the potential to do the most damage to cell tissue were hyperosmolar—which means they contain more salts, carbohydrates and proteins than are typically found inside cells of the vagina or rectum. Charlene also led the work in reformulating tenofovir gel to make it more “rectal-friendly” in later rectal microbicide studies. She is forever missed for her impeccable science, unwavering devotion to HIV prevention and her endearing one-of-a-kind laugh.



Their questions eventually led researchers to design the DESIRE (MTN-035) study, which was conducted in Malawi, Peru, South Africa, Thailand, and the U.S. between 2018 and 2020. Led by José, DESIRE—Developing and Evaluating Short-acting Innovations for Rectal Use—gave

participants the opportunity to try 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. After “trying on”

each of the three placebo methods, study participants said they could see all of them fitting into their daily lives, underscoring the importance of developing a range of HIV prevention products for people who practice anal sex.

“Studies like DESIRE are very important because they give people options,” attests Maria del Rosario Leon, head of community engagement at the IMPACTA clinical trials unit in Lima, Peru, a DESIRE site. “Our participants loved that they were asked what they thought. When we are talking about LGBT+ community, they don’t necessarily have a lot of options, so it was important for us to hear their voices and how they’d like to have a product delivered as a rectal microbicide.”

Pongpun Saokhieo, who has worked with MTN for 12 years as a study coordinator at the Research Institute for Health Sciences in Chiang Mai, Thailand, agrees. “I strongly believe that actual sex practice is the most important part to consider when developing and testing HIV prevention methods.”

Lasting friendships and a way forward

As the MTN prepares to close its doors as a network at the end of November (ongoing studies will continue until completion), it seems fitting to reflect on all that has been accomplished these past 15 years.

“It’s really been a long and winding road,” attests Jeanna Piper, M.D., senior medical officer in the Division of AIDS (DAIDS) at NIAID, who came to the NIH in 2006 specifically to work with MTN. Despite her training as an

obstetrician-gynecologist, Jeanna served as the DAIDS medical officer on every rectal microbicide study conducted by the network, becoming a bona fide rectal warrior. “We have gone from ‘is this even possible’ to ‘desire is crucial for uptake,’ ” says Jeanna. “We’ve worked hard to understand which products fit into the lives and sexual practices of people in different circumstances across the globe.”

“We’ve spent many years doing this work and have made a tremendous amount of progress,” agrees Craig. “The larger HIV prevention community needs to be reminded of the critical importance of this work so it doesn’t disappear. We’re now handing the baton off to those that do the larger studies, and we want to make sure they do them.”

What touches Alex the most is remembering the relationships that were initially scientific and professional, but became close friendships. “It’s really the people that made this work so meaningful. It has been the best part.”

“This has been one of the most fulfilling projects of my life and career,” says Jim. “Our ability to engage such a huge swath of people helped us end up with a truly international group. We’ve learned that we don’t have to hate the other things to promote microbicides, and we didn’t have to dismiss anyone else to get our point across.”

Along with friendships and collaborations, what also needs to be emphasized is the passionate communities and study volunteers who enabled this work to flourish over many years. Their significant interest and investment truly enabled the research to move forward. By incorporating sex-positive approaches to HIV prevention and considering the “pleasure principle,” MTN was better able to understand what people need from HIV prevention.

“The personal part for me in all this work is knowing that you’re giving back and helping in a way that might have helped some of the people we have lost to HIV/AIDS,” agrees Peter, overcome with emotion. “It’s an additional layer to know that what I do each day matters.”

Indeed. And if you’ve been a part of the MTN family for any length of time, you are more than fortunate because you can likely say the same.

- Clare Collins

Photos: Lisa Rossi (unless otherwise noted)

This is the final story in MTN’s **“A Look Back ...”**, 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. You can find the complete set of stories [here](#).