From Promise to Product: Advancing Rectal Microbicide Research and Advocacy

Pittsburgh May 2010
Letter from the chair

Optimism, reality, and the price of progress.

The challenges before us are as daunting as ever.

For instance, there is still massive denial that anal intercourse happens among heterosexuals. Consequently, an important driver in the global HIV epidemic remains invisible. This silence allows for people to entertain dangerous misconceptions from "anal intercourse is less risky than vaginal intercourse" to "you can’t get HIV from anal intercourse."

It is also increasingly clear that gay men and other men who have sex with men (MSM) in the West are not the only ones suffering high rates of HIV infection. Gay men in Africa and other regions of the developing world are also disproportionately impacted—and are more often than not completely ignored in national AIDS strategies. Consequently, very few of them receive any prevention or care services. Human rights abuses against these men are rising.

Many gay men and other MSM in these areas don’t even have decent access to water-based lubricants. How can we talk about rectal microbicides (RMs) in a context where men are using petroleum jelly, hand cream, butter, or motor oil as lubricants? Before RMs, we need water-based lubes—it sounds so simple, doesn’t it?

Speaking of lubricants, it’s concerning that regulatory authorities don’t generally require rectal safety testing of sexual lubricants before they end up in purses, on nightstands, and in some of our most sensitive areas. Consequently, it is unclear which products are safest to use.

Despite these concerns, and others we discuss in this report, there are reasons for optimism. We are, in fact, working to address everything I just mentioned. We’re not even close to getting to where we need to be, but we’re on our way, and that’s a good thing. Initial testing of lubricants for rectal safety has begun. And the RM field is maturing. We have one Phase I trial down, one in process, and one on tap. We’ve come a long way, baby.

At long last, the field has gone beyond simply testing vaginal products for rectal safety. We’re no longer an adjunct; what we’re talking about now is the efficacy of microbicides formulated specifically for rectal use. It’s breathtaking, considering that just a few years ago “efficacy” and “rectal microbicides” uttered in the same sentence would have been cause for a fair amount of collective eye rolling.

But discussing efficacy with a twinkle in our eyes is not enough; we need to start preparing for late-stage (Phase IIb, III) clinical trials now, beyond the escalation of funding that will be required. We need a Global Rectal Microbicide Development Plan—a map by which stakeholders can set priorities for research 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. IRMA is ideally situated to lead the creation of such a plan.

Because our global footprint is so large, and our advocacy network has become a global powerhouse, it may surprise people to know that IRMA is not an organisation with lots of staff and commensurate funding. In fact, it’s a project of the AIDS Foundation of Chicago, with a portion of one staff person—me. Without the in-kind efforts of our Steering Committee, other IRMA members, and allies, we couldn’t exist. We are grateful to AVAC—Global Advocacy for HIV Prevention, Broadway CARES/Equity Fights AIDS, and the Elton John AIDS Foundation for their ongoing support and guidance, but honestly, it’s not enough. If we are to continue uniting AIDS advocates, scientists, and policymakers around the globe in efforts to confront institutional and socio-cultural stigma, and denial; if we are to provide the necessary leadership to increase and diversify resources for RM research and development activities; if we are going to push for lubricant safety and keep shining a light on the role of anal intercourse in the pandemic, our work must be valued and supported.

Therefore, we call on the philanthropic community, including foundations and companies who support HIV/AIDS activities, LGBT health, and human rights, to follow the visionary leadership of our current funders and help sustain our ambitious agenda.

“For tomorrow belongs to the people who prepare for it today,” goes an African proverb. Help us lay the groundwork for a tomorrow, somewhere in the not-too-distant future, when safe, effective, and acceptable RMs are accessible to anyone who needs them.

Yes you can.

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1. Denial, neglect, stigma, and criminalisation: Notes on the global challenges to preventing HIV during anal sex

1.1 Code Red: HIV among gay men and other men who have sex with men (MSM)

1.2 Far and away: Universal access to comprehensive services for gay men and other MSM

1.3 First steps: The response to HIV among gay men and other MSM in developing countries

1.4 The D-List: The response to HIV among gay men and other MSM in high-income countries

1.5 Where do we go from here? The response to HIV among gay men and other MSM

1.6 Women and anal intercourse: An overlooked driver of the epidemic

1.7 En route to a safe, effective rectal microbicide: Maintaining anal health, preventing HIV and STIs

2. The state of rectal microbicide research

2.1 The Microbicide Development Program (MDP)

2.2 Combination HIV Antiretroviral Rectal Microbicide (CHARM) Program

2.3 Microbicide Safety and Acceptability in Young Men

2.4 Combined Highly-Active Antiretroviral Microbicides (CHAARM) Programme

2.5 RMP-02/MTN-006: Phase I rectal microbicide safety and acceptability trial of topically applied tenofovir compared with oral tablet

2.6 MTN-007: Phase I rectal safety and acceptability study of tenofovir gel

2.7 Biomedical, social, and behavioural research funded by amfAR

2.8 Aptamer Microbicide Development Program

2.9 Evaluating rectal safety and efficacy of microbicides in macaques

2.10 Assessing user preferences for rectal microbicide formulations: Gel vs. suppository

2.11 Assessing the rectal safety of sexual lubricants
3. Are current global investments in rectal microbicide research adequate to move from promise to product?

3.1 Methodology

3.2 Reminder: Results from IRMA’s previous resource tracking exercise in 2006

3.3 Investment in rectal microbicide research: Trends from 2007–2010

3.4 Estimated funding needs and resource gap for 2011–2020

4. IRMA’s world tour: Key activities 2008–2010

4.1 Building and maintaining a global network: IRMA’s cutting edge communications efforts

4.2 Spotlight on IRMA’s work at key international events

4.3 Act globally, think rectally

4.4 IRMA’s advocacy on the safety of lubricants used for anal sex

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

5.1 Increase activity in all areas of rectal microbicide research

5.2 Develop a Global Rectal Microbicide Development Plan

5.3 Recruit more researchers to the rectal microbicide field

5.4 Determine the safety of lubricants for rectal use

5.5 Generate more funding for rectal microbicide research

5.6 Diversify sources of funding for rectal microbicide research

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

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

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

5.10 Develop a global network of rectal microbicide advocates

Endnotes
Denial, neglect, stigma and criminalisation: Notes on the global challenges to preventing HIV during anal sex

Summary

- There is increasing recognition that gay men and other men who have sex with men (MSM) throughout the world—in developed and developing countries alike—have very high, disproportionate rates of HIV.

- Gay men and other MSM in developing countries remain largely under-represented and often completely invisible in national HIV and AIDS strategies, epidemiology, surveillance, and research; and they are woefully under-served by prevention, care, support, and treatment programmes.

- Anal sex between men and women is under-recognised, under-researched and under-characterised, resulting in a pressing need to address the attendant HIV prevention issues.

- While rectal microbicide research efforts continue, other viable options should be pursued aggressively to prevent transmission of HIV and other sexually transmitted infections through anal intercourse and to promote better anal health. For example: provision of male and female condoms, water-based lubricants, and human papillomavirus (HPV) vaccination.

1.1 Code Red: HIV among gay men and other men who have sex with men

Globally, it is estimated that gay men and other men who have sex with men (MSM)* are 19 times more likely to be living with HIV compared with the general population. In the AIDS 2008 Jonathan Mann Memorial Lecture on health and human rights, Saavedra, Izazea-Licea, and Beyrer stated:

“Gay, bisexual, and other MSM have been among the most affected populations by HIV since the AIDS pandemic was first identified in the 1980s. Evidence from a wide range of studies show that these men remain at the highest risk for HIV acquisition in both developed and developing countries, and that despite three decades of evidence of their vulnerability to HIV, they remain under-served and under-studied. Prevention strategies targeted to MSM are markedly under-funded in most countries, leading to limited access to health services including prevention, treatment, and care.”

*Some men who engage in sexual activity with other men identify as gay or bisexual, while others do not. Therefore, IRMA uses the phrase “gay men and other men who have sex with men (MSM).”
As the research and literature on the global HIV pandemic among gay men and other MSM finally expands, we are getting a clearer picture of the high rates of HIV among gay men and other MSM from all corners of the globe.\textsuperscript{3, 4} The evidence is compelling: gay men and other MSM are disproportionately affected by HIV. In many countries throughout Western Europe, North America, Latin America and the Caribbean, Southeast Asia, and sub-Saharan Africa, HIV prevalence rates among MSM are higher than among the general population of reproductive age adults.\textsuperscript{5, 6, 7, 8} This remains true even in countries with generalised epidemics, such as in sub-Saharan Africa.

HIV RATES AMONG GAY MEN AND OTHER MSM IN AFRICA\textsuperscript{9}

It is estimated that unprotected anal intercourse is 10 to 20 times more effective at transmitting HIV compared to unprotected vaginal intercourse.

One way to understand the relative burden of HIV between gay men and other MSM on one hand, and the general population of reproductive age on the other, is to look at the adjusted odds ratio. In other words: how much more likely are gay men and other MSM to be HIV-positive than reproductive age adults in the same countries? One systematic review of global literature from 2000–2006 showed that in Latin America, gay men and other MSM were 33 times more likely to be HIV-positive compared to reproductive age adults. In Asia, they were more than 18 times more likely, and in Africa, they were 3.8 times more likely to be HIV-positive compared to reproductive age adults.\textsuperscript{10, 11, 12} Similarly, in 2010 the U.S. Centers for Disease Control and Prevention (CDC) released an analysis of the relative burden of HIV among gay men and other MSM. It showed that in the U.S. they are 44 times more likely to be HIV-positive than other men, and 40 times more likely to be HIV-positive than women.\textsuperscript{13}

HIV AMONG GAY MEN AND OTHER MSM COMPARED TO REPRODUCTIVE AGE ADULTS; ADJUSTED ODDS RATIOS BY REGION\textsuperscript{14}

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<th>REGION</th>
<th>NUMBER OF COUNTRIES</th>
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Yet, as Saavedra, Izazea-Licea, and Beyrer have pointed out:

“Global responses have not been commensurate to these realities. MSM remain under-studied, under-served, under-funded and frequently ignored or denied by governments. We must ask why.”

It is unconscionable that nearly 30 years into the HIV pandemic, we are only beginning to have more robust data on the rates of HIV among gay men and other MSM in Africa and other parts of the developing world. As IRMA outlined in its 2008 report, many factors conspire to perpetuate this silence, including the ongoing criminalisation and stigma attached to same-sex behaviour and the resulting fact that gay men and other MSM remain hidden and ignored, languishing in the shadows of most public health interventions.

1.2 Far and away: Universal access to comprehensive services for gay men and other MSM

The Global HIV Prevention Working Group estimates that fewer than 10% of gay men and other MSM have access to appropriate behaviour change programmes to help reduce their risk of HIV infection.

In its 2008 special report *MSM, HIV and the Road to Universal Access—How Far Have We Come?*, amfAR, the Foundation for AIDS Research, found a discouraging discrepancy between the epidemiological data and the global response. Out of 128 countries reporting in 2008 on the progress they have made in implementing the 2001 Declaration of Commitment on HIV/AIDS:

- Almost half the countries reported no data whatsoever on HIV among gay men and other MSM for any of the five requested indicators: prevalence of HIV infection, rates of HIV testing, HIV knowledge, condom use, and access to prevention programming.
- 62% of countries reported no HIV seroprevalence data among gay men and other MSM.

"In other words, almost two-thirds of the countries surveyed appear to have no information on the extent of HIV/AIDS among their MSM residents," according to amfAR.

The HIV response in Africa has focussed largely on the dynamics of a "generalised epidemic," despite increasing evidence that there are specific groups at high risk for HIV, including gay men and other MSM. Even in a country like South Africa, where the HIV epidemic among gay men and other MSM preceded the generalised epidemic by several years, and where MSM are protected under the constitution and are included in the country’s national strategy, current policies and programmes are generally unresponsive to the needs of gay men and other MSM. An effective response requires that gay men and other MSM be included in surveillance, research, prevention, care, and treatment programmes. However, this is a considerable challenge in contexts where male-to-male sex is illegal, which is the case in 31 sub-Saharan African countries, including four countries where the death penalty is a possibility. Criminal, cultural, and religious barriers conspire to keep gay men and other MSM invisible.

"Like male and female condoms, male circumcision, prevention of mother to child transmission, and access to care and treatment, safe and effective vaginal microbicides, vaccines, PrEP, and rectal microbicides will be important tools in the prevention package we offer women and men at elevated risk.”

Kim Eva Dickson
World Health Organisation
Geneva, Switzerland
Gay men and other MSM, including HIV-positive gay men, face criminal prosecution and violence in many countries. Several horrifying examples in 2008–2010 include:

- The Ugandan Parliament began to review a bill that included severe sentences: men who engaged in homosexual behaviour more than once, as well as HIV-positive men who engaged in homosexual sex, could be sentenced to death.
- Political leaders in many countries, including Poland, Gambia, Jamaica, and Uganda, made homophobic remarks, calling for the arrest, detention, and even killing of homosexuals.
- AIDS activists in Senegal were sentenced to eight years in prison for “unnatural acts” and “belonging to a criminal association.”
- There were reports of gays in Iraq being tortured and killed by having their anuses glued shut and then force-fed diarrhea–inducing liquids.
- Inspired by religious leaders who were opposed to a gay wedding, a group of young people allegedly assaulted gay men in Kenya, calling for their death by fire.

The 2009 report *Ensuring Universal Access to Comprehensive HIV Services for MSM in Asia and the Pacific*, also by amfAR, recommends a significant increase in the range of HIV-related programming for gay men and other MSM in the developing countries in this region. As in many parts of the developing world, non-governmental organisations provide the bulk of current services, and have little support to do so. It is perhaps not surprising that HIV prevention programmes reach an alarmingly low proportion of gay men and other MSM in the region (an average of 2% in 11 countries in 2005).24 Accordingly, unless HIV prevention efforts improve, gay men and other MSM may soon account for the largest proportion of people living with HIV in Asia.25

### 1.3 First steps: The response to HIV among gay men and other MSM in developing countries

There are encouraging signs that issues concerning the rights and health needs of gay men and other MSM are starting to be recognised, studied, and addressed. However, much remains to be done.

At the 2006 International AIDS Conference (IAC) in Toronto, the Global Forum on MSM & HIV was created, drawing greater attention to the international crisis surrounding HIV and MSM. In 2008, *The Invisible Men: Gay Men and Other MSM in the Global HIV/AIDS Epidemic* was the theme of the Forum’s ground-breaking satellite meeting at the IAC in Mexico City. From the heads of the United Nations (UN), the Joint UN Programme on HIV/AIDS (UNAIDS), and the World Health Organisation (WHO), to prominent leaders from various sectors, there followed repeated calls for an acute concentration on the HIV-related needs of gay men and other MSM. In impassioned speeches, homophobia was denounced as one of the key obstacles to stopping the epidemic.
The sentiments continue to echo. Yet, however commendable, these words require tangible action.

The work on the ground is being waged by an increasing number of groups of gay men and other MSM in developing countries, and their allies. There are many examples of trailblazing organisations from all corners of the world providing HIV prevention care and support services to gay men and other MSM as they fight homophobia, violence, stigma, and discrimination in countries including Ghana, Ukraine, India, Sudan, Uganda, Nigeria, Laos, Nepal, and Peru.

