

## AIDSTAR-One SPOTLIGHT ON PREVENTION

# Ready, Set, Rectal Microbicides: An Update on Rectal Microbicide Research and Advocacy

Jim Pickett

**Until recently, microbicide research has focused on vaginal microbicides. Recent initiatives and ongoing studies highlight the need for safe and effective rectal microbicides as part of an essential HIV prevention toolkit.**

Around the turn of the millennium, the microbicide field was almost solely focused on the research and development of vaginal microbicides, and community engagement and advocacy aligned with this priority. If scientists and advocates considered rectal microbicides (RMs) at all, it was strictly in the context of the need to test vaginal products for rectal safety, with the understanding that when a vaginal microbicide made it to market, it would likely be used in the rectum as well, or would migrate there during vaginal intercourse.

The realities of the HIV epidemic, though, point to anal intercourse (AI) as a practice that both men and women engage in, and as a significant factor in the spread of HIV and other sexually transmitted infections (STIs). The work of a growing number of scientists and advocates has brought us to the early days of a new consciousness some are calling “the rectal revolution,” where researchers are investigating the role of RMs and related products as essential elements of HIV prevention. This summary describes where we are in the rectal revolution, and where we need to go.

### Microbicides at a glance

Microbicides are compounds that are being developed or tested for the prevention or reduced transmission of HIV or other sexually transmitted infections. Over 20 products (gels, creams, films, or suppositories) for application in the vagina or rectum are in various stages of testing, although, so far, no proven microbicide is available commercially.

If proven effective, microbicides could help prevent HIV in women where the virus is mainly spread through unprotected heterosexual intercourse, and could also help prevent transmission in men and women who practice anal sex. An advantage of microbicides is that, unlike such strategies as condom use, monogamy, and abstinence, microbicides can be used independently of the sexual partner's consent.

*Sources: World Health Organization 2012; Microbicide Trials Network 2012a.*

## Why Develop a Rectal Microbicide?

Research identifies two fundamental reasons to research and develop RMs for HIV prevention:

- **AI is a normal human behavior:** AI is a part of the spectrum of human sexual behavior, and is practiced the world over by an estimated 5 to 10 percent of men, women, and transgender people<sup>1</sup> with both heterosexual and same-sex partners (Microbicide Trials Network 2012b; McGowan 2011).
- **AI is a factor in HIV infection:** An act of unprotected AI is 10 to 20 times more likely to result in HIV infection compared to an act of unprotected vaginal intercourse (Leynaert, Downs, and de Vincenzi 1998; Vittinghoff et al. 1999). This suggests that AI plays a significant role in the HIV pandemic.

Advocacy for RMs, to be delivered in gel or lubricant form, developed in the mid-2000s. An important player in the rectal revolution, the [International Rectal Microbicide Advocates](#) (IRMA) was founded in 2005 with colleagues representing the [AIDS Foundation of Chicago](#), the [Canadian AIDS Society](#), the Community HIV/AIDS Mobilization Project, and the [Global Campaign for Microbicides](#). No other advocacy group existed—or currently exists—whose focus is on RM research and development. Many scientists and advocates agreed that, for labeling purposes, it was important to know, at the very least, whether or not a

***Anal intercourse is not a behavior exclusive to gay men and other men who have sex with men, but is a part of human sexual behavior, and is practiced the world over by men, women, and transgender individuals.***

given product being tested for vaginal efficacy caused rectal harm.

Initially, the majority of the HIV/AIDS community—scientists and advocates alike—dismissed the possibility of developing an RM that was safe, effective, acceptable, and accessible for use during AI as an HIV prevention method. It was not considered feasible. The pursuit was seen as hopeless, even laughable.

Biological challenges played a role in the lack of enthusiasm for RM research. The vagina is essentially an enclosed pouch, whereas the rectum leads to about four to six feet of colon, which is a lot of territory for a microbicide product to cover. The

vaginal lining is approximately 40 cell layers thick, whereas the rectum's mucosa is only one cell layer thick and is replete with the cells that HIV targets. Protecting the vagina from HIV infection seemed feasible; protecting the rectum appeared significantly more difficult, maybe even impossible.

The political and sociocultural context reinforced the dismissal of RMs. Pervasive

homophobia across the globe has resulted in a lack of adequate attention and resources devoted to gay men and other men who have sex with men (MSM)<sup>2</sup> despite the disproportional HIV burden borne by this population (amfAR and Johns Hopkins Bloomberg School of Public Health 2012). Few knew, or acknowledged, that AI is a widespread practice among heterosexuals, both men and women, gay men and other MSM, as well as transgender people. Thus,

<sup>1</sup> Literally meaning, "differently gendered," transgender is an umbrella term referring to people whose physical body does not align with their gender identity. Transgender does not imply any specific form of sexual orientation—transgender people may identify as heterosexual, homosexual, bisexual, pansexual, polysexual, or asexual.

