Less Silence More Science

Advocacy to Make Rectal Microbicides a Reality

irma international rectal microbicide advocates

Less Silence

This document is dedicated in memory of our departed colleagues and friends who made significant contributions to rectal microbicides advocacy and, even in their absence, continue to inspire us.

Oludare Oduyume *(Nigeria)*
John Shaw *(U.S.)*

The John Shaw Memorial Scholarship Fund was created by IRMA in the fall of 2007 to honor John and to provide assistance to members wishing to attend Microbicides 2008 in New Delhi, India, February 24 – 7, 2008. Nine advocates were awarded a total of U.S. $10,000 to defray conference expenses. Donors to the fund include Elton John AIDS Foundation, the San Francisco AIDS Foundation, Community HIV/AIDS Mobilization Project and AIDS Foundation of Chicago.

More Science

Advocacy to Make Rectal Microbicides a Reality

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Letter from the chair

In the spring of 2005, a small group of advocates gathered to brainstorm ways to improve awareness and advocacy for the research and development of rectal microbicides and to magnify their place on the expanding prevention technology map. At that time, the silence surrounding rectal microbicides was palpable.

How could it be that so little was being done to find new ways to make anal intercourse safer? After so many years of disease transmission, wasn't the time to scale up rectal microbicide research long over due?

The answer was a loud and resounding ***yes!*** The result; the International Rectal Microbicide Working Group (IRMWG). From that day forward there would be an impassioned movement dedicated to strategically advancing our collective interest in the promise of rectal microbicides.

500
40
6

I will take this opportunity to thank those individuals who joined me back in 2005 to birth this effort: Anna Forbes of the Global Campaign for Microbicides (GCM), Julie Davids of the Community HIV/AIDS Mobilization Project (CHAMP), and Marc-André LeBlanc of the Canadian AIDS Society (he now runs the Global North Programs for GCM).

While our goal was clear, we didn't yet have the vision needed to get there. We knew it would be critical to link community advocates with the researchers, scientists, policy makers and funders who were doing some incredible, if unnoticed, work in the field. We also knew that to be successful we would need to draw on the passion and brilliance of people around the world – people who could unlock the necessary ideas and resources.

At the top of our minds, then and now, were the women and men across the globe of all sexual persuasions who engage in anal intercourse and desperately need new prevention technologies that go beyond latex.

And here we are, releasing **Less Silence, More Science - Advocacy to Make Rectal Microbicides a Reality** at Microbicides 2008 in New Delhi. Like our first publication, released at the Cape Town conference, we hope this new document will create visibility, legitimacy and urgency for this cause. We are certain this report will propel all of our work forward.

individuals

countries

continents

After concluding a process that included our entire membership, we retired our old name (IRMWG) and are now known by the much more mellifluous, IRMA (International Rectal Microbicide Advocates). Today our membership numbers over 500 individuals and organizations from 40 countries on six continents. Our web presence has grown from one simple page into an actual website - featuring a URL that dreams are made of: www.rectalmicrobicides.org.

I know I speak for everyone in our far-flung network when I say I am deeply honored to be collaborating with such an incredible array of smart, passionate advocates and scientists - you - and am profoundly grateful for the vision and financial support of leaders such as Broadway CARES/Equity Fights AIDS, the Elton John AIDS Foundation, the Playboy Foundation, the San Francisco AIDS Foundation, our founding organizations, and all the other organizations and individuals who are so vital to our mission and who are duly thanked in this report. I would like to extend special thanks to the AIDS Foundation of Chicago (AFC) – my home – for such extraordinary support these past three years.

For today, tomorrow, and the day after that, we will continue to advocate for more science and an end to the silence that dooms the lives of so many. We invite you to join us.

Sincerely,

Jim Pickett

Chair, International Rectal Microbicide Advocates,
Director of Advocacy, AIDS Foundation of Chicago

Acknowledgements

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Contents

*Part of the NIH/UCLA-led Microbicide Development Program (U-19)

Introduction

Since its creation in 2005, International Rectal Microbicide Advocates (IRMA) has seen significant growth and success. From a handful of advocates, IRMA has built a network of well over 500 advocates, researchers, and policy makers from 40 countries on six continents.

irma international rectal microbicide advocates

New name, new look, same goals

Originally founded as the International Rectal Microbicides Working Group (IRMWG), the group re-branded our name at the end of 2007, created a new logo, and launched a new website (www.rectalmicrobicides.org). Amidst all this change, IRMA remains committed to the same goals we developed from our inception:

- To advocate for accelerated research, development and access to safe, effective and acceptable rectal microbicides;
- To promote rectal safety studies on all viable vaginal microbicide candidates;
- To support, where appropriate, the research of other new prevention technologies, such as male circumcision, vaccines and oral prevention (PrEP), and to promote existing prevention methods such as male and female condoms as part of a range of prevention options;
- To serve as a central forum for exchange, debate, and networking on rectal microbicides; and,
- To convene diverse perspectives and scientific disciplines to improve understanding and action around rectal microbicide research and development.