In late 2009, the Global Fund to Fight AIDS, Tuberculosis and Malaria announced that it had approved, in principle, a landmark U.S. $47 million grant for a community-strengthening programme aimed at reducing the rapid and alarming spread of HIV and AIDS among gay men and other MSM and among transgender people in South Asia. The grant proposal was submitted by Naz Foundation International (NFI), PSI (Population Services International), the United Nations Development Programme Regional Center based in Colombo (UNDP/RCC), and the South Asian MSM and AIDS Network (SAMAN), a coalition of community-based organisations dedicated to MSM and HIV issues at the country level. The five-year project will encompass Afghanistan, Bangladesh, Bhutan, India, Nepal, Pakistan, and Sri Lanka. It is the first time the Global Fund will support a major regional project in Asia specifically addressing MSM, transgender people, and HIV.
1.4 The D-list: The inadequate response to HIV among gay men and other MSM in high-income countries

Gay men and other MSM in high-income countries have always accounted for a high proportion of HIV cases. In many high-income countries, the number of new infections among gay men and other MSM has been increasing for over a decade, along with rates of unprotected sex and sexually transmitted infections (STIs). This may be partly due to the fact that even in these settings, prevention programmes all too often fail to prioritise populations at high risk for HIV—including gay men and other MSM, transgender people, persons who inject drugs, sex workers, prisoners, and immigrants. “The level of resources directed towards focussed prevention programmes for these groups is typically quite low, even in concentrated epidemics,” according to UNAIDS.

One notable example of this comes from the U.S. As mentioned previously, the CDC estimated that gay men and other MSM in the U.S. are 40 to 44 times more likely to be HIV-positive than other men and women. Despite this fact, according to information provided by the CDC at the 2009 National HIV Prevention Conference, a much smaller proportion of funding for some HIV prevention programmes is specifically targeted to gay men and other MSM, compared to other populations. The CDC’s Department of HIV/AIDS Prevention provides funding annually to 59 health departments across the country (50 states, D.C., Puerto Rico, U.S. Virgin Islands, and six large cities). In 2007, only 29% of this department’s funding for health education/risk reduction programmes and 11% of funding for counselling, testing, and referral programmes was allocated to gay men and other MSM. This is despite the fact that gay men and other MSM represent over half (53%) of new infections in the U.S. While the programmes examined represent only a portion of U.S. funding for HIV prevention, they nonetheless provide a revealing, and sad, picture of priorities.

1.5 Where do we go from here? The response to HIV among gay men and other MSM

A report released by NAM in 2009, *Appropriate prevention and care services for men who have sex with men and transgender people in resource-limited settings*, provides a summary of the potential elements of a successful response to HIV, and is adapted here.

Strengthen the evidence base: One of the first steps required to respond to the epidemic in MSM is to improve the quality of the data used to inform and develop policy. For instance, MSM need to be included in regular HIV/AIDS surveillance; MSM-related questions should be included in population-based surveys; and the access of MSM to prevention and care should be monitored.

Prioritise the human rights environment: The UNAIDS Action Framework on Universal Access for Men who Have Sex with Men and for Transgender People emphasises that improving “the human rights situation for men who have sex with men... [is] the cornerstone to an effective response to HIV.” It recommends that “MSM... are appropriately addressed in national and local AIDS plans, that sufficient funding is budgeted for work, and that this work is planned and undertaken by suitably qualified and appropriate staff...”

Involve gay men and other MSM “in the planning, implementation, and review of HIV-related responses, including the support of nongovernmental and community-based organisations, including organisations of people living with HIV” as well as “training and sensitising health-care providers to avoid discriminating against, and ensure the provision of appropriate HIV-related services for, MSM...”

*“With the current trend of increased HIV incidence through anal sex, rectal microbicides need to be a priority as a prevention option, especially for marginalised MSM.”

Abdullrahman Orosanya
Mohammed-Saheed
IRMA-Nigeria Member
Lagos, Nigeria

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From Promise to Product: Advancing Rectal Microbicide Research and Advocacy 13
Ensure access to effective prevention, treatment, and comprehensive care: The UNAIDS framework recommends that all interventions should be evidence-informed, developed with, and protect the rights of, MSM and transgender people and should include safe access to:

- Information and education about HIV and other STIs, and support for safer sex and safer drug use, through appropriate services;
- Condoms and water-based lubricants;
- Confidential, voluntary HIV counselling and testing;
- Detection and management of STIs through the provision of clinical services;
- Referral systems for legal, welfare, and health services, and access to appropriate services;
- Safer drug-use commodities and services;
- Appropriate antiretroviral and related treatments, where necessary, together with HIV care and support;
- Prevention and treatment of viral hepatitis;
- Referrals between prevention, care, and treatment services; and
- Services that address the HIV-related risks and needs of the female sexual partners of MSM.

Advocates, researchers, policy makers, and donors have the basis on which to build an effective response due to:

- The increasing amount of research in the past two years dedicated to gay men and other MSM throughout the developing world;
- The emergence and development of local and national groups addressing the needs of gay men and other MSM in developing countries;
- The renewed attention paid to the HIV epidemic among gay men and other MSM in high-income countries; and,
- The burgeoning focus on these issues at regional and international conferences and in the work of multilateral agencies such as WHO and UNAIDS.

An effective response to HIV among gay men and other MSM must address the biomedical, social, and political factors that are unique to these groups. The stigmatisation, demonisation, and persecution faced by gay men and other MSM in many parts of the world cannot be ignored. Planning for the development and eventual roll-out of rectal microbicides (RMs) must take these realities into account. Otherwise, even safe, effective, acceptable, and accessible RMs will be of little utility to the millions of men who need them. To achieve the goals presented in this section, we must ensure that all stakeholders—advocates, funders, policy makers, and researchers—are held accountable for tangible progress over the coming years.

“Rectal microbicides are incredibly important, and need to be developed.”

Zeda Rosenberg
International Partnership for Microbicides
Silver Spring, U.S.
1.6 Women and anal intercourse: An overlooked driver of the epidemic

By Kathleen Morrow (Brown University, IRMA Steering Committee member, U.S.)

Unprotected receptive anal sex is a high-risk behaviour when it comes to HIV transmission. What many often underestimate is the impact receptive anal sex may play in male-to-female and female-to-male transmission of the virus. The assumption is that women acquire HIV from penile-vaginal sex. In fact surveillance data do not make the distinction between vaginal or anal transmission among women who become infected with HIV. As a result, prevention programmes have not adequately addressed the risk of anal transmission in women.

Depending on which study you read, 20–75% of women report that they have engaged in receptive anal sex. In absolute numbers, conservative estimates indicate that globally up to seven times more women engage in receptive anal sex than men. After all, women make up about half the population, while gay men and other MSM constitute a much smaller proportion.

While more studies have been published recently to support the need to know more about this phenomenon, there are still many questions to be thoroughly and comprehensively addressed:

- Are there differences in mechanisms of transmission between women and men who engage in receptive anal sex that warrant specific consideration?
- What is the prevalence of condom use for vaginal versus anal sex among women who engage in both behaviours? In other words, are women who have anal sex using condoms more often, less often, or with similar frequency when they engage in vaginal sex versus anal sex? Does engaging in receptive anal sex somehow make a woman more vulnerable to HIV infection? If so, what are the variables that moderate or mediate that effect?
- Do we know all we need to know about condoms and lube when it comes to anal sex? How does condom use (type of condom, e.g.) and/or lube use (type of lubricant, amount used, etc.) impact risk?
- What do we know about specific “routines” or “rituals” that are part of peoples’ anal sex practices and how do those practices impact risk? Do hygiene behaviours associated with anal sex mediate risk? Doucheing? Enemas? What about hair plucking or shaving around the anus? What about anal bleaching? We have theories about these practices, but little scientific evidence.
- What better information could prevention science provide that would help people make better choices about whether and how to engage in anal sex?
- What attitudes, beliefs, and motivations could be targeted to increase safer anal sex practices among women and/or their sexual partners?
- What behavioural skills do we need to teach—or prevention products do we need to make available—to women who engage in anal sex to increase safer anal sex practices?
- What are the contextual models of anal sex initiation that impact risk? That is, what do we know about how women first come to engage in anal sex that may impact their risk? Does a woman’s first anal sex act that is forced, coerced, or freely chosen impact her risk if she continues to engage in anal sex in the future?
• What about other anal sex contexts? How do the different sexual activities of women (and their partners) affect their levels of risk and which women are at greatest risk? How do we quantify and understand differences in risk as a function of sexual sequencing? How does commercial sex and the phenomenon that anal sex brings more money impact women’s risk? What about the continuing belief systems around preserving virginity by engaging in anal sex? What about the impact of beliefs regarding pain versus pleasure in sexual encounters, and power and control?

We need a full spectrum of scientific research to be undertaken to address the physical and behavioural factors of HIV transmission that are unique to women who engage in anal sex. The enquiry must begin with basic science to better understand transmission and infection in the female rectum and continue on toward the development of RMs that take women’s anal sex practices into account. We also must develop social and behavioural theory to devise intervention strategies for women and their partners that clearly and distinctly address the risks associated with anal sex.

Further Reading:

1.7 En route to a safe, effective rectal microbicide: Maintaining anal health, preventing HIV and STIs

While RM research efforts continue, other potentially viable options should be pursued aggressively to prevent transmission of HIV and other STIs through anal intercourse (AI) and to promote better anal health. However, it is often confusing when trying to determine what we know—and what we don’t know—about various prevention strategies, how they relate to anal sex, and the extent to which they are readily available. Are female condoms appropriate for anal sex? Does medical male circumcision reduce the risk of acquiring or transmitting HIV through AI? Can men benefit from vaccines against human papillomavirus (HPV)? Are water-based lubricants available? How are these tools made accessible?

“In the evaluation of the first generation of vaginal microbicides, we may have underestimated the impact of HIV infections acquired from anal intercourse, which may have led to a substantial level of efficacy dilution. Although this certainly needs to be addressed in future vaginal microbicide trial designs, it also indicates the urgent need for a rectal microbicide in our goal of preventing the spread of HIV among women and men.”

Benoit Masse
Statistical Center for HIV/AIDS Research Seattle, U.S.
1.7.1 Anal health

By Ross Cranston (University of Pittsburgh, IRMA Steering Committee member, U.S.)

As the RM development agenda moves forward, it would be a failure in the field of preventative sexual health to ignore the spectrum of disease that may present in the anal canal. Receptive AI is associated with an increased risk of anal fissure, fistula, ulceration, and abscess, in addition to STIs that are specific to the anal canal, such as herpes simplex virus and HPV. These inflammatory conditions already have been associated with an increased risk of HIV infection. All of these conditions have an impact on sexual function and quality of life, though they are mostly transient. They may also influence the use of a RM.

HPV infection is strongly linked to the development of cervical cancer. There has been considerable success with a cervical cancer prevention programme that includes screening women using Pap smears with follow-up colposcopy—a medical procedure that provides an illuminated magnified view of the cervix—if warranted by the severity of the Pap diagnosis. The cervix and anal canal are biologically similar, and HPV infection is also linked to the development of anal cancer. Since the 1980s, it has been recognised that MSM are at high risk of developing this condition. More recently, HIV-positive MSM have emerged as the highest risk group for anal cancer, with rates of up to 70 times those seen in the general population.

Techniques such as anal Pap testing and high-resolution anoscopy (HRA)—similar to cervical colposcopy—have been developed to identify the anal lesions that are most likely to progress to cancer. Such lesions can subsequently be removed. However, there are limitations. Anal Pap testing has limited specificity to diagnose pre-cancerous lesions and currently individuals with any type of anal Pap abnormality require assessment by HRA that is time-consuming, costly, and not widely available. Additionally, although current treatment methods are effective, new lesions commonly develop over time.

In part due to these issues, there are no international guidelines for the diagnosis and treatment of anal pre-cancer, which has resulted in considerable inertia in addressing the issue. While there is a strong research imperative to improve both anal Pap testing and current treatment methods, there remains a fundamental lack of awareness of these issues among gay men and other MSM, women who participate in AI, and their healthcare providers and advocates. There is a pressing need for more effective education, promotion of risk awareness, and advocacy for those at risk.

Further reading:

1.7.2 HPV vaccination

By Ross Cranston (University of Pittsburgh, IRMA Steering Committee member, U.S.)

Human papillomavirus is one of the most common viral infections in humans. There are more than 100 different HPV types that cause a spectrum of disease that extends from hand and foot warts to anogenital dysplasias (abnormal precancerous cells) and cancers. Up to 75% of the general population is likely to be exposed to anogenital HPV infection in their lifetime.
Clinical trials have been conducted in young women using HPV vaccines against the HPV types most commonly associated with cancer of the cervix, vagina, vulva, penis, and anal canal (HPV 16 and 18), and the types that cause anogenital warts (HPV type 6 and 11). The results of these studies show that the vaccines provide extremely high rates of protection against new infections with these HPV types in women not previously exposed to these HPV types. Later studies also confirm prevention of HPV-associated cervical dysplasias related to these viruses in the same population.

While these findings are very encouraging, the studies show that the vaccine’s effectiveness is reduced when women have been previously exposed to one or more of the HPV types contained in the vaccine. This indicates that the vaccine is best given before sexual exposure to HPV.

The HPV vaccine also has been studied in boys and has been shown to prevent genital warts. Further studies among HIV-positive boys, girls, men, and women have reported that the vaccine stimulates an anti-HPV immune response, but studies showing effectiveness to prevent infection or dysplasia have yet to be done.

By early 2010, Gardasil (sold in some countries as Silgard) had been approved in 119 countries, and Cervarix had been approved in nearly 100 countries. In many cases, they are approved for both girls and boys. However, in some cases—like the U.S. for example—public health authorities have not recommended the vaccines for boys, despite advocating its use in girls.

Such opinions have ramifications. They place men at risk for anogenital warts, which are frequently associated with psychological stress and discomfort associated with treatment. The consequences are especially significant for gay men and other MSM, who already are affected disproportionately by HPV-associated anal cancer. The absence of public health recommendations for the HPV vaccine in boys is a missed opportunity to prevent the consequences of this infection, including the development of anal cancer, particularly as widespread anal dysplasia (pre-cancer) screening for those already infected with HPV has yet to be defined and implemented.

1.7.3 Anal intercourse and female condoms: What’s the deal?

By Cindra Feuer (AVAC, IRMA Steering Committee member, U.S.)

Unprotected AI is the sexual activity most associated with risk of HIV infection; therefore it’s imperative that research be conducted to find new methods of protection. As we know, RM research is well on its way, but the female condom, already approved for vaginal use, has not been tested for efficacy in anal sex. However, there is evidence that female condoms, like male condoms, are indeed being used off-label during anal sex.