<sup>2</sup> MSM is a shorthand term denoting HIV risk used broadly to describe gay men, bisexual men, and other men who have sex with men who may identify as "straight." This article uses "gay men and other MSM" in an acknowledgment that many men in the global north and global south claim gay identities, and that "MSM" on its own is not an accurate or complete way to describe such people.

evidence-free assumptions relegated the rectal portion of the microbicide field to a small, dark corner.

Despite this array of challenges, including only a small fraction of total microbicide funding specifically directed to RM research and development, the field has moved from simply being an adjunct to vaginal studies to a force in its own right. This is due to a handful of visionary, passionate, and dogged scientists; funding from the United States (which has supported at least 97 percent of RM research); and growing community engagement (IRMA 2010a). The small group that gave birth to IRMA is now more than 1,200 strong and consists of advocates, scientists, policymakers, and funders from over 100 countries. The RM community is working to advance research and the development of safe, effective, acceptable, and accessible RMs for all humans who engage in AI and need protective options beyond male and female condoms.

### Rectal Microbicide Studies

Although homophobia and the denial of heterosexual AI remain challenging, the science on RM has flourished and trials of RM products have begun. The following Phase I trials have provided important information about the products examined, and an upcoming Phase II trial represents a major step forward in RM research.

**UC-781 trial:** Scientists working on the University of California, Los Angeles (UCLA's) [Microbicide Development Program](#) initiated the first Phase I RM safety trial, investigating the safety and acceptability of UC-781, in December 2006. Rectal application of UC-781 gel, a potent antiretroviral (ARV) drug, was shown to be safe and acceptable to the 36 men and women in the trial. Phase I trials normally focus solely on safety and acceptability, but researchers used a novel approach in this trial: taking rectal tissue biopsies from participants and exposing them to HIV ex vivo in the laboratory. The drug significantly reduced HIV transmission in these assays (Anton et al. 2011).

The innovative use of the ex vivo challenge in this study provided an efficacy signal as well as data on safety and acceptability. Drug development is time intensive and expensive. An assay that is able to discern an efficacy signal, or the lack of one, early in the clinical development of a microbicide candidate is an important contribution to the field, and something to seriously consider when deciding whether to advance a drug in the development pipeline or to shelve it.

Unfortunately, UC-781's sponsor, [CONRAD](#),<sup>3</sup> has shelved this candidate microbicide. CONRAD chose to concentrate its microbicide development efforts on tenofovir gel, which became the focus of both vaginal and RM research and development. No work on UC-781 has taken place since this trial.

**RMP-02/MTN-006** tested the same vaginal formulation of tenofovir gel that reduced HIV acquisition by an estimated 39 percent overall in the CAPRISA (Centre for the AIDS Programme of Research) 004 trial that was conducted in South Africa (Karim et al. 2010). In September 2009, 18 men and women began enrolling in the trial, which was sponsored by the Microbicide Trials Network (MTN) and UCLA's Microbicide Development Program. The study tested the safety and acceptability of single- and multiple-day rectal applications of tenofovir, a single oral dose of tenofovir, and a placebo.

Laboratory tests showed that HIV was significantly inhibited in rectal tissue samples from participants who applied tenofovir gel to their rectums daily for one week compared to tissue from those who used a placebo gel. Although a slight anti-HIV effect was noted in tissue from participants who applied a single dose of tenofovir gel, the finding was not statistically significant. The single dose of oral tenofovir did not provide any protection against HIV in rectal tissue samples. The study also discovered that only 25 percent of the participants liked tenofovir gel, compared to 50 percent

<sup>3</sup> CONRAD is a leading organization in contraceptive development established by a cooperative agreement between Eastern Virginia Medical School and the U.S. Agency for International Development.

who had used the placebo gel. Some individuals who used tenofovir gel experienced gastrointestinal distress, cramps, and diarrhea. [Results](#) were presented at the 18th Conference on Retroviruses and Opportunistic Infections, or CROI (Anton and McGowan 2011).

RMP-02/MTN-006 provided two important messages. First, daily rectal applications of the vaginal formulation of tenofovir gel showed significant activity against HIV in rectal tissue samples tested in the laboratory—more than with a single rectal application of the gel or a single dose of oral tenofovir. Second, rectal application was not entirely acceptable, nor was it entirely safe. Any RM that causes diarrhea in the real world is a nonstarter.

**MTN-007** studied a reformulated version of the tenofovir gel. Researchers retained the same concentration of tenofovir (one percent), but reduced the glycerin in the gel in an attempt to make it more acceptable and “rectal friendly.” This Phase I safety and acceptability study, launched in October 2011, included 65 men and women from three sites in the United States. [Results](#) were presented at the 19th CROI in March 2012 (McGowan et al. 2012). This reduced glycerin formulation of 1 percent tenofovir gel was found to be safe and acceptable. Researchers recommended advancing this candidate to Phase II.