Focus on safety

In these very early stages of rectal microbicide development, the primary focus of research is safety: examining the rectal safety of sexual lubricants (section 2.12), urging the collection of rectal safety data from late stage vaginal microbicide trials (section 3.1), determining the measures for assessing basic rectal safety (section 2.3), and of course, evaluating the safety of potential rectal-specific microbicides (sections 2.1 and 2.2).

We hope this document will:

- Serve as an authoritative reference on recent developments and current efforts in rectal microbicide research;
- Illustrate key advocacy goals and strategies;
- Provide a description of the resources and activities of IRMA; and,
- Inspire people working in HIV prevention, whether in advocacy, research, policy or funding, to become involved in rectal microbicide advocacy and research.

1 Rectal microbicides in context: the global HIV pandemic, anal intercourse and human rights

1.1 The global HIV/AIDS pandemic outpaces global prevention efforts

On the eve of World AIDS Day in 2007, the Joint United Nations Programme on HIV/AIDS (UNAIDS) announced that over 33 million people were living with HIV worldwide, including 2.5 million people newly infected with the virus in 2007. Over 2 million people died of AIDS-related illnesses in 2007.[1]

No region of the world is spared. Sub-Saharan Africa remains the most affected region, where, unlike other areas, the majority of people living with HIV are women (61%). The Caribbean remains the second most affected region, proportional to its population, and the HIV pandemic continues to grow in Asia, Eastern Europe, and Central Asia.[2]

There are indications of a re-emerging HIV epidemic among gay men and other men who have sex with men (MSM) in industrialized countries, including North America, Western Europe and Australia. The number of MSM reported with HIV or AIDS is now increasing in many countries, including the United States and countries of Western Europe.[3]

In some regions (Latin America, Australia and New Zealand, North America, Western Europe), unprotected sex between men is recognized as an important driver of the pandemic.[4] In these cases, the majority of infections are likely driven by unprotected anal intercourse (UAI). But what about sex between men in other regions? What about UAI between men and women globally? We will address these questions in the next section.

Clearly, with over 6,800 new infections every day across the world[5], there is a need to scale up global prevention efforts significantly. The Global HIV Prevention Working Group, convened by the Bill & Melinda Gates Foundation and the Henry J. Kaiser Family Foundation, estimates that globally, only 9% of risky sex acts are undertaken while using a condom, and that prevention services reach less than 10% of men who have sex with men and persons who inject drugs, and less than 20% of sex workers.[6]

The Working Group calls for massive and urgent scaling up of existing global HIV prevention methods. According to the group, "if comprehensive HIV prevention were brought to scale, half of the infections projected to occur by 2015 could be averted…We could slow and even begin to reverse the trajectory of the global HIV epidemic by using the prevention tools currently at our disposal."[7]

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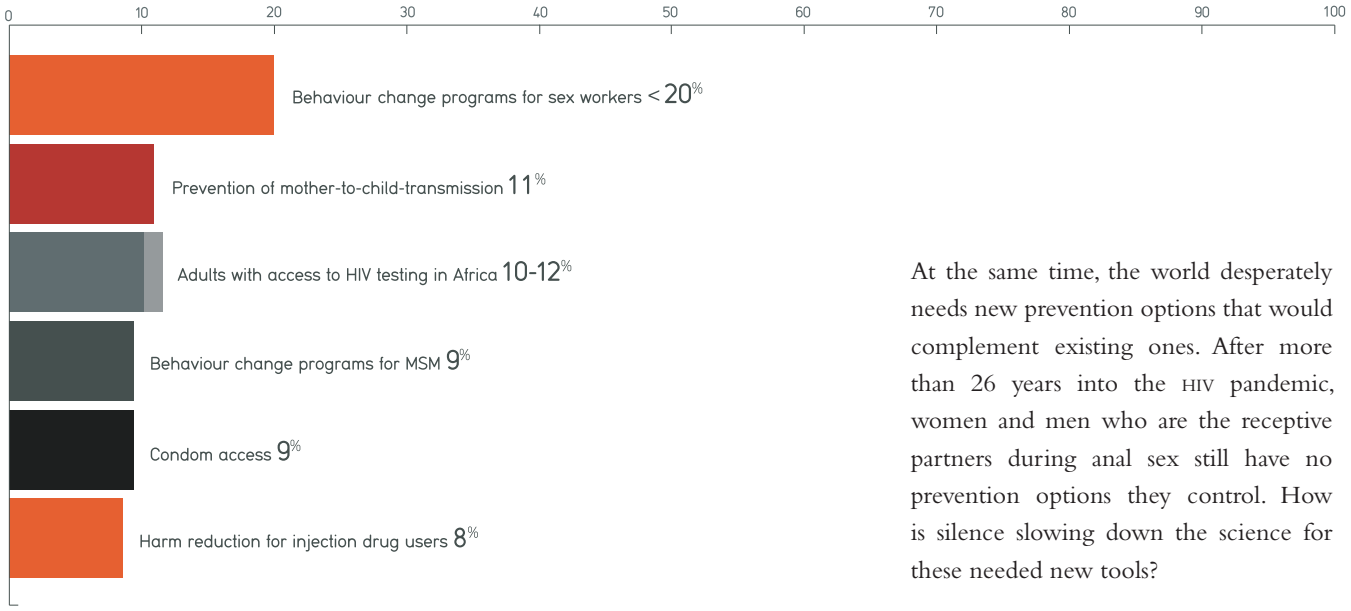
6,800
new infections every day across the world, there is a need to scale up global prevention efforts significantly