Is this a good thing or bad thing? Well, experts cannot say for certain until safety and efficacy studies are conducted, but because both male and female condoms work similarly as physical barriers, it’s reasonable to assume that using a female condom anally is better than not using any protection at all. Male condoms were never tested anally either, but the lack of U.S. Food and Drug Administration (FDA) approval of male condoms for anal sex has never been problematic. This is because the penis-shrouding function of the male condom remains the same for both vaginal and anal sex. On the other hand, the female condom is designed specifically for insertion into the vagina, with a flexible inner ring that is secured to the cervix. This design may not transfer safely or effectively when used in the anus, underscoring the need for clarity through clinical trials.
Studies show that anywhere from 13%-21% of gay men and other MSM in the U.S. have used the female condom for AI. Unfortunately, because there is no definitive research, many health providers do not readily promote the female condom for AI. This may be a lost opportunity. Additionally, the little information available to the public on the female condom, for example on government-run websites, is often inconsistent or vague.

The field needs to conduct new safety studies of the female condom and AI, as former ones were inconclusive. Clinical trials comparing the efficacy of the female condom to the male condom during AI are needed, as well as feasibility studies. Once the facts are determined, and safety and efficacy are demonstrated, marketing the female condom for AI must be widespread but also targeted to men, in addition to women, so perhaps a name change would be in order.

Until then, people desperate for protective options will continue to use the female condom during AI. Therefore, interim guidelines with clear, consistent information must be developed. The community must remain steadfast in advocating for research into new options for AI protection like microbicides and pre-exposure prophylaxis (PrEP), but a more immediate need is the evaluation of the existing female condom for its use in AI.

Adapting materials from The Fenway Guide to LGBT Health, the Chicago Female Condom Campaign has created recommendations for anal use that can be found on its website: www.rigonit.org. This site also features a link to an instructional video, created for a program in Burkina Faso, which demonstrates the proper use of a female condom between men.

Further reading:

1.7.4 Medical male circumcision and anal intercourse
By Chris Beyrer (Johns Hopkins University, U.S.)
and Tim Farley (World Health Organisation, Switzerland)

Three randomised controlled trials of circumcision done in South Africa, Uganda, and Kenya have shown that circumcised men were about 60% less likely to acquire HIV infection through unprotected vaginal intercourse than uncircumcised men.

These studies complement the wealth of data showing lower HIV prevalence rates in settings with high prevalence of male circumcision, as well as prospective studies showing a strong protective effect of circumcision on an individual’s risk of acquiring HIV.
The way circumcision works to reduce the risk of HIV infection is now fairly well understood. The moist inner aspect of the foreskin is like other mucosal membranes (for example the inside of the mouth, vagina, and rectum) with many cells which are targets for HIV infection. Once a man has been circumcised and the skin over the surgery site has fully healed, the remaining foreskin and the head of the penis become more keratinised—more like the shaft skin which is much more resistant to HIV infection.

Trial data have not shown that circumcision reduces the likelihood an HIV-positive man will transmit HIV to his HIV-negative partner through vaginal sex. In fact, the only trial to be completed suggested the opposite. This trial enrolled Ugandan married couples in which the husbands were HIV-positive and the wives were HIV-negative. The wives of the men who were circumcised in this trial were at somewhat greater risk of getting HIV than the women married to uncircumcised men. The increased risk may have occurred when couples started having sex again before the skin on the man’s penis had fully healed—a process that is thought to take about six weeks.

Much less is known about the impact of circumcision on the risk of HIV infection following unprotected AI. This holds true for all persons engaging in AI, including women, gay men and other MSM. There has been no randomised controlled trial examining the impact of circumcision on the risk of HIV transmission during AI. This means that the only evidence for or against circumcision for gay men and other MSM, and for men who engage in AI with women, is from observational, not experimental, studies.

Since medical male circumcision reduces the risk of HIV acquisition during insertive vaginal intercourse, a similar effect may be hypothesised for insertive AI. However circumcision is not likely to reduce risk during receptive AI, among men or women. Many gay men and other MSM engage in both insertive and receptive AI. Since receptive AI is about 11 times riskier than insertive AI, circumcision may have less benefit for gay men and other MSM than for men who only have vaginal sex with women, because their major risk is from receptive AI when not protected with a condom.

The epidemiology shows that this is likely to be the case. Observational studies on circumcision and HIV risks among gay men and other MSM populations haven’t shown the same consistency that led to the African circumcision trials. Some U.S. studies have found a higher risk of HIV infection among uncircumcised men, suggesting that circumcision was protective. But another study found no protection for men reporting unprotected insertive AI. In a study completed in Peru and Ecuador, gay men and other MSM reporting only insertive AI showed a trend for lower HIV prevalence among circumcised men, though power was limited. An Australian study showed no overall difference in HIV incidence between circumcised and uncircumcised MSM. However, it was the first study to demonstrate a significantly lower risk of HIV acquisition in circumcised compared with uncircumcised gay men and other MSM who reported a preference for the insertive position during unprotected AI. A report from a recently completed HIV vaccine trial similarly suggested a lower incidence of HIV following unprotected insertive AI among circumcised compared with uncircumcised men, but the reductions were not statistically significant. This is due in part to the small proportion of uncircumcised men—only 14%—in the study.

Although the data from observational studies in gay men and other MSM are not as clear as for heterosexual men, the biologic basis for reduced HIV risk following unprotected insertive AI is similar. However, a gold standard, randomised controlled trial of circumcision among exclusively or predominantly insertive gay men and other MSM in different settings and countries may be difficult...
to conduct. A trial may be feasible—ethically and logistically—in some populations of gay men and other MSM with high HIV incidence where predominantly or exclusively insertive sub-groups can be identified. Possible settings for such trials include Peru, some South African groups of gay men and other MSM, India, and Thailand.

The policy implications of data showing a lower risk of HIV acquisition by circumcised men following unprotected insertive AI, even once confirmed, are not clear. The mainstay of HIV and STI risk reduction for both insertive and receptive AI is consistent condom use. Promoting medical male circumcision among gay men and other MSM would only reduce the risk of HIV infection during unprotected insertive AI with a partner known to be HIV-positive, or a partner whose HIV status is not known. The question is how frequently that occurs compared with other acts of intercourse, and whether the frequency of such acts can be reduced through promoting condom use and knowledge of HIV status.

Many gay men and other MSM already use condoms strategically, with higher rates of condom use during intercourse between partners who are serodiscordant (where one partner is HIV-positive, and the other partner is HIV-negative) or where one partner’s HIV status is not known. Circumcised gay men and other MSM are probably at lower risk of HIV infection than uncircumcised men, but the difference in risk is likely small and almost irrelevant unless the risk of HIV from unprotected receptive AI can be reduced or eliminated.

### 1.7.5 Availability of lubricants

*By Jim Pickett (AIDS Foundation of Chicago, IRMA Chair, U.S.) and Chris Beyrer (Johns Hopkins University, U.S.)*

At the IRMA-sponsored satellite session held prior to the 2009 International AIDS Society Conference in Cape Town, South Africa, Dr. Chris Beyrer of Johns Hopkins Bloomberg School of Public Health presented pioneering data on the epidemiology of HIV among gay men and other MSM in Africa and the implications for RM (presentation available here [www.rectalmicrobicides.org/community.php](http://www.rectalmicrobicides.org/community.php)).

After contextualising the challenges faced by African gay men and other MSM—including criminalisation, stigma, human rights abuses, lack of access to prevention and care, and limited HIV surveillance—Beyrer provided data from over a dozen countries, revealing high burdens of HIV among gay men and other MSM. AI was common, he reported, as was the use of lubricant.

However, according to Beyrer, the majority of African gay men and other MSM are not using water-based lube—which is compatible with condoms—primarily due to lack of access. For instance, in a 2008 study of gay men and other MSM in Namibia, Botswana, and Malawi, 12.9% of the men who indicated they always used condoms reported using water-based lubricant. Unfortunately, as high as 38.8% of those reporting always wearing condoms used petroleum-based lubricant (which degrades condoms), saliva, or no lubricant at all. While the research on lubricant use among this population suggests that a lube-based RM will be highly acceptable, the current lack of education around and access to water-based lubricant must be addressed immediately.

Many men and women use sexual lubricants during AI, yet we know very little about their relative safety for rectal use. Obtaining data on the relative safety of products used as sexual lubricants for anal sex would be valuable for public health reasons. For example, this data could be used to promote use of safer lubes, while discouraging use of lubes that are less safe. Section 2.11 of this report describes the current state of research and Section 4.4 describes IRMA advocacy for more data on the safety of lubricants for rectal use.
2 The state of rectal microbicide research

Summary

- The ground-breaking U-19 Microbicide Development Program (MDP) will end in 2010, and has included a number of important studies on rectal microbicides (RMs), including the world’s first RM safety trial.

- Three new research projects will focus on RM research in the coming years: the Combination HIV Antiretroviral Rectal Microbicide (CHARM) Program and the Microbicide Safety and Acceptability in Young Men study in the U.S.; and, the Combined Highly-Active Antiretroviral Microbicides (CHAARM) Programme in Europe.

- Some of the next RM safety trials will be testing antiretroviral-based microbicides, including tenofovir (Viread™) gel and UC781 gel, and will be conducted through the Microbicide Trials Network (MTN) as well as the Integrated Preclinical Clinical Program for HIV Topical Microbicides (IPCP-HTM).

- amfAR–The Foundation for AIDS Research has supported many RM research projects throughout the world.

- A range of other projects have focussed on product acceptability, testing of candidates for rectal use, and the rectal safety of lubricants.

In the 2008 report *Less Silence, More Science: Advocacy to Make Rectal Microbicides a Reality*—available on the IRMA web site at www.rectalmicrobicides.org—IRMA reported on a number of projects conducted through the Microbicide Development Program (MDP), described below. In fact, about half the projects described in the overview of rectal microbicide (RM) research efforts were MDP projects, including a description of the world’s first RM safety trial.

Now that the MDP is coming to an end (see Section 2.1), a number of new large research programmes are poised to fill the gap, including two RM-specific programmes that will be conducted in the U.S. (see Sections 2.2 and 2.3) and a European-based microbicide research programme that will focus on RMs (see Section 2.4). There are also two new RM safety trials to be conducted by the U.S.-based Microbicide Trials Network (MTN) (see Sections 2.5 and 2.6).

A number of independent studies and research projects have been conducted over the past two years, including: a half-dozen RM-specific projects funded by amfAR–The Foundation for AIDS Research...
(see Section 2.7); basic research projects focussed on developing and testing new compounds to be used as candidate microbicides (see Sections 2.8 and 2.9); a study on product acceptability (see Section 2.10); and a study testing the rectal safety of sexual lubricants (see Section 2.11).

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<thead>
<tr>
<th>SECTION</th>
<th>RESEARCH PROJECT</th>
<th>YEAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1</td>
<td>The Microbicide Development Program (MDP)</td>
<td>2004–2010</td>
</tr>
<tr>
<td>2.2</td>
<td>Combination HIV Antiretroviral Rectal Microbicide (CHARM) Program</td>
<td>2010–2014</td>
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<tr>
<td>2.3</td>
<td>Microbicide Safety and Acceptability in Young Men</td>
<td>2010–2013</td>
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<tr>
<td>2.4</td>
<td>Combined Highly-Active Antiretroviral Microbicides (CHAARM) Programme</td>
<td>2010–2014</td>
</tr>
<tr>
<td>2.5</td>
<td>RMP-02/MTN-006: Phase I rectal microbicide safety and acceptability trial of topically applied tenofovir compared with oral tablet</td>
<td>2009–2011</td>
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<tr>
<td>2.6</td>
<td>MTN-007: Phase I rectal safety and acceptability study of tenofovir gel</td>
<td>2010–2011</td>
</tr>
<tr>
<td>2.7</td>
<td>Biomedical, social, and behavioural research funded by amfAR</td>
<td>2007–2010</td>
</tr>
<tr>
<td>2.8</td>
<td>Aptamer microbicide development program</td>
<td>2005–2011</td>
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<tr>
<td>2.9</td>
<td>Evaluating rectal safety and efficacy of microbicides in macaques</td>
<td>2008–2009</td>
</tr>
<tr>
<td>2.10</td>
<td>Assessing user preferences for rectal microbicide formulations: Gel vs. suppository</td>
<td>2005–2007</td>
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<tr>
<td>2.11</td>
<td>Assessing the rectal safety of sexual lubricants</td>
<td>2009</td>
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As the field of RM research continues to evolve and expand, there is a stronger need than ever for additional resources (see Section 3) and for better coordinated efforts to plan for the future through the development of a Global Rectal Microbicide Development Plan (see Section 5.2).

This section provides a brief overview of each RM research project mentioned above. IRMA thanks the scientists who provided their expertise to ensure accuracy and clarity of their studies. Readers without a scientific background may find that some of these summaries, especially those describing basic research studies, use very technical language. To assist the reader, a glossary at the end of Section 2 provides definitions for a number of technical terms.

### 2.1 The Microbicide Development Program (MDP)

Principal investigator: Peter Anton  
Institution: University of California, Los Angeles (U.S.)  
Funder: U.S. National Institutes of Health (NIH)  
Years: 2004–2010

The MDP was funded by the U.S. NIH Integrated Preclinical Clinical Program for HIV Topical Microbicides (IPCP-HTM), and dedicated to testing the safety and efficacy of potential topical vaginal microbicides used rectally. It was led by the University of California, Los Angeles (UCLA) with collaborative institutions including Johns Hopkins University, University of Pittsburgh/Magee Women's Research Institute, Columbia University, St. George's Hospital and Medical School in London and the Health Protection Agency at Porton Down (near London) as well as CONRAD and Gilead.

Some MDP studies are not described below, including a study of rectal applicator acceptability and a challenge experiment using explants to assess products using a combination of antiretroviral drugs.¹
2.1.1 Prevention of infection in primates when pre-treated rectally with tenofovir gel

MDP-associated researchers in the UK investigated whether rectally-applied tenofovir gel had any protective efficacy in a rectal challenge experiment with macaques. Of 20 macaques, nine animals received tenofovir gel rectally up to two hours prior to virus challenge with SIV, four macaques received placebo gel, and four macaques remained untreated. In addition, three macaques were given tenofovir gel two hours after virus challenge. Remarkably, eight of nine given the tenofovir gel two hours prior to being exposed to SIV were completely protected (using a variety of measures of infection) whereas all untreated and three of four placebo animals were infected. There also was a strong positive association between the concentration of tenofovir in the blood plasma 15 minutes after rectal application of the gel and the degree of protection, providing a potential surrogate for future trials to test. Importantly, in a finding similar to the results from the first Phase I trial in humans (see Section 2.1.7), colorectal explants from macaques treated with tenofovir in vivo resisted infection when exposed to SIV ex vivo. These results indicate that colorectal pre-treatment with antiretroviral drugs, such as tenofovir, has potential as a strategy for the prevention of HIV transmission in a clinical setting.

Explant susceptibility to infection: These are tests to see if a product prevents the growth of HIV (or SIV in the case of primates) when the rectal tissue is exposed to HIV (or SIV) in the lab. These tests are run on small pieces of rectal mucosal tissue collected from subjects after they have received the candidate RM in the clinic.