**MTN-017**, the follow-up to MTN-007, represents a major milestone: the first Phase II expanded safety and acceptability study of an RM. The trial will begin later in 2012 in three sites in the United States. Sites in Thailand, Peru, and South Africa will follow in early 2013. The 186 gay men, other MSM, and transgender women who will be recruited into MTN-017 will more than double the total number of human beings who have participated in RM clinical trials to date. Also, the trial is the first to include participants from countries outside of the United States.

The study will investigate the safety and acceptability of the reduced glycerin tenofovir gel, and will directly compare acceptability and adherence to daily oral Truvada. MTN-017 features an open-label, crossover

design in which each individual will follow three different regimens, each lasting eight weeks. One regimen will consist of the participant applying the gel to the rectum daily. A second regimen will ask participants to apply the gel rectally before and after AI. In the third regimen, participants will take oral Truvada every day. The order in which participants will follow the study regimens will be assigned randomly, with a break between each regimen.

The procedures carried out as part of MTN-017 will determine how much of each drug is absorbed in blood, rectal fluid, and tissue, and will also assess any changes in cells or tissue. Study participants will be asked about any side effects, what they like and dislike about using the gel either daily or with sex, and whether they would consider using the gel in the future. Gel acceptability and adherence will be directly compared to oral Truvada, which has been shown to reduce the risk of HIV acquisition in a number of studies among different populations (Grant et al. 2010; Baeten et al. 2012).<sup>4</sup>

Results from MTN-017 could lead to another first—the launch of a large-scale, Phase IIb/III efficacy trial of an RM, feasibly in 2015.

### **Meanwhile, other fascinating work is underway:**

- The [Combination HIV Antiretroviral Rectal Microbicide Program](#) (CHARM) was funded by the [U.S. National Institutes of Health](#) in 2009 as an \$11 million five-year grant intended to advance candidate microbicides from discovery into early clinical development. Rather than simply testing existing vaginal formulations, CHARM will develop rectal-

<sup>4</sup> On July 16, 2012, the [U.S. Food and Drug Administration approved Truvada](#) for pre-exposure prophylaxis in combination with safer sex practices to reduce the risk of sexually acquired HIV-infection in adults at high risk. Soon after, the South African HIV Clinician's Society published guidelines for the use of pre-exposure prophylaxis among gay men and other MSM in the [Southern African Journal of HIV Medicine](#), and on July 20 the [World Health Organization issued its first guidance](#) to countries that are considering offering pre-exposure prophylaxis for HIV-negative people at high risk.

specific products from the beginning. A purely rectal formulation of tenofovir gel (which is different from the reduced glycerin formulation discussed earlier) has been developed already, and other ARV drugs such as maraviroc are being considered for development.

- [Project GEL](#) is a federally funded RM acceptability study led by Drs. Ian McGowan and Alex Carballo-Diéguez with a safety testing component that is currently recruiting young gay men and other MSM who are at high risk for HIV acquisition.
- Scientists at the [Population Council](#) are trying to develop a microbicide that would be both safe and effective in either the vagina or the rectum. They have conducted early work on a combination product containing MIV-150 (an investigational ARV), zinc acetate, and carrageenan gel. Further evaluation of this combination is dependent on funding.

Many scientists and advocates share the desire to develop microbicides that are both ARV-based and non ARV-based. People living with HIV should be able to have a microbicide option at their disposal, and ARV-based options are not appropriate for this population for a couple of reasons. One, they may already be taking ARVs for treatment and an ARV-based microbicide could interfere with their therapy. Secondly, if HIV-positive people are not on ARV treatment and they use an ARV-based microbicide that contains only one or two drugs, the virus could become resistant in what would essentially be a condition of suboptimal therapy. Treatment guidelines call for a combination of three drugs to properly treat HIV and keep the virus from replicating.

At the moment, the microbicide field is almost singularly focused on ARV-based products. Other agents are being considered, but are very early in the pipeline. It is important to note that ARV-based microbicides will not be protective against a host of other STIs. In an ideal future scenario, microbicides will act broadly against a number of pathogens, and vaginal microbicides with contraceptive qualities will also be available.

**Related research:** Research on the feasibility and effectiveness of RMs comprises just one element of the rectal revolution. This brief summary does not include the vital work underway characterizing AI in every part of the world, or efforts to improve anal health that go beyond simply preventing HIV. Nor does it include exciting formulation and delivery research—for example, the possibility of delivering RMs as a lubricant by means of a specially designed applicator, or via a film, similar to currently available breath strip products that are placed on the tongue, dissolve quickly, and freshen breath. Rectal microbicides that would be long acting and less adherence dependent are also being contemplated.

