5 From Promise to Product: Advancing Rectal Microbicide Research and Advocacy

Summary

Ten goals to move the rectal microbicide (RM) field forward over the next two years:

1. **Increase activity in all areas of RM research (basic, pre-clinical, clinical, socio-behavioural).**
2. **Create a Global RM Development Plan.**
3. **Recruit more researchers to the RM field.**
4. **Determine the safety of lubricants for rectal use.**
5. **Generate more funding for RM research.**
6. **Diversify sources of funding for RM research.**
7. **Frame the discussion of RMs and other HIV prevention options in the context of anal health.**
8. **Recognise anal intercourse as a driver of the HIV pandemic—among gay men and other men who have sex with men (MSM), and between women and men.**
9. **Address the burden of HIV among gay men and other MSM around the world.**
10. **Broaden the existing global network of RM advocates.**

Building on the solid foundation of its first five years, IRMA is set to help lead the way in moving the promise of a safe and effective rectal microbicide (RM) towards an actual product. To achieve this reality, IRMA has identified 10 key areas in which the RM field must progress significantly over the next two years. Many of these objectives are similar to the ones identified in IRMA's 2008 report *Less Silence, More Science: Advocacy to Make Rectal Microbicides a Reality*. As noted earlier, we have seen some success in advancing this agenda since 2008—but there is much more to do. Achieving these goals requires an increased urgency.

5.1 Increase activity in all areas of rectal microbicide research

Section 2 of this report gives a sense of the increasing volume and variety of ongoing RM research. Over a period of less than a decade, the RM field has evolved from barely registering on the radar, to being little more than an adjunct to vaginal microbicide development, to establishing itself as an integral part of the HIV prevention research agenda. There is consensus. Developing a rectal-specific product that is both safe and effective is no longer dismissed as impossible at worst, unlikely at best.

As notable an authority as Dr. Anthony S. Fauci, Director of the National Institute of Allergy and Infectious Diseases at the U.S. National Institutes of Health, highlighted the imperative for safe and effective RMs in a statement on National Women and Girls HIV/AIDS Awareness Day in March of 2009. He underscored the need for women to have new prevention options for AI as part of a comprehensive prevention package.

With recognition in the research and advocacy communities secured, it is time to move beyond the "cheerleading" phase of advocacy for RMs. To achieve viable products for people who engage in AI, the RM field requires a much greater breadth and depth of activity across the full spectrum of basic/pre-clinical, clinical, and socio-behavioural research. This includes work on rectal-specific microbicide formulations, applicators designed for rectal use, product acceptability and user preferences, rectal mucosal immunity, translational research, animal toxicology, pharmacokinetics and pharmacodynamics, clinical trials, and the establishment of safety markers and correlates of immunity.

It remains imperative that vaginal microbicides be tested for rectal safety, since they are likely to be used that way once they are made available. Accurate information must be provided to eventual vaginal microbicide users through appropriate product labelling and community education efforts.

Consensus Statement

In May of 2007, IRMA forged a consensus statement on rectal safety of vaginal microbicides, in collaboration with the African Microbicides Advocacy Group (AMAG), the Global Campaign for Microbicides (GCM), and the Alliance for Microbicide Development (AMD). It was agreed that:

- Trial sponsors should fund rectal safety trials alongside all efficacy trials of candidate vaginal microbicides.
- Donors should provide more resources for the field to conduct rectal safety trials.
- Regulatory agencies should provide guidance describing reasonable rectal safety data needed to approve vaginal microbicides.
- If available data show signs of rectal toxicity, IRMA, AMAG, GCM, and AMD do not recommend halting or delaying the introduction of a vaginal microbicide, due to the absolute urgency to make such a product available to women around the world. Instead, it is recommended that eventual users be informed that the vaginal microbicide is not meant to be used rectally and that available data show signs of rectal toxicity. Product labelling and community education efforts in this situation should emphasise that using such a product may cause harm to the rectal mucosa and may increase the risks of HIV transmission if used while engaging in unprotected anal intercourse (AI).
- If no data are available, the group does not recommend halting or delaying the introduction of the vaginal microbicide and instead recommends that eventual users be informed that the vaginal microbicide in question is not meant to be used rectally, has not been proven to be effective when used rectally, and that there are no data on rectal safety for the specific product. The group calls on the field to work diligently to avoid such a situation, since gathering rectal safety data should pose no delays to efficacy trials. Short safety trials can be conducted parallel to efficacy trials.

Currently the U.S. Food and Drug Administration does not require rectal safety data on vaginal microbicides to be licensed.

Rectal microbicides must be safe, effective, acceptable, and accessible for use by all persons who engage in AI. However, most RM formulations currently under research are not appropriate for use by persons living with HIV. Current research into new prevention technologies, including microbicides, focusses largely on products that contain antiretroviral drugs (ARVs) used to treat persons living with HIV. Use of such products by HIV-positive individuals may generate drug-resistant strains of the virus in the user, limiting their treatment options. This is of special concern in the developing world, where multiple drug regimens are not yet a reality. Additionally, an ARV-containing microbicide would not be available over the counter, thereby reducing access to the product.