2.1.2 Enema comparison study for safety and acceptability

This study, conducted at Johns Hopkins University, was designed to evaluate the safety and acceptability of three different types of enemas, and to explore the possibility of using an enema as a microbicide delivery method. Nine research participants had baseline evaluations followed by a series of three different types of enema at least two weeks apart, given as a single dose in the hospital to enable comparisons of the enema effects on the colorectal mucosa. The three types used were: Fleet™ enema (hyper-osmolar), tap water (hyposmolar), and Normosol-R™ (isosmolar). Changes in rectal permeability, microscopic appearance of tissue, signs of rectal inflammation, and the ability of HIV to infect rectal tissue explants after each enema dose were the study endpoints. Participants completed computerised questionnaires in private for each type of enema after it was used. They were also instructed to use the enema at home prior to receptive anal intercourse (AI) and to complete a questionnaire about the enema’s acceptability. Finally, a phone interview was conducted to get more detailed information comparing all three products. To determine how a drug added to the enema might behave, nuclear medicine imaging methods tracked the 24-hour distribution of the enema in the rectum and colon. The study is complete, and data are currently being analysed. An important outcome will be to determine if particular enema types potentially affect the rectal lining and whether that correlates with ex vivo HIV infection. As well, the relative distribution of the enema as a potential RM carrier and the acceptability of the different enemas will inform drug development.

Products can be isosmolar, hyposmolar or hyper-osmolar. Iso-osmolar products have the same concentration of solutes (osmolarity) as normal cells, and thus have little effect on cells’ integrity. Hypo-osmolar products tend to make cells swell up with water that can lead to cell collapse. Hyper-osmolar products have a lower concentration of solutes than normal human cells. Therefore, when in contact with mucosal membranes, they tend to “suck” away water from cells, making them dry up, and thus potentially increasing the risk of abrasion and HIV infection.
2.1.3 Rectal microbicide vehicle comparison study

This study was designed to measure the safety, acceptability, and colonic distribution of four different types of vehicles (drug carriers) as potential formulations to administer RMs. Understanding the safety, acceptability, and distribution of these potential microbicide vehicles on their own is critical. It is important to know they will not increase the risk of HIV infection before adding the complexities of active anti-HIV drugs to the mixture. It’s necessary to evaluate how likely these carriers will be used during sex, and how they will distribute to areas of the rectum likely to be exposed to HIV through sex. The four vehicles selected for this study included a water-soluble gel, water-soluble liquid, fat-soluble gel, and fat-soluble liquid. These were developed to cover a range of different physical and chemical characteristics that might be needed to carry an active microbicide ingredient into the rectum (see Section 2.1.4). The study used the same approach to measure safety, acceptability, and distribution as the Enema Comparison Study described in Section 2.1.2. By early 2010, the enrollment of eight research participants was complete, and most of the study vehicle doses had already been given. The study is anticipated to be completed by June 2010.

2.1.4 Development of rectal-specific formulations for use in RM development

The goals of this study were to (i) develop non-drug-containing vehicles that provide the most flexibility to incorporate specific anti-HIV drugs later, but that can be tested in vivo now (see Section 2.1.3); (ii) identify the critical formulation parameters that likely impact vehicle distribution and function when actually used in rectal administration of microbicides in humans; and (iii) begin laboratory studies to evaluate formulations of UC781 (an antiretroviral microbicide gel provided by CONRAD) based on the results of the above vehicles in human studies.

Placebo Development: The placebo development effort resulted in a series of four formulations with a wide range of characteristics.

I. Aqueous Formulations
   a. Fluid—easily spreadable; fluid with viscosity consistent with rapid rectal/colonic distribution.
   b. Gel—erodible; semisolid with viscosity parameters consistent with erosion and distribution instigated by rectal intercourse.

II. Lipid Formulations
   a. Fluid—easily spreadable; fluid with viscosity consistent with rapid rectal/colonic distribution.
   b. Gel—erodible; semisolid with viscosity parameters consistent with erosion and distribution instigated by rectal intercourse.

Testing included pharmaceutical function and stability as well as in vivo and in vitro toxicity. A 10-day rabbit rectal irritation study showed no toxicity with any of the placebo formulations.

As part of the rectal vehicle development efforts, the group also conducted condom compatibility testing for a large number of commonly used commercial lubricants. These studies found a wide range of properties in these products as well as potential associated problems. A new condom compatibility method was developed using a Texture Analyser, used to quickly screen new formulated products for condom compatibility.
Incorporation of UC781, in anticipation of making a rectal-specific formulation of UC781 as a RM: Incorporating UC781 in typical aqueous-based formulations is challenging because UC781 repels water and has limited solubility. This has been done successfully with the aqueous gel vehicle but presents a problem with the aqueous fluid, due to sedimentation. In contrast, the lipid placebo formulations are attractive since UC781 can be formulated as a solution, thereby maximising dissolution and drug delivery. UC781 showed significantly enhanced solubility in two lipid solvents but was not stable in either one. These data will be pivotal in selecting the carrier formulation for UC781 (and later, tenofovir) that will be most appropriate for human testing.

2.1.5 Rectal signs, symptoms, and behaviours among men and women

This study recruited 896 men and women in Los Angeles and Baltimore (U.S.). From 2006-2009, study participants completed computer-administered self interviews about rectal sexual behaviour, hygiene, and anorectal symptoms, and underwent high resolution anoscopy (HRA) to detect rectal and anal clinical signs. Half the men sampled practiced receptive AI (RAI) in the past month and half the women in the past year. Frequencies of behaviours, reported symptoms, and HRA-noted clinical signs were recorded and analysed.

The population studied was 51.3% male, 55.2% African-American, and 45.3% HIV-positive, with a median age of 39.6 years. By HRA, 22% had haemorrhoids, 4.1% had patches of possibly precancerous cells, 3.6% had internal bleeding, 3% had swelling, and 2.9% had redness. These clinical signs had the strongest associations with reported symptoms (ORs 2.6-4.5). In multivariate models, more signs by HRA were associated with: being Black and male (OR 0.43, CI 0.19-0.95), other ethnicity and male (OR 0.15, 95% CI 0.03-0.69), having had a colonic >1 times in the past year (1.38, 95% CI 0.97-1.97) and more partners in the past month (OR 1.01, CI 1.0-1.02). Importantly, having RAI in the past week was not associated with more signs.

These are the first large-scale findings to report baseline levels of rectal signs, symptoms, and behaviours that might be expected in U.S.-based STI/HIV prevention trials, for those who do and do not practice RAI. Most detected signs were correlated with reported symptoms, suggesting self-reports may be useful for interim monitoring of side effects and to help distinguish microbicide and/or applicator-induced findings from possible baseline norms.

2.1.6 Rectal lubricant use and risk for rectal STIs

Sexual lubricants are commonly used during RAI among men and women. Since there remains the possibility that lubes on their own may alter or increase vulnerability to rectal sexually transmitted infections (STIs)—possibly via mucosal irritation—information on this issue is critical to the development of rectally used, drug-containing lubricants. This association was examined within the study described in Section 2.1.5. Participants completed computer-administered self interviews about sexual and hygiene behaviour, and were tested for rectal STIs (gonorrhea and chlamydia). 302 of the 896 participants reported RAI in the past month (men) or year (women). The study evaluated frequencies for lube use before last RAI and associations with demographics, HIV status, and other behaviours.
Overall 76% reported lube use before last RAI and 8.3% tested positive for a rectal STI (5.6% of women and 10.2% of men). 11.7% of lube users were positive for a rectal STI vs. 4.5% who did not use lube (p<0.05). Lube use was significantly associated with rectal STI after controlling for gender, HIV status, city, condom use, and number of sex partners in the past month.

These first data suggest use of some lubes used rectally may actually increase vulnerability to rectal STIs, highlighting a need for more research on types of lubes, their use during RAI, and potential mechanisms for how they may facilitate STI and HIV transmission. These efforts need to continue in parallel with RM development.

See Section 2.11 for more information on the assessment of the rectal safety of sexual lubricants, and Section 4.4 for a description of IRMA’s ongoing advocacy for more data on the safety of lubricants for rectal use.

2.1.7 Phase I safety trial of a rectal microbicide in humans: Testing UC781

This first randomised, double-blinded, placebo-controlled Phase I rectal safety study used the vaginal formulation and dosing of UC781 gel (0.1% vs. 0.25% vs. placebo; 12 per group), in 36 sexually abstinent HIV-negative men and women. The trial included several dozen tests and evaluations of safety, pharmacokinetics and acceptability that were described Section 2.1 of Less Silence, More Science: Advocacy to Make Rectal Microbicides a Reality.

The primary safety goal of the trial was assessing the frequency of > Grade 2 adverse events (AEs), using the newly developed U.S. NIH Division of AIDS’ Rectal Toxicity Table, Amendment III, and an extensive panel of assays to assess potential mucosal injury. AEs are either Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), or Grade 4 (potentially life-threatening). There were no procedure-related AEs (108 procedures completed with 3,024 intestinal biopsies) or any Grade 3 or 4 AEs. Eighty-four Grade 1 and eight Grade 2 AEs were reported in five of 36 subjects. Extensive indices of mucosal injury showed no differences when comparing before versus after product exposure or between treatment groups.

As a novel goal, the trial assessed whether UC781 applied in vivo (applied rectally in participants) could suppress ex vivo infection in explants from these participants, after single and seven-day exposures. Following in vivo exposure to a single high dose (0.25%) of UC781 gel, HIV infection was significantly inhibited ex vivo (in explants). Explant data resulting from seven-day participant exposure (self-administered) was more variable.

This study showed the UC781 gel to be safe and well tolerated when used rectally. Participants were highly compliant, all procedures were completed, and all 36 enrolled participants (26 men, 10 women) completed the trial. No significant differences were seen in mucosal injury assays between high dose (0.25%), low dose (0.1%), or placebo groups. A noteworthy result showed that explants exposed in vivo to 0.25% UC781 gel for 30 minutes demonstrated significant suppression of ex vivo explant HIV infection. Ex vivo assessment of in vivo effects of microbicides is an exciting, potentially valuable new efficacy indicator for possible use early in the development process, prior to formal Phase IIb/III trials.
2.1.8 Acceptability of UC781 gel as a rectal microbicide

As part of the trial described above, acceptability was assessed using structured questionnaires and qualitative in-depth interviews. Participants' reports suggest that a UC781 gel formulation is highly acceptable and comparable to a placebo gel. The gels received favourable ratings overall and on attributes such as colour, smell, and consistency. All of the participants reported high intentions to use a gel like the one they used in this study.

2.2 Combination HIV Antiretroviral Rectal Microbicide (CHARM) Program

Principal investigator: Ian McGowan
Institution: University of Pittsburgh School of Medicine (U.S.)
Funder: U.S. NIH
Years: 2010–2014

CHARM will develop rectal-specific antiretroviral microbicides. These candidate microbicides will include tenofovir, UC781, and a combination of tenofovir and UC781.

The programme has three scientific projects. Project 1, conducted by Dr. Charlene Dezzutti at the University of Pittsburgh, will undertake the preclinical evaluation of microbicide safety and efficacy using a range of assays including colorectal cell lines and human intestinal explant tissue. Project 2 will exploit a recently developed transgenic mouse model of HIV infection to evaluate product efficacy in vivo and will be undertaken by Dr. Victor Garcia-Martinez at the University of Texas. Project 3 will undertake a series of pre-Phase I human studies that will provide preliminary data on the safety, pharmacokinetics, and efficacy of the microbicide candidates.

A particular strength of these studies will be the ability to conduct infection studies on intestinal explants from participants who have been exposed to the microbicide product in vivo. The clinical studies will be undertaken at the University of Pittsburgh School of Medicine, UCLA, and the Johns Hopkins School of Medicine.

By the end of the program, hopefully one or more rectal-specific antiretroviral microbicides will have been generated that can be clinically evaluated in future Phase I rectal safety studies.

For more information visit http://charm.microbicides.us

2.3 Microbicide Safety and Acceptability in Young Men

Principal investigators: Ian McGowan and Alex Carballo-Diéguez
Institutions: University of Pittsburgh School of Medicine (U.S.) and Columbia University (U.S.)
Funder: U.S. NIH
Years: 2010–2013
This study will be conducted with an ethnically diverse sample of HIV-negative 18-30 year-old men who report engaging in RAI using condoms inconsistently or not at all. The ultimate goal is to test whether or not this highly vulnerable population could safely use the microbicide candidate UC781, and whether or not patterns of placebo use are indistinguishable from UC781 use, suggesting that the product would be used correctly and consistently in real-life circumstances.

Acceptability and adherence will first be studied using a placebo gel applied with a specifically-designed rectal delivery device in, or prior to, real-life sexual encounters. Subsequently, the safety of UC781 will be studied among those men who show the highest adherence to gel use (defined as using the study product during \( \geq 80\% \) episodes). This safety phase will consist of a single dose of gel followed by one week of daily dosing with the gel.

At the beginning of each of these two stages, all participants will receive condom-use counselling following the Personalized Cognitive Risk-Reduction Counselling protocol, a risk-reduction counselling method to prevent HIV and STIs that showed efficacy in a randomised controlled trial. All of the participants will be closely monitored with clinical, laboratory, and behavioural assessments. Quantitative and qualitative research methods will be used, as well as a combination of self-reports, biomarkers, and the counting of products returned by the participants unused.

The study will be undertaken by the University of Pittsburgh and the HIV Center for Clinical and Behavioral Studies (Columbia University and NYS Psychiatric Institute). There will be three clinical trial sites: the University of Pittsburgh; Fenway Community Health in Boston; and the University of Puerto Rico Clinical Trial Unit in San Juan.

### 2.4 Combined Highly-Active Antiretroviral Microbicides (CHAARM) Programme

Principal investigators: Charles Kelly and Robin Shattock
Institutions: King’s College London (UK) and St. George’s Hospital and Medical School, University of London (UK)
Funder: European Commission’s Seventh Research Programme Framework
Years: 2010–2014

The CHAARM project will develop new microbicides, and combinations thereof, to help maintain a pipeline of promising candidates. Combining two or more microbicides in a single product may be more effective than using a single microbicide and, importantly, may reduce the likelihood of HIV becoming resistant to an antiretroviral product.

The project involves scientists with expertise in a wide range of different disciplines from 31 institutions in 12 countries, including eight member states of the European Union, as well as Switzerland, South Africa, the United States, and Ukraine. CHAARM will develop rigorous procedures for testing efficacy and safety using new model systems as well as identify new microbicides and combinations. The programme will include human studies to determine microbicide safety and will investigate biomarkers associated with health or damage at mucosal surfaces. It will also investigate formulation and potential scale-up of microbicide production.
The project aims to develop microbicides for both rectal and vaginal application. The exact nature of the work on RMs may change as the project evolves. At this point, these efforts may include: developing or progressing new products with an emphasis on combinations; using an integrated strategy for testing efficacy and safety in vitro in which cervicovaginal and rectal explants, as well as colonic and vaginal derived cell lines, will be used; conducting studies to investigate both gel and vaginal ring formulations, including rectal gel formulations; and conducting pharmacokinetic studies and performing challenge experiments of the most promising compounds in macaques (vaginal and rectal challenge).