### Additional Concerns

**Lubricant safety:** IRMA has prioritized the issue of lubricant safety for several years. Many men and women use sexual lubricants during AI, yet we know very little about the relative safety of these lubricants. We can be assured that RMs, once developed, will be safe to use. But there are hundreds of sexual lubricants on the market that have not gone through the rigorous safety evaluations that any candidate microbicide must undergo. Sexual lubricants used for intercourse, anal or vaginal, have not been tested for safety in humans. A number of studies (in the lab and in humans) have revealed that some lubricants cause cell inflammation and damage, and another study identified an association between lubricant use and transmission of rectal STIs (IRMA 2010a).

It is unclear what laboratory tests should be used to assess lubricant safety. Even when a study shows that a lubricant causes damage in the laboratory, we don't know how that finding transfers to the real world. We don't know to what extent—if any—using such a lubricant might lead to a higher risk of acquiring HIV or other STIs. Based on current evidence, we do know that lubricants with higher osmolarity (a measure of the concentration of soluble components—or solutes—present in a solution) are associated with higher levels of inflammation and cell damage.

We need to determine whether lubricants used rectally increase, decrease, or have no impact on the risk of acquiring HIV and/or rectal STIs. Even when RMs that have been shown to be safe and effective and are widely available, potentially in the next decade, they will still be competing with hundreds of other lubricants that will remain on the market.

Another concern is lubricant availability; for many men and women around the world, sexual lubricants are not accessible in the first place. Although the science hasn't been able to tell us much about lubricant safety yet, we do know that condom-compatible lubricants facilitate condom use during AI, and that they help prevent condom breakage. Condom-compatible lubricants should be part of any HIV prevention campaign or program that distributes condoms, especially to individuals who engage in AI. Sadly, on a global level, this is the exception, not the rule. This must change.

IRMA's new Global Lube Access Mobilization, or GLAM, campaign is focused on increasing access to condom-compatible lubricants in Africa, where the lack of availability is especially acute. This is noted as one of seven priorities developed by African advocates, scientists, and allies through IRMA's [Project ARM](#) (Africa for Rectal Microbicides), and described in the new report [On the Map: Ensuring Africa's Place in Rectal Microbicide Research and Advocacy](#) (IRMA 2012).

**Tracking RM funding:** Another priority for IRMA is documenting the funding provided specifically for RM research, and forecasting the level of resources that will be needed to advance the pipeline. IRMA last completed a resource tracking and forecasting exercise in 2010, publishing the results in a report titled [From Promise to Product: Advancing Rectal Microbicide Research and Advocacy](#) (IRMA 2010b). In consultation with leading researchers, IRMA conservatively calculated approximate annual funding needs from 2011 to 2020. The group called for an increase over then current funding (approximately \$7.2 million in 2010) to \$10 million annually between 2011 and 2014. They identified the need for a further increase to \$44 million per

year beginning in 2015 through 2020 to ensure that a minimum of two candidates reach late-stage testing. These numbers must be revised significantly upward in light of new evidence (such as the efficacy of pre-exposure prophylaxis among gay men and other MSM, as well as heterosexual serodiscordant couples) that will radically change, and complicate, trial designs (Grant et al. 2010; Baeten et al. 2012).

To put these numbers in context, of the total global investment in microbicide research and development (\$247 million in 2010), three percent was spent on RM research (HIV Vaccines & Microbicides Resource Tracking Working Group 2011).

There is concern that the needed increase in funding support for RM research and development will be hard to find in the current economic climate. But scientists and advocates have fought the odds on RMs from the beginning, and this is another challenge that can be overcome. Our prevention toolbox needs RMs to supplement current and future prevention strategies. RMs will undoubtedly play an important role in "draining the swamp" that is HIV.

Yes, the rectal revolution is here, but we still have a long and winding road, complete with twists, turns, and enormous hills to traverse before the promise of RMs is truly realized. We must deliver on that promise.

### About the Author

A gay man living with HIV since 1995, Jim Pickett is Director of Prevention Advocacy and Gay Men's Health at the AIDS Foundation of Chicago. He is Chair of the International Rectal Microbicide Advocates, a network of more than 1,200 advocates, scientists, policymakers, and funders, and he leads a multinational project concerning ARV-based prevention called Mapping Pathways. In 2010 and 2011, POZ magazine honored him as one of 100 U.S.-based "people, things and ideas that reinvent—and improve—how we tackle HIV" who are "making big splashes right now." In 2005, he was inducted into Chicago's Gay and Lesbian Hall of Fame by Mayor Richard M. Daley. He has also run four marathons

to raise money for HIV/AIDS prevention and care programs.

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