Research must be undertaken to develop both ARV-based and non-ARV-based products to meet the prevention needs of people living with HIV, those who are HIV-negative, as well as those who don't know their status. It is concerning that there are no non-ARV-based microbicide formulations in efficacy trials, and very few in early pre-clinical and clinical development at the moment.

5.2 Develop a Global Rectal Microbicide Development Plan

For a number of scientific, practical, and financial reasons, RM research has only recently entered the clinical research stage. Therefore, current research consists of small-scale safety studies, with an eye towards eventual efficacy trials. In 2008, the world's first Phase I rectal safety trial (testing a microbicide containing the ARV UC781) was completed successfully. In 2010 there is one more Phase I trial up and running (testing a microbicide containing the ARV tenofovir) and another pending, with a possible start date later in the year.

It is important for the field to prepare for late-stage (Phase IIb, III) clinical trials now. IRMA proposes the creation of a Global Rectal Microbicide Development Plan by which stakeholders would ascertain research priorities and coordinate efforts across a full range of scientific activities, from discovery through Phase III. In this era of limited resources and competing priorities, every dollar committed to RMs needs to be spent smartly and strategically. The global investments projection presented in Section 3 could provide a starting point for planning, implementation, and ongoing critical analysis of potential new products as they advance through the pipeline. Without a map that everyone is following, we're sure to get lost along the way. A Global Rectal Microbicide Development Plan, with ongoing input from every corner of the research and advocacy fields, is the way forward.

It goes without saying that the work of convening stakeholders and developing, implementing, monitoring, and adjusting such a plan requires dedicated resources and should be funded adequately. Advocacy efforts in general are underfunded, and this should change.

5.3 Recruit more researchers to the rectal microbicide field

To ensure progress in all relevant areas, a greater number of researchers from a variety of disciplines should be recruited. In 2010, all the principal investigators directly involved in RM research could fit comfortably in a small classroom, with the approximate number hovering around 10. Over the next few years, IRMA would like to see a much greater number of researchers join these efforts, from a variety of countries, institutions, and disciplines. Currently, those working on RM research reside primarily in the U.S. A full, multinational classroom is the goal.

5.4 Determine the safety of lubricants for rectal use

We know very little about the relative safety of lubricants men and women use during AI, as these products generally are not tested for rectal safety. Obtaining such data would be valuable for public health reasons. For example, this data could be used to promote use of lubes found to be safer, while discouraging use of lubes that are less safe. Therefore, IRMA continues to press for more information on the rectal safety of lubricants (see Section 4.4). As reported in Section 2.11 of this report, IRMA's efforts have contributed to advancing knowledge on this issue. While we await a safe and effective RM, we surely can help ensure that the existing lubes do not facilitate HIV transmission.

5.5 Generate more funding for rectal microbicide research

"If you are looking for a really good conversation topic, especially on a first date, get yourself involved in rectal microbicide studies. It is a quick and easy way to gauge one's comfort level in talking about anal sex and more importantly, research that may save the lives of others someday."

Scott Wilfong
Trial Participant
Baltimore, U.S.

In 2006, IRMA called for an increase in global funding for RM research. This did not come to pass. IRMA's most recent analysis (see Section 3 of this report for details) found that funding has remained flat since that time. U.S. $7.2 million will be spent globally on RM research in 2010.

IRMA has revised its assessment of funding needs for the next 10 years. To strengthen current research activities, and importantly, to increase the field's capacity for testing multiple agents and products, U.S. $10 million is required annually over the next four years (2011–2014), and U.S. $44 million is required annually over the subsequent six years (2015–2020). This would represent a 40% increase over current funding levels for 2011-2014, and a more than six-fold increase for the years 2015-2020.

IRMA and its partners should develop and implement advocacy strategies to generate more funding aligned with the priorities and needs of the anticipated Global Rectal Microbicide Development Plan, and researchers should apply for more RM-specific research funding.

5.6 Diversify sources of funding for rectal microbicide research

According to IRMA calculations, the U.S. public sector accounts for the largest proportion of all global RM funding. In fact, until 2010 the U.S. public sector contributed nearly 100% of global funding. While we are grateful for such strong, visionary U.S. support, relying so heavily on a single funding source is a great risk. Any shift in the budgeting priorities of the U.S. government could decimate or even eliminate most of the available RM research funds worldwide. To alleviate this risk, IRMA seeks to diversify the funding portfolio by advocating for contributions from foundations and from national governments outside of the U.S.

One of the potential sources of increased support is Europe. As described in Section 3 of this report, funding for RM research from European sources has been quite limited until recently. IRMA strongly urges European countries, institutions, and foundations that currently support general microbicide research to contribute additional funding specific to RM research.