For more information, please visit www.chaarm.eu

2.5 RMP-02/MTN-006: Phase I rectal microbicide safety and acceptability trial of topically applied tenofovir compared with oral tablet

Principal investigators: Peter Anton and Ian McGowan
Institutions: UCLA (U.S.) and University of Pittsburgh School of Medicine (U.S.)
Funder: U.S. NIH
Years: 2009–2011

The RMP-02/MTN-006 trial is a collaborative effort between IPCP-HTM and MTN. The study involves 18 participants and is evaluating the safety and early pharmacokinetic profile of vaginally-formulated tenofovir gel applied rectally in a single dose, followed by once-daily dosing for seven days, compared to a single oral dose of tenofovir. The study is designed as a Phase I rectal safety trial to support the vaginal microbicide application, should vaginal efficacy be demonstrated. As of this writing, the study is almost fully enrolled and should be completed in 2010.

MTN was established in 2006 and brings together international investigators, community, and industry partners who are devoted to reducing the sexual transmission of HIV through the development and evaluation of products applied topically or administered orally. For more information on MTN, visit www.mtnstopshiv.org

2.6 MTN-007: Phase I rectal safety and acceptability study of tenofovir gel

Principal investigator: Ian McGowan
Institution: University of Pittsburgh School of Medicine (U.S.)
Funder: U.S. NIH
Years: 2010–2011

MTN-007 is a Phase I, randomised, blinded, placebo-controlled safety and acceptability study of rectally applied tenofovir gel. Participants will be randomised to receive a single dose of tenofovir gel, a placebo gel, or Nonoxynol-9 (N-9) gel—used as a positive control. One week later they will be given a seven-day supply of the study gel. Approximately 63 men and women at sites in the U.S. will participate in the trial, scheduled to start in late 2010.
2.7 Biomedical, social, and behavioural research funded by amfAR

In recognition of the important yet understudied relationship between AI and the spread of HIV, amfAR funded several research projects aimed at increasing our understanding of biomedical and socio-behavioural aspects of rectal HIV transmission and its prevention.

In a report issued in early 2009, amfAR provided a review of its findings and discussed their implications, identified remaining knowledge gaps, and suggested strategies to promote this field of enquiry. For more information on these projects, which were funded in the 2007-2010 period, please consult Advancing New Ideas in AIDS Research. The projects related to RM research and development included:

- **Development of a standard microbicide delivery device**, Alex Carballo-Diéguez, Research Foundation for Mental Hygiene, Inc. (U.S.)

- **Exploring epithelial injury in regions of the rectum and colon most susceptible to HIV infection following intercourse**, Craig Hendrix, Johns Hopkins University School of Medicine (U.S.)

- **Rectal transmission of HIV-1 in genetically engineered mice with an immune system that mimics that of humans**, Roberto Speck, University Hospital of Zurich (Switzerland)

- **Colorectal responses to HIV-1 and modulation by microbicides**, Carolina Herrera and Robin Shattock, St. George’s University of London (UK)

- **Understanding how HIV and rectal cells interact at the point of infection**, Dr. Charlene Dezzutti, Magee-Women’s Research Institute and Foundation (U.S.)

- **Modelling the impact of a rectal microbicide**, Anna Foss, London School of Hygiene and Tropical Medicine (UK)

amfAR-funded researchers (and IRMA chair Jim Pickett) gathered in March 2009 for a Think Tank to share their progress and discuss cutting-edge strategies for understanding and preventing rectal transmission of HIV. To read a summary and watch a video from this meeting, and to learn more about amfAR’s support for RM research, visit [www.amfar.org/lab/article.aspx?id=7442](http://www.amfar.org/lab/article.aspx?id=7442)

2.7.1 Modelling the potential impact of a rectal microbicide used by gay men and other men who have sex with men in Bangalore (India) and Lima (Peru)

Before this study, there were no estimates of the likely public health impact of a RM in any low- or middle-income country. IRMA is especially proud to have been instrumental in determining one of the communities used in this modelling study, namely Lima, thanks to the existence of IRMA-ALC (see Section 4.3.4 for a description).

Dr. Anna Foss and colleagues at the London School of Hygiene and Tropical Medicine used detailed epidemiological and behavioural data from Bangalore and Lima—two settings in which the HIV
epidemic remains concentrated in high-risk groups, including gay men and other MSM—to parameterise and fit a compartmental epidemiological model. The joint transmission dynamics of HIV, syphilis, and genital herpes were simulated among three behavioural subgroups of gay men and other MSM, defined by their typical role during AI—insertive, receptive, or both. The potential evolution of the HIV epidemic was investigated with and without a five-year RM intervention. Various scenarios of RM availability, consistency of use, and per sex act efficacy against HIV were explored.

Despite large differences across settings, if condom use is maintained following RM introduction, the model projected that the percentage of infections averted would be similar across both settings.

For example, the preliminary model predicts that about 12% of HIV infections could be averted among gay men and other MSM in both settings over five years (2010-2015), in a scenario where:

- 30% of gay men and other MSM can access an RM;
- it is 60% efficacious against HIV;
- it is used in over half of non-condom-protected sex acts; and,
- condom use remains at pre-RM levels.

However, if 20% fewer sex acts are condom-protected after RM introduction (and other factors remain as in the scenario described above), then impact lessens, and HIV infections are predicted to increase among gay men and other MSM in Lima (by about 10%). The potential indirect impact of RM use among these men, in terms of lowering their HIV/STI prevalence to reduce transmission to their wives/cohabiting female partners, typically offers only marginal benefits to these women.

The public health benefit from an effective RM could be considerable if used consistently, but condom use must be maintained in order to avoid potentially increasing HIV/STI risk. The findings highlight the importance of pursuing further research and investment for developing RMs. Vaginal microbicides that could be used by female partners would likely also be an important breakthrough, since condom use is reported to be low in these partnerships but underlying risk is high.

Further details will be presented at the Microbicides 2010 conference in May 2010.

2.8 Aptamer Microbicide Development Program

Principal investigator: Ian McGowan
Institution: University of Pittsburgh School of Medicine (U.S.)
Funder: U.S. NIH
Years: 2005–2011

The purpose of this grant is to develop aptamers as novel candidate microbicides for the prevention of HIV-1, herpes simplex virus 2 (HSV-2), and human papillomavirus (HPV) transmission. Aptamers are RNA molecules that have been generated through a process that identifies and enriches molecules which show affinity for binding to components of viruses such as HIV. To date this project has focussed on the preclinical evaluation of HIV gp120 RNA aptamers in cell lines and the colorectal explant model.
Compared to drugs like tenofovir, the HIV aptamers appear to have modest activity in the explant system. One possible explanation is that bacterial-associated enzymes present in the rectal compartment actually break down the aptamers and prevent them from working as microbicides. Characterising the mechanism of this process will have important implications for the development of future RNA-based microbicides.

### 2.9 Evaluating rectal safety and efficacy of microbicides in macaques

**Principal investigator:** Dorothy Patton  
**Institution:** University of Washington (U.S.)  
**Funder:** U.S. NIH  
**Years:** 2008–2009

This study developed a standardised protocol for an assessment of preclinical rectal safety and (chlamydial) efficacy assessment of topical microbicide candidates in a nonhuman primate model. It evaluated a total of 12 test compounds for rectal safety, and one compound for efficacy, against rectal chlamydial infection.

The model distinguished products with deleterious effects on the rectal environment, and included the specific criteria used to recommend moving products into preclinical rectal efficacy trials or to recommend products for reformulation. The study observed significant adverse effects in two products. The single product that underwent efficacy evaluation was not observed to be protective against rectal chlamydial infection.

### 2.10 Assessing user preferences for rectal microbicide formulations: Gel vs. suppository

**Principal investigator:** Alex Carballo-Diéguez  
**Institution:** Columbia University (U.S.)  
**Funder:** U.S. NIH  
**Years:** 2005–2007

This study assessed whether gay men and other MSM prefer a gel or a suppository as an RM delivery vehicle. Study participants included 77 HIV-negative gay men and other MSM with a recent history of inconsistent condom use during RAI who acknowledged being at risk of contracting HIV. In this randomised acceptability trial, participants compared 35ml placebo gel with 8g placebo rectal suppositories used up to three RAI occasions each.

Participants preferred the gel over the suppository (75% versus 25%, p=0.001) and so did their partners (71% versus 29%, p=0.001). The gel received more favourable ratings overall and on attributes such as colour, smell, consistency, and feeling in rectum immediately after insertion and/or 30 minutes after insertion, as well as during the application process. Participants reported favourably on the gel and did not report significant instances of leakage, soiling, bloating, gassiness, stomach cramps, urge to have a bowel movement, diarrhea, pain, or trauma. Participants also preferred the gel in terms of feelings during anal sex, sexual satisfaction, partners' sexual satisfaction, and liking the product when condoms were used and when condoms were not used.
The study concluded that a gel had greater acceptability than a suppository as a potential microbicide vehicle in this sample recruited from one of the populations most likely to benefit from RM availability.

### 2.11 Assessing the rectal safety of sexual lubricants

**Principal investigator:** Charlene Dezzutti  
**Institution:** University of Pittsburgh (U.S.)  
**Funder:** U.S. NIH  
**Year:** 2009

Because lubricants may decrease trauma to mucosal tissue during sex, it is thought that they could help reduce the risk of acquiring HIV. However, safety and anti-HIV activity is currently unknown for over-the-counter (OTC) lubricant gels. Based on the results from IRMA’s global survey on the use of lubricants for anal sex, six OTC lubricant gels were tested: five water-based (Astroglide, Elbow Grease, ID Glide, KY Jelly, and PRÉ) and one condom compatible, silicone-based (Wet Platinum).

The study showed that PRÉ was pH 7, iso-osmolar, with moderate viscosity. Elbow Grease, ID Glide, and KY Jelly were pH 4 to 5, 9 to 13-fold above iso-osmolar, with varying degrees of viscosity. Astroglide was pH 4, 21-fold above iso-osmolar, with low viscosity. KY Jelly made it impossible for Lactobacillus to survive, but the other lubricants were considered to allow acceptable levels of Lactobacillus to survive. PRÉ was not toxic up to 1:10 dilution. Elbow Grease, ID Glide, and KY Jelly were not toxic up to 1:100 to 1:200 dilutions. Astroglide was not toxic up to 1:1500 dilutions. Wet Platinum had no toxicity. PRÉ had no impact on the epithelial cells whereas the other water-based lubricants disrupted the epithelial cells. All lubricants exposed to colorectal and ectocervical explants allowed those explants to survive in their presence. Histology showed intact epithelium for PRÉ and Wet Platinum, while epithelial stripping was observed for Astroglide, Elbow Grease, ID Glide, and KY Jelly. Lubricants had no measurable anti-HIV activity.

These data suggest that PRÉ and Wet Platinum were safest. The hyper-osmolar nature of the other lubricant gels was associated with cellular toxicity and may lead to increased risk of HIV infection.

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**What do we know about the rectal safety of sexual lubricants?**

In addition to the recent study described above, a few others have assessed the relative safety of sexual lubricants, though not always looking at rectal safety specifically. These studies looked at:

- Using *in vitro* and mouse assays to determine cellular toxicity, increased risk of HSV-2 infection, and epithelial sloughing caused by lubricants

- Testing the osmolarity of lubricants

- Using slug mucosal irritation assays to evaluate mucosal irritation caused by lubricants

The question remains: what do all of these studies tell us? We’re not sure. We still don’t know what assays should be used to determine the rectal safety of lubricants. Furthermore, even when studies find a wide range of values for their safety markers, we still don’t know to what extent—if any—some of these markers might indicate a higher risk of HIV transmission.
Relatively high levels of cellular toxicity, mucosal irritation, cell damage caused by hyperosmolar or hypo-osmolar products, inflammation, or epithelial sloughing could in theory increase the risk of HIV infection. However, this remains to be proven.

It is important to keep in mind that:

- Some level of inflammation and irritation occurs naturally in rectal mucosa, even among healthy individuals;
- Anal intercourse itself, as well as enemas and douching, causes some transient damage; and
- Rectal epithelium regenerates quickly after minor damage or sloughing.

We must be able to compare normal levels of inflammation, irritation, cell damage and epithelial sloughing that occur among healthy individuals and those that are a result of AI. The question then becomes: does AI with lubes cause increased levels, similar levels, or lower levels of these markers compared to AI without lubes? Even if we were to find that some lubes cause higher levels of disruption, we would still need to investigate whether this translates into a higher risk for HIV transmission.

These questions remain to be answered, and we are still left with little data that can be translated into useful information that the public can use to make choices about lubricants. One thing to consider: if lubricants increase the use of condoms, that is probably a more important factor in preventing HIV transmission than any potential risk from lubes. For the moment, the use of lubes compatible with condoms is still considered to be an important risk-reduction tool for rectal transmission of HIV, and is likely to remain so. One day we may have valuable information on the relative safety of different lubricants, allowing users to make better informed decisions about which products they use.

See Section 4.4 for a discussion of IRMA’s advocacy on the safety of lubricants for rectal use.
Glossary

IRMA thanks the Global Campaign for Microbicides for much of this glossary. Many of the following terms may be found in their "Microbicides Essentials Course," available at www.hivpreventionresearch.org

Acceptability: How a product or service fits the physical, social, and cultural needs of a user or a community. Products and services that do not meet these needs are unlikely to be widely used, no matter how well they work.

Adherence: Using a medication or product correctly; following instructions properly. In clinical trials, the term adherence usually refers to how well the trial participant adhered to the trial design, i.e. did they use the trial product as directed.

Anoscopy: An examination using a small tube that is inserted into the anus and rectum. By shining a light into this tube, the doctor has a clear view of the lining of the lower rectum and anus.

Antiretroviral drugs (ARVs): The drugs used to treat people living with HIV/AIDS. ARVs work by blocking key steps of the HIV life cycle, usually by interfering with one of the proteins that the virus uses either to enter or to reproduce inside a target cell.

Assay: A test to find and measure the amount of something, such as the amount of HIV in a person’s blood.

Biomarker: A substance found in blood, other body fluids, or tissue, that is a sign of health or disease. Biomarkers are often used to measure how sick a person is, or to determine how well a person is responding to treatment. The amount of HIV in an infected person's blood, for example, can be used both as a marker of disease progression and as a measure of response to ARV treatment.

Blind/double-blind: Refers to clinical studies in which neither the participants nor the researchers know which participants are receiving the active compound and which are receiving placebo. This type of study design is used to prevent bias. The collected data are "unblinded" only at the end of the study, when the final data analysis is done.

Cell lines/cultures: Cells and/or tissues that are grown in the laboratory and are used for research.

Challenging experiment: A test where primates are exposed in a lab to SIV (the simian equivalent of HIV). Typically, some of the animals are given a test product beforehand, while others are not. Differences in infection rates between the two groups can be attributed to the test product. Similar tests are sometimes done with human tissue explants and HIV.

Efficacy: The ability of a particular product or intervention (for example, surgery or medication) to produce the desired beneficial effect.

Enzymes: The construction workers of the cell. Almost all processes in a living cell are carried out by enzymes.

Epithelium: The tissue that lines both the outside and inside cavities of the human body. The epithelium on the outside of the body is called the skin. The epithelium on the inside of the body is called the mucosa or mucous membrane. This tissue is composed of a layer or layers of specialised cells and serves to enclose and protect parts of the body, to produce secretions and excretions, and to function in the absorption of nutrients.