Accordingly, IRMA calls on the governments of all high-income countries—whose national HIV epidemics are primarily driven by unprotected AI—to make their first contributions to funding RM research. Additionally, we call on the philanthropic and commercial sectors of these countries to follow the leadership of amfAR–The Foundation for AIDS Research, by providing much needed support for RM research efforts (see Section 3 for a description of amfAR's contributions.)

5.7 Frame rectal microbicides and other HIV prevention options in the context of anal health

IRMA will continue to advocate for AI to be recognised and directly addressed in responding to HIV and sexually transmitted infections (STIs). We recognise that anal sex is still taboo and criminalised in many countries, rendering RM advocacy and research challenging.

The future of anal sex must be discussed in the context of general anal health and anal sexual practices. Such a holistic approach requires a better understanding of the attitudes and beliefs surrounding AI, and the stigma, discrimination, and criminalisation that often are attached to this behaviour. It also requires RM research and development to take into account AI practices within various populations, the context within which AI occurs, user preferences and acceptability, behaviours that accompany AI (e.g. use of condoms, lubes, douches, and enemas), and common conditions such as haemorrhoids, inflammation, ulceration, and fissures that may impact RM efficacy and acceptability.

"We need to develop microbicides that will be effective no matter what kind of sex people have."

Sharon Hillier
University of Pittsburgh, Microbicide Trials Network
Pittsburgh, U.S.

There are important actions that can be taken immediately to support better anal health for people who engage in anal sex. These include screening and treatment for STIs and promoting universal access to water-based lubes, male and female condoms, and vaccines against some STIs. In particular, HPV vaccination should be offered to boys and men as well as girls and women, and people who engage in AI should be screened regularly for HPV and provided with appropriate treatment and follow-up.

Further research into prevention options and strategies for AI beyond male condoms remains a top priority. The goal should be prevention of both HIV and STIs. Science should evaluate the safety and effectiveness of all of the following: pre-exposure prophylaxis (PrEP), treatment as prevention, medical male circumcision and female condoms for AI; the use of lubes, douches, and enemas; sero-adaptive behaviours such as sero-sorting and sero-positioning; and other harm reduction approaches to unprotected AI.

5.8 Recognise anal intercourse as a driver of the pandemic—among gay men and other MSM, and between women and men

In the *Less Silence, More Science: Advocacy to Make Rectal Microbicides a Reality* report from 2008, IRMA called for greater attention to the role of AI as a driver of the pandemic, including AI between women and men. Unfortunately, there remains a remarkable, though perhaps not surprising, lack of attention to AI in a heterosexual context.

The facts remain largely the same then and now:

- Knowledge of the global incidence, prevalence, and context of AI remains inexcusably sparse.
- In absolute numbers, it is likely that many more heterosexual women (conservatively up to seven times more) practice receptive AI than gay men,[1] due to their greater numbers.
- Globally, almost all AI is unprotected.
- We must consider the possibility that unprotected AI, even when practiced rarely, may be a significant source of HIV transmission globally. The risk of HIV transmission through an act of unprotected AI is substantially higher than through an act of unprotected vaginal intercourse.[2, 3]

We have reported on the dearth of research conducted on AI between women and men, and on AI in the context of generalised HIV epidemics. We have called for greater attention to these issues and demanded more research in a number of key areas. This work remains to be done.

5.9 Address the burden of HIV among gay men and other MSM around the world

In its policy brief on *Reaching Men Who Have Sex with Men (MSM) in the Global HIV & AIDS Epidemic*, the Global Forum on MSM and HIV identifies "five key strategic areas where attention is needed in order to halt and begin to reverse the spread of HIV among MSM," namely:

- Increased investments in effective HIV prevention, care, treatment, and support programmes for MSM;
- Expanded coverage of quality HIV-related services for MSM;
- Increased knowledge and research on MSM and HIV;
- Decreased stigma, discrimination, and violence against MSM; and,
- Strengthened international, regional, sub-regional, and national networks of MSM[4].

IRMA also provides a suggested list in Section 1.5 of actions required to address the enormous, mostly neglected burden of HIV among gay men and other MSM around the world.

There is no time to waste.

5.10 Develop a global network of rectal microbicide advocates

IRMA will continue to provide multiple platforms for members to engage in advocacy and educational activities. We will continue to expand our membership to include a broader range of researchers, advocates, donors, and policy-makers from around the world. Beginning with a handful of individuals in 2005, the network currently includes over 850 people from more than 60 countries.

It's time to reach 1,000 and beyond. You can help.

IRMA members should urge partners and allies, including governments, international health agencies, funding bodies, and influential researchers and advocates, to support the quest for RMs proactively. Join IRMA's efforts and demand RMs for every person who needs them.

From promise to action to product—the measure of progress will be the development of safe, effective, acceptable, and accessible RMs, requiring the concerted efforts of advocates, researchers, policy makers, and funders from all parts of the world.

> *"Every day you may make progress. Every step may be fruitful. Yet there will stretch out before you an ever-lengthening, ever-ascending, ever-improving path. You know you will never get to the end of the journey. But this, so far from discouraging, only adds to the joy and glory of the climb."*
>
> —Winston Churchill