Explant: Tissue taken from the body, usually by biopsy (the removal of a piece of tissue for examination), and cultured in the laboratory (see cell lines/cultures).

EX Vivo: A Latin phrase that means "out of the living," and that refers to doing experiments on tissue in an artificial environment outside a living organism with the minimum alteration of natural conditions. This could include tests done in a lab on explant tissue, for example.

Formulation: The way in which a drug or product is administered. A single drug or product may be available in multiple formulations, including as a pill, gel, or cream.

gp120: The protein on the surface of HIV that recognises and binds to receptors and co-receptors on the surface of target cells.

Histology: The study of the microscopic anatomy of cells and tissues of plants and animals. It is performed by examining a thin slice (section) of tissue under a light microscope or electron microscope.

In vitro: A Latin phrase that means "in glass," and that refers to an artificial environment created in a laboratory test tube to study different organisms or tissues.

In vivo: A Latin phrase that means "with the living," and refers to doing experiments on living organisms.

Lactobacillus: A type of bacteria found in the vagina and gastrointestinal tract. A disruption of these bacteria can cause a change in the natural pH level of the vagina or rectum.
Molecule: The smallest particle of a compound that has all the chemical properties of that compound. Molecules vary widely in their size and structure.

Mucous membrane (mucosa): The layer of tissue that lines and protects the inside of the body. Mucous membranes are found inside the nose, mouth, lungs, genital tract, and many other parts of the body. These tissues are called mucous membranes because they make mucous, which keeps them moist (see epithelium).

pH: A measure of the acidity or alkalinity of a solution. Solutions with a pH less than 7.0 (the pH of water) are considered acidic. Solutions with a pH greater than 7.0 are considered alkaline. For example, vinegar has a pH of 2.9, whereas soap has a pH of 9.0 to 11.0. The normal pH for a healthy vagina usually ranges from 3.5 to 4.5, while a normal pH for the rectum is 7.2 to 7.8.

Pharmacokinetic (PK) studies: Studies that measure how a compound is absorbed, distributed, metabolised, and excreted by the body.

Phase I trial (also called a safety trial): This is a small study, enrolling approximately 25-40 volunteers. It tests for safety, side effects, and proper dosage. Often, a series of Phase I studies will be conducted with increasingly diverse groups of people to give investigators better information about whether to move forward to Phase II.

Phase II trial (also called an expanded safety trial): This is a larger study, enrolling approximately 200-400 volunteers, and it looks for further safety issues and side effects, as well as a suggestion of whether the drug is doing what it is designed to do. Phase II studies also offer some information about acceptability of the product.

Phase IIb trial: This is a study that is larger than a Phase II, but smaller than a Phase III that can provide an indication of efficacy, or compare different approaches (for example, two different drug dosing levels).

Phase III trial (also called an efficacy trial): This is a large study enrolling thousands of volunteers. This phase continues to test for safety and to determine efficacy (whether the product works in the way it is intended).

Placebo: A substance that looks and feels just like the study product, but which does not contain any active ingredients. In the case of candidate microbicides, most placebos are gels that look and feel like the test microbicide but are not expected to have anti-HIV activity. These are often called comparator gels.

Placebo-controlled: Clinical studies in which participants are split (randomised) into an intervention group that receives the test compound, and a control group that receives a placebo.

Positive control: A procedure that is very similar to the actual experimental test, but which is known from previous experience to give a result that is hypothesised to occur in the treatment group (in other words, a result that is positive).

Preclinical (testing): Tests of candidate drugs or compounds that are carried out in the laboratory or in animals, before trials in humans are carried out.

Qualitative research: Aims to gather an understanding of human behaviour and the reasons that govern such behaviour. Qualitative means a non-numerical data collection or explanation.

Quantitative research: Aims to develop and employ mathematical models, theories, and/or hypotheses pertaining to phenomena. The process of measurement is central to quantitative research.

Randomised, controlled trial (RCT): A clinical trial in which participants are assigned at random to either the intervention group (using the product with the active agent being tested) or control group (using a placebo agent). Randomising participants in this way reduces bias and makes the intervention and control groups "statistically equivalent"—in other words, any differences between the groups should be solely due to the prevention or treatment method being tested.

Safety: Potential short- and long-term effects, both bad and good, of drugs or treatments.

Solute: A substance dissolved in another substance. For example, salt in water.

Toxicity: An effect produced by a drug that is detrimental to the patient’s health.

Transgenic mouse model: Tests that are done using mice whose immune systems have been modified genetically to resemble more closely those of a human.

Viscosity: A measure of how fluid a substance is; how "thin" (like water) or "thick" (like honey) it is.
3 Are current global investments in rectal microbicide research adequate to move from promise to product?

Summary

IRMA’s resource tracking analysis and scientific-agenda setting have identified the following:

- Between 2007–2010, global spending on rectal microbicide (RM) research totalled U.S. $25 million. Of this amount, the U.S. public sector contributed 91.6%, European public sector contributions represented 5.3%, and the philanthropic sector contributed 3.0%.

- In 2010, global spending on RM research will be approximately U.S. $7.2 million.

- An estimate of U.S. $10 million invested annually from 2011–2014, increasing to U.S. $44 million annually from 2015–2020, would allow for the field to develop and advance at least two candidates forward to late-stage testing (Phase Ib/II).

- Compared to 2010 levels, annual global spending on RM research must increase by 40% for the next four years (2011–2014), and it must increase at least six-fold in the years 2015–2020.

3.1 Methodology

In 2010, IRMA updated the resource tracking exercise it conducted in 2006, and revised its estimates of the funding required to expand and maintain a healthy research pipeline of rectal microbicide (RM) candidates.

IRMA indentified RM research funding levels for 2007–2010 through the following methods:

- Snowball sampling, starting with RM researchers known through the IRMA network;
- Searching for all relevant projects through the U.S. National Institutes of Health (NIH) Research Portfolio Online Reporting Tool (RePORT);
- Contacting the other funders identified through the 2006 tracking exercise directly;
- Contacting the European Research Directorate-General; and,
- Reviewing the compiled list for accuracy and completion with each of these stakeholders.
The HIV Vaccines and Microbicides Resource Tracking Working Group was established in 2004 to generate data on global investments in preventive HIV vaccine and microbicide research and development, and policy and advocacy activities. In 2006, the Working Group expanded its tracking efforts to include other experimental HIV prevention options, such as adult male circumcision, herpes simplex virus 2 suppression, and pre-exposure prophylaxis (PrEP). In its 2009 report, the Working Group provided an estimate of total RM spending for research and development: U.S. $5 million in 2008. Given the scope of the overall resource tracking exercise, it was unable to provide specific details on RM investments, projects, and studies.

In close consultation with microbicide researchers, IRMA projected the required funding needed to maintain a robust RM research pipeline. The assessment of resources devoted to RM research for all of 2010 is a projection based on information available in the first quarter of the year.

Data limitations

While basic science and clinical research on vaginal microbicides are crucial to the eventual development of a safe and effective RM, this survey tracks research focussed specifically on the research and development of products for rectal use. A calculation of the limited resources directed toward RM policy and advocacy initiatives, while important, is not included here.

Commercial sector involvement in RM research is quite limited. There are some in-kind contributions, such as the provision of antiretrovirals (ARVs) to research institutions to test as potential RM candidates; however, the commercial sector often is unwilling to reveal actual dollar investments publicly. While the estimates provided in this document do not include contributions from the commercial sector in 2007–2010, we acknowledge that companies like Gilead have made their products available without cost. Gilead’s active participation in deliberations regarding microbicides and PrEP also benefits the field.

3.2 Reminder: Results from IRMA’s previous resource tracking exercise in 2006

In 2006, IRMA conducted a resource tracking exercise to determine both the total level of funding provided globally for RM research between 2000 and 2006, and to estimate the level of funding required to bring a small number of candidates through all stages of research over the following 10 years.

IRMA found that total investments in RM research between 2000 and 2006 were U.S. $34 million. Disbursements in 2006 were U.S. $7.2 million.

Between 2000 and 2006, the U.S. public sector contributed 97.4% of overall investments. The philanthropic and commercial sectors accounted for 2.6% of spending. No evidence of specific RM investments could be uncovered from member states of the European Union, other countries, or multilaterals during this period.

In 2006, IRMA estimated annual spending of at least U.S. $35 million would be required over 10 years—totaling U.S. $350 million—to realise a comprehensive RM research programme. Based on this estimate, yearly investments would have needed to increase five-fold from 2006 levels.
### 3.3 Investment in rectal microbicide research: Trends from 2007–2010

IRMA found that U.S. $25 million was spent on RM research between 2007 and 2010. During this period the U.S. public sector contributed almost U.S. $22.9 million (91.6% of global funding), European public funding sources contributed approximately U.S. $1.3 million (5.3%), and the philanthropic sector contributed a little over U.S. $750,000 (3.0%).

**Public sector investments from 2007–2010:** U.S. $24.2 million from public sources was invested in RM research. The U.S. NIH contributed over U.S. $22.5 million and the California HIV/AIDS Research Program, funded by the State of California, contributed almost U.S. $400,000. The European Commission provided U.S. $1.3 million through a project funded by the Seventh Framework Programme (FP7).1

**Philanthropic sector investments from 2007–2010:** amfAR–The Foundation for AIDS Research, contributed over U.S. $750,000, and has been the primary philanthropic investor in RM research for over a decade.

**Commercial sector investments from 2007–2010:** As mentioned, IRMA was unable to quantify private sector investments in RM research for this period. However, there have been valuable in-kind contributions from companies such as Gilead and others.

When combined with the data from the earlier IRMA resource tracking exercise, total investments in RM research show a modest increase from 2000–2003, followed by fluctuations hovering between U.S. $5–7 million per year from 2004–2010.

The level of funding over the next few years is likely to remain stable due to recently announced projects in the U.S. and Europe. The Combination HIV Antiretroviral Rectal Microbicide (CHARM) Program will receive U.S. $11 million over five years, starting in 2010. The project entitled “Microbicide Safety and Acceptability in Young Men” will receive U.S. $6.5 million over four years, also starting in 2010. Both projects are funded by the U.S. NIH, and are dedicated specifically to RM research. The Combined Highly-Active Antiretroviral Microbicides (CHAARM) Programme will receive 12 million euros (approximately U.S. $16 million) over five years from the European Commission’s Seventh Research Framework Programme, starting in 2010. Part of its work will focus on RM research. See Sections 2.2–2.4 for descriptions of these three programmes.

#### RECTAL MICROBICIDE RESEARCH SPENDING BY YEAR (2000–2010), IN U.S. DOLLARS

![Graph showing annual funding by sector from 2000 to 2010.](image)

Over the 11-year period of investments in RM research IRMA has tracked, the public sector has provided 97.3% of the funding (mostly from the U.S.), the philanthropic sector has provided 2.5% of funding, and the commercial sector has provided 0.2%.

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1. The Framework Programmes are the main financial tools through which the European Union supports research and development activities covering almost all scientific disciplines.
3.4 Estimated funding needs and resource gap for 2011–2020

In consultation with leading researchers in the field, IRMA calculated approximate annual funding needs for RM research and development over the next 10 years (2011–2020), based on the following:

### ASSUMPTIONS AND TARGETS

<table>
<thead>
<tr>
<th>Existing ARV-based products</th>
<th>New ARV-based products</th>
<th>Combination products</th>
<th>Non-ARV-based products*</th>
<th>Trial site development</th>
<th>Developments in the HIV prevention field</th>
<th>More funding, more researchers, more research projects</th>
<th>Cost of research**</th>
</tr>
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<tr>
<td>Two single-agent antiretroviral vaginal microbicide candidates will be tested for rectal safety, and one of the two candidates will eventually be tested for rectal use in a large-scale efficacy trial.</td>
<td>Three new microbicide candidates based on ARVs will be developed over the next 10 years, and two will advance as far as Phase I/II safety testing.</td>
<td>Four microbicide candidates combining more than one active ingredient—for example two different classes of ARVs—will be formulated and tested for rectal use over the next 10 years, and one of these candidates will eventually be tested for rectal use in a large-scale efficacy trial.</td>
<td>Two new microbicide candidates that are not based on ARVs will be developed over the next 10 years, and one will be formulated and tested for rectal safety.</td>
<td>Trial site development and maintenance will occur over the next 10 years to prepare for and support clinical trials of RM candidates. This work would most likely be conducted in North America, Latin America, and the Asia-Pacific region.</td>
<td>The current standard prevention package offered to clinical trial participants will not change significantly. If this prevention package changes—for example if PrEP is shown to be effective and is routinely offered to trial participants—a significant expansion of resources will be required to conduct large-scale RM trials. Comprehensive prevention packages result in fewer seroconversions among trial participants, and trials would need to run longer and/or recruit more participants to reach the number of seroconversions required to assess an intervention’s efficacy.</td>
<td>New, dedicated investments in RM research will allow a greater number of projects to be conducted by an increasing number of researchers from various fields, and from various parts of the world.</td>
<td>Discovery, preclinical evaluation, and formulation will cost a minimum of U.S. $1-2 million for each experimental product.</td>
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<td>Phase I trials will cost approximately U.S. $1.5 million and last around nine months. Each viable product will undergo two Phase I trials.</td>
<td>Phase II trials will cost about U.S. $3 million and may last one and a half years.</td>
<td>Phase IIb/III trials will cost at least U.S. $120 million and last at least three years.</td>
<td>Trial site development and maintenance work is variable but can cost U.S. $2 million per year.</td>
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* Ideally, RMIs should be safe, effective, acceptable, and accessible for use by all persons who engage in anal intercourse. Currently, research into new prevention technologies focuses largely on oral and topical products that contain some of the same ARVs used for treatment by persons living with HIV. These products are unlikely to be appropriate for use by someone who is HIV-positive, because the use of such products may generate drug-resistant virus which would limit treatment options. This is of special concern in the developing world where alternatives to first-line drug regimens are not yet a reality. Both ARV-based and non-ARV-based products should be developed to meet multiple user needs, including the prevention needs of people living with HIV and those who are HIV-negative. 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.

** These cost estimates were developed in consultation with leading researchers in the field, and with input from the Alliance for Microbicide Development, which has been developing its own estimates of the average cost of each stage of microbicide research.
The following chart illustrates how the various classes of candidate microbicides, described in the assumptions from the table above, would progress through development and testing from 2011–2020.

MODEL OF RECTAL MICROBICIDE DEVELOPMENT PORTFOLIO EVOLUTION (2011–2020)

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<td><strong>SINGLE-AGENT ARV-BASED PRODUCTS</strong></td>
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3.4.1 Increased funding required

Based on the assumptions, targets, and estimated costs described, and applying these estimated costs to the theoretical research portfolio illustrated in the Gantt chart above, IRMA anticipates that U.S. $10 million are required annually over each of the next four years (2011–2014), followed by U.S. $44 million annually from 2015–2020, to ensure an adequate number of candidates are pursued from bench to clinical efficacy trials.

In other words, compared to the 2010 spending level of U.S. $7.2 million, annual global spending on RM research must increase by 40% for the next four years (2011–2014), and it must increase at least six-fold in the years 2015–2020 to ensure a minimum of two candidates reach late-stage testing.

ANNUAL RECTAL MICROBICIDE RESEARCH FUNDING NEEDS (2011–2020)
3.4.2 More diverse funding required

For the 2007–2010 timeframe, IRMA was only able to identify four RM-specific funders: the U.S. NIH, the European Commission (through FP7), amfAR, and the California HIV/AIDS Research Program (funded by the State of California). In 2010, they collectively contributed U.S. $7.2 million to RM research.

By way of comparison, in 2008, a more extensive array of donors from around the world provided U.S. $244 million to general microbicide research. RM research is included in that total, accounting for approximately 2.2% of microbicide funding that year. An even broader array of donors provided U.S. $868 million to HIV vaccine research.

IRMA applauds the donors that have supported new prevention technology research and calls for a greater number of donors to support microbicide, vaccine, and PrEP studies.

Developing the diversity of RM funders would not only increase the amount of resources available, but would ensure greater sustainability as well. Given that the domestic HIV epidemics in many donor countries primarily affect gay men and other MSM, and are driven by unprotected anal intercourse, the funding disconnect is rather unfortunate. RMs would provide an important prevention option for their citizens as well as people from around the world.

Past and current contributions to vaccine and microbicide research have come largely from the development and foreign affairs budgets of individual countries. While funding for RM research could feasibly draw from these same sources, financial support through the domestic health and research budgets of these countries would also be quite appropriate considering their epidemic profiles. With the exception of the U.S. and the European Commission, these funding streams remain dry.

Obviously, given the relative infancy of RM research and development, hundreds of millions of dollars are not required annually. The RM funding scenario laid out here calls for very modest sums, and would have a significant impact for millions of women and men around the world who engage in AI. Reducing other line items in the prevention portfolio to enhance funding for RMs is not acceptable. Appropriate funding must be allocated for all new prevention technologies.

“There will be continued commitment of the NIAID DAIDS Prevention Sciences Program to the development and deployment of a safe, acceptable and effective rectal microbicide, through support of investigator initiated research. Specifically in the field of rectal microbicides, we expect to see the development of rectal-specific formulations for microbicides, as well as a movement toward creating rectal microbicides with more than one active ingredient (combination microbicides).”

Jim Turpin
Microbicides Research Branch,
National Institutes of Health
Bethesda, U.S.
4 IRMA's world tour: Key activities 2008-2010

Summary

- IRMA maximises a range of innovative communications tools that allow researchers, advocates, policy makers, and funders from around the world to remain engaged in rectal microbicide (RM) advocacy.

- IRMA maintains a presence at key international events, to ensure greater visibility for RMs and the HIV prevention needs of people who engage in anal intercourse.

- Through a network of active members from around the world, IRMA ensures that stakeholders in all regions of the globe are engaged in moving forward the RM agenda.

- IRMA continues to promote the need to determine the safety of lubricants for rectal use.

4.1 Building and maintaining a global network: IRMA's cutting edge communications efforts

Since its founding in 2005 by four people in two countries, IRMA has faced the challenge of building a global network to connect researchers, advocates, policy makers, and funders. Facilitating communication with stakeholders across disciplines and time zones was, and remains, critical to building, nurturing, and maturing an advocacy movement. IRMA has made good use of a variety of communication tools to achieve this goal.

The Joy of Tech
IRMA relies on both traditional and cutting-edge technology to connect its members and create awareness, including the following:

- Listserv: IRMA maintains and moderates a highly utilised, interactive listserv on rectal microbicides (RMs). Many IRMA members have pointed out that this is the only space of its kind, where members can discuss and debate in real time a range of issues related to HIV prevention: vaginal and rectal microbicides, anal intercourse (AI) among women and gay men and other men who have sex with men (MSM), pre-exposure prophylaxis (PrEP), medical male circumcision, human papillomavirus (HPV) vaccination, female condoms, efficacy, resistance, treatment as prevention, sexual lubricants, human rights, and more.
• **Teleconferences:** Regular global teleconferences feature leading RM researchers and advocates. For members unable to attend conferences and meetings in person, these teleconferences provide an invaluable opportunity to learn the latest developments from experts in the field. Nearly 500 people participated in the 15 teleconferences IRMA held in 2008 and 2009. Recordings and PowerPoint presentations from the calls are available on the IRMA website.

• **Website:** IRMA maintains a resource-rich website, ([www.rectalmicrobicides.org](http://www.rectalmicrobicides.org)). The site received 6,906 visits from 5,228 unique visitors in 2009.

• **Blog:** IRMA has a very active blog ([www.irma-rectalmicrobicides.blogspot.com](http://www.irma-rectalmicrobicides.blogspot.com)) that can be followed directly on the blog site, via Facebook, and through a syndication service called Feedburner, among other means of accessibility. There have been 650 posts since the blog was launched in early 2008 (as of March 21, 2010) and it received 14,244 visits from 9,240 unique visitors in 2009 alone.

• **Social networking:** IRMA maintains a dynamic presence on the social networking sites Facebook and Twitter and on the photo-sharing site Flickr. In addition to information dissemination, these tools, including the blog and the website, personalise the movement by shining a spotlight on the faces behind the work. By early 2010, IRMA had over 335 members on its Facebook group and over 800 followers on Twitter.

Over the past two years, IRMA has held 15 free global teleconferences addressing topics including the following:

- The anal canal: An important transition zone for rectal microbicide development
- Epidemiology of HIV among MSM in Africa: Implications for rectal microbicides
- Efficacy and effectiveness—What is good enough? Who decides?
- Implications of anal intercourse and rectal use of products in vaginal microbicide trials
- Microbicides: The herstory of a movement
- Understanding the habits and preferences of people having anal sex: Implications for rectal microbicide development
- IRMA exclusive: A preview of new rectal microbicide safety studies
- The female condom: Where the girls—AND boys—are
- Modelling the impact of a rectal microbicide used by men who have sex with men in Lima, Peru and Bangalore, India
- What’s in a name? Working with male-male sexualities, masculinities and genders in South Asia
- Women and anal sex: Yet another reason for rectal microbicide advocacy
- Successful implementation of HIV prevention trials in Peru

Check the IRMA blog ([www.irma-rectalmicrobicides.blogspot.com](http://www.irma-rectalmicrobicides.blogspot.com)), IRMA web site ([www.rectalmicrobicides.org](http://www.rectalmicrobicides.org)), or listserv (join at rectalmicro@gmail.com) for information on upcoming calls.
Additionally, IRMA is a member of the Microbicides and Media and Communications Initiative, a resource offering the latest strategies and best practices for managing media coverage before, during, and after clinical trials.

From very modest origins, IRMA has become a forceful advocacy network currently consisting of over 850 researchers, advocates, policy makers, and funders in over 60 countries on six continents. This exponential growth, and the resulting expansion of awareness and interest in RMs, is due largely to IRMA’s effective utilisation of electronic methods of communication. With few other resources, IRMA has used electronic communication tools to build and nurture a large, multinational advocacy network that is dynamic, engaging, and informative. These methods also support a central forum for exchange, debate, and networking and allow for the regular convening of diverse perspectives and scientific disciplines to improve understanding and action around RM research and development.

The IRMA website includes a wealth of downloadable resources:

- Information on upcoming teleconferences, as well as slides and MP3 recordings of past calls
- Slide sets from IRMA member presentations around the world
- IRMA-produced materials, including reports, a basic fact sheet, a customisable PowerPoint presentation, and other awareness materials
- The "Meet a Friendly Rectal Microbicide Advocate" feature, where the biographies of dozens of advocates and researchers can be found, putting faces to names and personalising the work
- Information on the members who comprise the IRMA Steering Committee
- Links to papers, articles, reports, and other relevant resources
- A link to the webpage of IRMA-América Latina y el Caribe, featuring articles, presentations, and other resources in Spanish

Visit www.rectalmicrobicides.org early and often for all your rectal microbicide information needs!
4.2 Spotlight on IRMA’s work at key international events

4.2.1 Delhi Direct

IRMA drew attention to RMs at the Microbicides 2008 (M2008) conference held in New Delhi, India in February of that year.

amfAR—The Foundation for AIDS Research, the UCLA AIDS Institute, and the University of Pittsburgh School of Medicine presented a Rectal Microbicides Update at a satellite symposium. The update had the following objectives:

• Provide an overview of recent advances in RM development;
• Discuss improvements in RM applicator design;
• Highlight the role of nonclinical studies in screening RM candidates; and,
• Underscore advocacy directed towards increasing funding for RMs.

Current IRMA members who presented their research included Drs. Alex Carballo-Diéguez, Ross Cranston, Charlene Dezzutti, and Ian McGowan. IRMA chair Jim Pickett discussed advocacy goals and objectives as well. The 2008 IRMA report *Less Silence, More Science: Advocacy to Make Rectal Microbicides a Reality* was released at this symposium.

IRMA members and others presented a popular training on media and communications skills called "The Media—Microbicide Friend or Foe" and held an informal social for members and allies in the Advocacy Corner.

PowerPoint presentations can be found here: www.rectalmicrobicides.org/community.php. The IRMA report *Less Silence, More Science: Advocacy to Make Rectal Microbicides a Reality*, and a number of media stories highlighting IRMA’s efforts at M2008 can be found here: www.rectalmicrobicides.org/materials.php.

The John Shaw Memorial Scholarship Fund created by IRMA provided partial support for nine international advocates to attend the conference.

4.2.2 Viva Mexico

Rectal microbicide research and advocacy—and IRMA—played prominent roles at the 17th International AIDS Conference (AIDS 2008) held in Mexico City in August 2008.


The presentation is available here: www.rectalmicrobicides.org/community.php.

“That the sexual orientation of human beings can be defined as a sexual act is accepted as a given by both heterosexuals and homosexuals, either consciously or unconsciously. Undoing this belief is critical to making rectal microbicides available to all who need them.”

Nesha Haniff
Academic, Advocate
Kingston, Jamaica
Additionally, during this session IRMA released Menos Silencio, Más Ciencia: Iniciativa para que los Microbicidas Rectales sean una Realidad, the Spanish-language edition of its 2008 publication Less Silence, More Science: Advocacy to Make Rectal Microbicides a Reality. With growing awareness of the implications of AI on the epidemic in the global north and south, IRMA is using the Spanish edition to promote the research and development of RMs among the more than 300 million native Spanish speakers worldwide. The translation came about largely due to the efforts of IRMA-ALC (América Latina y el Caribe), IRMA’s regional “sister” network based in Lima, Peru. IRMA-ALC focuses attention on RM advocacy and research efforts in Latin America and the Caribbean, and its vision is to be the principal promoter of RM research in the region.

Jerome Galea, an IRMA Steering Committee member based in Peru and a co-founder of IRMA-ALC, explained that “in all of Latin America and the Caribbean, there have been only two small studies involving microbicides, both for vaginal products. These studies represent important steps in microbicidal research. However, in much of Latin America, HIV is transmitted by unprotected anal intercourse. We must press forward with advocacy and research to bring safe, effective, and acceptable rectal microbicides to the men and women who need them.”

The Global Voice (La Voz Global), the official AIDS 2008 conference newspaper, covered IRMA’s pre-conference workshop, reporting on the urgent need to develop RMs and commenting that “anal sex practices are widespread among the general population, making it strange that it is exclusively associated with male homosexual practices.”

IRMA activities at AIDS 2008 were rounded out by poster presentations by IRMA and IRMA-ALC, advocacy activities in the Global Village, and a special dialogue with writer Elizabeth Pisani, (author of The Wisdom of Whores: Bureaucrats, Brothels, and the Business of AIDS) co-sponsored by IRMA and the Caucus for Evidence Based Prevention. As reported by Population Action International’s Jennifer Johnson in the Caucus’ daily conference newsletter, the dialogue was “a frank discussion among advocates, framed around Pisani’s idea of the ‘sacred cows of HIV.’”

In a conference highlight, Zeda Rosenberg, Chief Executive Officer of the International Partnership for Microbicides, publicly affirmed the need for RMs to a huge audience in the session “Vaccines and Microbicides: Where Do We Go from Here?” “Rectal microbicides are incredibly important and need to be developed,” she said.

### 4.2.3 Mother City

In July of 2009, IRMA co-sponsored a special satellite session at the 5th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention in Cape Town, South Africa—the first time this meeting dedicated an entire session to RMs. “Rectal Microbicide Development—An African Perspective” described the role of AI in HIV transmission and discussed recent research on developing RMs for the prevention of AI-associated HIV infection. Data from the African continent was highlighted. The presenters in the satellite session were Chris Beyrer (Professor of Epidemiology, Johns Hopkins Bloomberg School of Public Health), James McIntyre (Executive Director, Perinatal HIV Research Unit, University of the Witwatersrand and the Anova Health Institute), Ian McGowan (Professor of Medicine, University of Pittsburgh School of Medicine), IRMA’s Jim Pickett, and Sibongile Dladla (MSM Project Director, Perinatal HIV Research Unit, University of the Witwatersrand). The presenters spoke on a broad range of topics, including: epidemiology, lubricant availability among African MSM, accessing African MSM in health care and prevention studies, and an update on RM research, development, and advocacy.

PowerPoint presentations from the session are available here: www.rectalmicrobicides.org/community.php.

“Being part of IRMA implies speaking up in each of our own ways about rectal microbicides. If you have the opportunity to speak, no matter how informally, give it a go! With IRMA’s excellent library of resources, you can easily put together a professional presentation with slides that are up-to-date and easy to explain.”

Jerome Galea Advocate, IRMA Steering Committee Member, Founder IRMA-ALC Lima, Peru
Nature Medicine (August 2009) published an editorial on the proceedings. "The field is picking up momentum now," said McGowan in the article, indicating that a new phase of clinical trials was beginning. While these trials have created optimism in the field, "it's still not clear whether there's enough will from funders to do a full-scale efficacy trial for any rectal microbicide," said Robin Shattock, an immunologist at St. George’s, University of London. "That's the biggest hurdle."

Satellite co-sponsors included AVAC—Global Advocacy for HIV Prevention, the Microbicide Trials Network, and Health4men, a gay men’s health project in Cape Town.

IRMA goes to Oxford!

In October 2009, IRMA Steering Committee member Jerome Galea was invited to present at a seminar series on evidence-based interventions at the Department of Social Policy and Social Work at Oxford University in the UK. Jerome focussed his presentation on current developments in the field, building his entire presentation around materials available on the IRMA website and adapting it as needed.

Visit the IRMA website at www.rectalmicrobicides.org for a wealth of resources you can use to initiate dialogue in your community.

Looking forward in 2010, IRMA is co-sponsoring "Be Heard!"—the Global Forum for MSM and HIV’s pre-conference at the 18th International AIDS Conference in Vienna. Chair Jim Pickett will speak at the Australasian HIV/AIDS Conference in Sydney in October.

4.3 Act globally, think rectally

Beginning with four members in two countries, IRMA now has active members across the globe. This overview provides select snapshots of advocacy activities that have taken place in Africa, Latin America and the Caribbean, Australia, Europe, and North America.

4.3.1 Africa

In Nigeria, initial RM activities actually pre-date IRMA. In 2004, Alliance Rights—an organisation serving as a voice for gay men and other MSM in Nigeria since 2001—took on the challenge of advocating for RMs. With support from the New HIV Vaccines and Microbicides Advocacy Society (NHVMAS), Alliance Rights organised a number of fora to discuss RMs and their relevance for Nigerians. These fora included events at the 2005 International Conference on AIDS and STIs in Africa (ICASA), and at the African AIDS Vaccine Programme (AAVP) stakeholders meeting convened in 2007 in Abuja, Nigeria.

Several Nigerian RM advocates attended the Microbicides 2008 international conference, including two advocates who were able to attend thanks to financial support from IRMA’s John Shaw Memorial Scholarship Fund. Following the conference, a group of the Nigerian attendees formed a group called IRMA-Lagos. The group expanded in 2009 to become IRMA-Nigeria, with branches in Lagos and Ibadan. Its membership includes gay men and other MSM, sexual minorities, and HIV/AIDS researchers and advocates throughout Nigeria. IRMA-Nigeria educates the community about microbicide development efforts in order to ensure support for research, development, and future availability in Nigeria.
The Ibadan branch, based at the University College Hospital, includes public health physicians, researchers, and medical students and urges researchers from the HIV field to get more involved with microbicide research. Increasing the visibility of RMs within the university community, thereby making an impact on society at large, is the group's primary objective. IRMA-Ibadan encourages collaboration among its members to attract funding and to expand the research agenda in Nigerian universities, especially in the areas of planning and evaluation.

IRMA-Lagos organised a “sensitisation” event on microbicides with the goal of raising awareness about microbicides, including the need for RMs, and to encourage the participants to get involved in RM advocacy. Over 60 people attended, including members of an HIV support group, sex workers, and health workers. Organisers were quite encouraged to see that by the end of the event all the participants showed a level of understanding, and a majority of them joined IRMA-Nigeria. Photos from this event are available at: www.irma-rectalmicrobicides.blogspot.com/2009/06/irma-nigeria-holds-microbicides.html.

The success of IRMA-Nigeria is in part responsible for the large number of abstracts submitted from Nigeria for consideration at both Microbicides 2008 and Microbicides 2010, many of which focussed on microbicides in general and on RMs in particular.

Currently, IRMA’s Steering Committee includes Community Vice-Chair Kadiri Audu of Lagos, and Dr. Olanrewaju (Lanre) Onigbogi of Ibadan.

"Bearing in mind the ongoing work in this field and the enthusiasm of IRMA-Nigeria members, it is anticipated that the amount of high-quality work focussing on rectal microbicides research will increase. The group envisions a cohort of researchers and advocates who will come out of Nigeria and compete internationally to get funding for rectal microbicides research and advocacy."

—Lanre Onigbogi, IRMA-Nigeria

In Kenya, IRMA activities have been incorporated into the work of Ishtar MSM, an organisation that promotes health and social well-being for gay men and other MSM. Through wellness workshops, open forum discussions, and outdoor activities, RMs are discussed as a possible new HIV prevention tool. Members of the community were especially interested in discussing a potentially expanded array of prevention tools after an acute shortage of lube led to a stagnation in prevention activities.

IRMA Steering Committee member Lourence Misedah has presented in different fora on the need for RMs as a new preventive measure and on the need for further research, including a consultation on gay men and other MSM held in Nairobi and hosted by the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the United Nations Development Programme (UNDP).

Peer educators, who play a big role in Ishtar MSM’s outreach, also have advocated with a variety of stakeholders. Notably, with technical assistance from IRMA, they were able to provide input during the review of the Kenya National AIDS Strategic Plan, especially on the issue of access to existing HIV prevention tools. Ishtar MSM is now looking to expand RM-related activities to areas outside Nairobi.
“Despite living in a country where gay men and other MSM are included in the National AIDS Strategic Plan, it’s with deep sadness and pain that I still see a lack of programming on the ground to meet our prevention needs. As a result, there is an acute shortage of lubricants, for example. How long will we be in the shadows? There’s a need for innovative prevention measures for a healthier and safer tomorrow for gay men and other MSM in Kenya. The time to act is now! There’s hope in rectal microbicides.”

—Lourence Misedah, Ishtar MSM (Kenya) and IRMA Steering Committee member

4.3.2 Australia

The HIV epidemic in Australia remains concentrated among gay men and other MSM, with unprotected AI among men the key factor associated with newly acquired HIV infections. While condom use remains generally high, and is indeed normative in many sexual contexts, there has been considerable discourse about the need for alternatives in a sustained safe sex culture. Studies report that in the absence of biomedical prevention tools some gay men and other MSM engage in harm reduction behaviours intended to decrease the need for condoms, such as negotiated safety, sero-adaptive techniques including strategic positioning (the practice of assuming the insertive or receptive position for anal sex based on serostatus), and consideration of clinical markers such as viral load.

The primacy of unprotected AI as the driver of the Australian epidemic means that a safe and effective RM would have considerable impact. Accordingly, RM research, development, and advocacy have been highlighted in several national and international events there.

In 2007, IRMA Steering Committee member Bridget Haire presented a general overview of the RM field at the Australian Microbicide Symposium, including the challenges of the rectal compartment compared to the vaginal compartment, the prevalence of anal sex in heterosexual as well as homosexual sex, and the role of advocacy in creating demand for a rectal product. This was followed up in July of the same year with a presentation by IRMA Scientific Vice-Chair Ian McGowan in Sydney at the International AIDS Society conference on HIV Pathogenesis and Prevention, featuring research on the investigational microbicide UC781, and a wealth of material on the processes of testing safety for rectal use. The role of RMs was discussed further at a community symposium convened by AVAC—Global Advocacy for HIV Prevention, held as part of the IAS meeting.

In 2008, RMs were on the agenda at the Australia Biomedical Prevention and Microbicides Symposium, which Haire helped to organise. With a focus on strategic issues within biomedical prevention, including the importance of establishing rectal safety of vaginal products, the meeting considered the role of anal sex in research aimed at heterosexual practices and the development of specific rectal products.

Through this period, the Australian Federation of AIDS Organisations (AFAO) provided both cash and in-kind support to IRMA, through funding teleconferences and supporting staff to pursue IRMA-driven activities. The Global Campaign for Microbicides (GCM), a strong IRMA ally, also provided funding for both Australian Microbicide Symposia.
4.3.3 Europe

By mobilising its European partners and allies, including Steering Committee members, IRMA advocates for an increase in European-initiated funding and research for the development of RMs.

The United Kingdom has been most active in this regard. The UK Campaign for Microbicides—a partner of GCM—convened a Rectal Microbicides Working Group for two years. As noted in IRMA’s last report, IRMA also worked with the Terrence Higgins Trust (THT) to address false RM claims from a UK-based lubricant manufacturer.

Before GCM had to close its European office because of funding cuts in 2009, it worked with IRMA and GCM partners in a dozen European countries to develop strategies on how to move forward a European RM agenda. However, once GCM offices closed, IRMA was left with limited capacity to continue this work. IRMA attempted to secure funding to convene a meeting of European donors, researchers, and advocates. However, no donor has yet stepped up to provide the necessary support for such a meeting.

In the meantime, IRMA Steering Committee members and allies continue to engage with key European partners in an effort to ensure that:

- A greater number of European advocates join RM advocacy efforts;
- A greater number of European researchers participate in RM research;
- Key European countries, institutions, and donors fund RM research and advocacy activities; and
- European stakeholders raise awareness of the need for more HIV prevention options, including RMs, for Europeans and for the women and men around the world who engage in anal sex.

4.3.4 Latin America and the Caribbean

IRMA’s Latin American chapter, IRMA-ALC (IRMA-América Latina y el Caribe), was launched in 2008 by HIV prevention and treatment researchers and advocates (including IRMA Steering Committee members Jerome Galea and Dr. Jorge Sánchez) with the aim of promoting education and research efforts on RMs in Latin America and the Caribbean. Founding members represent the UCLA Program in Global Health-Latin America and Impacta Salud y Educación in Lima, Peru; Equidad in Guayaquil, Ecuador; and the Fundação Oswaldo Cruz in Rio de Janeiro, Brazil.

IRMA-ALC’s first steps in advocacy included the launch of IRMA’s report, Less Silence, More Science: Advocacy to Make Rectal Microbicides a Reality in Spanish. Menos Silencio, Más Ciencia: Iniciativa para que los Microbicidas Rectales sean una Realidad was released at AIDS 2008 in Mexico City. Concurrently, IRMA-ALC members continue to give various presentations to local organisations, universities, and professional groups about RMs, building awareness and stimulating interest in RM research and advocacy.

There are many unknowns regarding the acceptability and feasibility of conducting RM clinical trials in Latin America and the Caribbean and the subsequent introduction of a future product. It is unclear if existing data and experiences from the U.S. will translate to this region.
With minimal funding, IRMA-ALC members have taken steps to begin research efforts, laying the groundwork for larger investigations. To this end, IRMA-ALC members analysed the Latin American data from IRMA’s global survey on the use of lubricants for anal sex (see Less Silence, More Science: Advocacy to Make Rectal Microbicides a Reality for a global overview of the survey results). The Latin American-specific data, highlighting lubricant use for anal sex and the potential acceptability of a future RM, were presented at Microbicides 2008 in New Delhi, at AIDS 2008 in Mexico City, and at the 2009 meeting of the International Society for Sexually Transmitted Disease Research in London.

In 2009–2010, the UCLA AIDS Institute and the UCLA Center for AIDS Research launched a RM study in IRMA-ALC’s three founding countries of Peru, Ecuador, and Brazil. The study, entitled “Acceptability of Rectal Microbicides (RM): Barriers and facilitators of RM use among men who have sex with men in 4 South American cities,” is the first of its kind in the region. The study will systematically explore acceptability among diverse populations, including sex workers, transgendered persons, and both gay and non-gay identified men who have sex with men. The project also will examine culture-specific customs, beliefs, and stigma related to anal sex. A total of 256 people will participate.

“We hope that the data collected in this study will provide the foundation for a future, larger research agenda leading to the development of rectal microbicide clinical trials in the region, as well as expanded acceptability studies, which will be critical in preparing for adequate roll-out and dissemination of RM.”

—Jorge Sánchez, IRMA-ALC

In 2009, the London School of Hygiene and Tropical Medicine received funding from amfAR to develop a mathematical model that would estimate the impact of RMs in two cities: Bangalore, India and Lima, Peru. The influence of IRMA-ALC’s work contributed to Lima being chosen as a site for this study. See Section 2.7.1 for a description.

4.3.5 United States

In 2008 and 2009, IRMA members presented on RM research and advocacy at venues throughout the United States, including the University of Illinois-Chicago, Philadelphia’s annual Prevention Conference, the 2008 National Gay Men’s Health Summit in Seattle, Chicago’s 2009 National LGBTI Health Summit, and at events in Cleveland and Iowa among others. The Funders Concerned About AIDS featured IRMA’s advocacy initiatives on one of its teleconferences.

A wide range of U.S.-based media outlets covered RMs as a result of IRMA’s outreach, including stories on the websites RH-Reality Check, the Bilerico Project, Bloggernista, The Body.com, and AIDSmeds.com. Print outlets publishing articles on RM included the Windy City Times, Positively Aware, HIV Plus, and the Bay Area Reporter. In addition, articles in organisational newsletters published by Gay Men’s Health Crisis and the National Association of State and Territorial AIDS Directors, among others, raised visibility on the field’s progress. IRMA’s Jim Pickett has made multiple guest appearances on popular podcasts such as Feast of Fun and the Windy City Queercast, using each appearance to raise RM visibility.

**WORLD MAP HIGHLIGHTING KEY ACCOMPLISHMENTS OVER THE PAST 2 YEARS**

**US:** The world’s first Phase I trial testing the rectal safety of a microbicide is completed in Los Angeles. A new Phase I trial launches, and another is scheduled to begin, in 2010.

**Mexico:** IRMA presents on RMs at a meeting on gay men and other MSM.

**US:** IRMA raises the profile of RMs through presentations at local and national events, articles in print and electronic publications, and interviews on popular podcasts.

**Europe:** NGOs discuss strategies to increase European involvement in RM research, funding and advocacy efforts.

**Peru, Brazil, Ecuador:** Launch of IRMA-América Latina y el Caribe, and a four-city RM acceptability study.

**Nigeria:** Launch of IRMA chapters in Lagos and Ibadan. Training fora are held. Researchers and advocates are encouraged to join RM efforts.

**Kenya:** Peer educators from Ishtar MSM, an IRMA partner, advocate to include the prevention needs of MSM in the National AIDS Strategic Plan.

**India:** Launch of IRMA report Less Silence, More Science: Advocacy to Make Rectal Microbicides a Reality.

**South Africa:** IRMA co-sponsors a meeting on “Rectal Microbicides: An African Perspective.”

**Australia:** Two national microbicides symposia discuss RMs in the context of new prevention technologies.
4.4 IRMA's advocacy on the safety of lubricants used for anal sex

Many men and women use sexual lubricants during AI, yet we know very little about the relative safety of these lubes. Obtaining safety data on products used as sexual lubricants for anal sex would be valuable for public health reasons.

Accordingly, IRMA prioritises advocacy for data collection on the rectal safety of lubricants. Wholly absent in current HIV prevention activities, a translation of this type of data into useful information for users, funders, programme directors, and policy makers would be of significant benefit to the field. Lessons learned in this undertaking will also provide valuable insights into message development on the safety and efficacy of vaginal and rectal microbicides, when these products become available.

Due to the paucity of this type of information, IRMA launched a global web-based survey in 2007 (see an overview of the results from this survey in IRMA’s previous report: *Less Silence, More Science: Advocacy to Make Rectal Microbicides a Reality*). The survey provided valuable information on lube use, preferences, and acceptability among nearly 9,000 men and women from over 100 countries, establishing a prioritised list of the most widely-used lubes to test for rectal safety.

A working group comprised of advocates and researchers was convened by IRMA to discuss the feasibility of testing sexual lubricants for rectal safety. While the working group identified significant scientific challenges that remain unaddressed to this day, there has been some progress (see Section 2.11 of this report for more information).

IRMA’s action on lubricant safety includes the following activities:

- Encouraging researchers to test lubes for rectal safety and to share their findings;
- Facilitating dialogue among leading researchers and advocates within the working group on rectal safety of lubricants;
- Compiling articles and studies related to lube safety, particularly for rectal use, and maintaining an updated background document on this issue;
- Making IRMA’s list of most widely-used lubes available to anyone interested in testing lubes; and
- Keeping IRMA membership updated on developments in this area.

Please join IRMA’s growing network of engaged individuals and organisations. Help us expand awareness of the need for new prevention options for women and men around the world who engage in anal intercourse, and directly address the stigma and silence that continue to surround this human behaviour.

Visit www.rectalmicrobicides.org today for information on how to join.
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

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.

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, 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.
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*

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
Endnotes

1. Denial, neglect, stigma, and criminalisation: Notes on the global challenges to preventing HIV during anal sex


20. Ibid.


35. Ibid.

36. Ibid.


58. From Promise to Product: Advancing Rectal Microbicide Research and Advocacy 1.