Global Coverage for Select HIV Prevention Strategies in 2005
Global HIV Prevention Working Group, 2007; WHO/UNAIDS/UNICEF, 2007



At the same time, the world desperately needs new prevention options that would complement existing ones. After more than 26 years into the HIV pandemic, women and men who are the receptive partners during anal sex still have no prevention options they control. How is silence slowing down the science for these needed new tools?

After more than
26 years
into the HIV pandemic, women and men who are the receptive partners during anal sex still have no prevention options they control

1.2 Criminalization of behaviours and human rights violations: Challenges to a global response to prevent HIV transmission through anal intercourse

At the end of 2007, no less than 85 member states of the United Nations still criminalized consensual same sex acts among adults.[8] Often called sodomy laws, some statutes regulate specific sexual acts (for example, anal sex) regardless of gender or sexual orientation while others prohibit a range of same-sex sexual activities. Many laws are quite broad in their scope, including the prohibition of any "unnatural" or "indecent" sexual act.[9]

Punishments include fines, imprisonment (from 3 years to life), corporal punishment, hard labour, and death.[10]

In this political climate, it is not surprising that many gay men, other MSM, as well as women and men who engage in anal intercourse (AI) face significant barriers to accessing information and tools needed to protect themselves from HIV infection. This is exacerbated by a deplorable dearth of programs and services for same-sex practicing people in most developing countries.

"The vulnerability of same-sex practicing men and women is not due to any biological predisposition, but is the result of an interlocking set of human rights violations and social inequalities that heighten HIV risk. Anti-gay discrimination is fuelling the African HIV/AIDS epidemic."

— International Gay and Lesbian Human Rights Commission. Off the Map: How HIV/AIDS Programming Is Failing Same-sex Practicing People in Africa, 2007.

1.3 Anal intercourse worldwide: less silence, more science

Our knowledge of the incidence, prevalence and context of AI globally is still woefully inadequate. However, there is a growing body of literature available. Research on AI between men is now more in-depth, and research on AI between women and men is increasing.

What we know

Because data collection methods vary tremendously between surveys, broad global statements about the incidence and prevalence of AI are currently difficult to make, if even possible.

Anal intercourse is a widely practiced behaviour among MSM. Among gay men in the United States—who are estimated to comprise 2.3%[11] to 13%[12] of the U.S. population—the vast majority (95%) report having engaged in AI.[13] Less is known about this behaviour among heterosexuals, although AI is increasingly reported.[11,14] While rarely discussed in the scientific literature,[15] AI is increasingly understood as a more common practice among heterosexuals. In the U.S. and UK, between 10% and 35% of heterosexual women report practicing receptive anal intercourse (RAI)[11, 12, 16, 17] and lifetime reports of AI with opposite-sex partners are as high as 40% for U.S. males.[11] In absolute numbers, seven times more heterosexual women than gay men in the U.S. practice RAI.[14] In more specialized study populations, the proportion of heterosexuals engaging in anal sex ranges from a high of 32% of sexually active women at high risk of HIV exposure in the previous 6 months[18] to a low of 23% of "non-virgin" university students who reported ever engaging in AI.[19] While few studies collect data on the incidence of AI between men and women, it seems relatively frequent. A household survey revealed that most engaged in this activity one to five times per month and 7% of sexually active respondents reported AI at least once a month during the year prior to the survey.[20]

In absolute numbers,
7 times more
heterosexual women than gay men in the U.S. practice receptive anal intercourse

Anal intercourse between men and women has been linked to an increased likelihood of HIV transmission within serodiscordant couples in the U.S.[21] and Brazil[22] and has been associated with HIV infection among men and women attending sexually transmitted infections (STI) clinics in India.[23] This increased risk is likely due to greater efficiency of transmission and low frequency of condom use during AI between men and women. The unadjusted probability of transmitting HIV is 0.08 per contact for RAI,[24] as compared to 0.001 per coital act for vaginal intercourse.[25] This is most likely because the lining of the rectum (single columnar epithelium) is both more fragile and contains more CD4 cells than the lining of the vagina and part of the cervix (stratified squamous epithelium), making it more vulnerable to HIV infection. Connections between AI and STIs other than HIV are less clear. While AI has been associated with gonorrhea in the general population, the relationship has not been seen in STI clinic patients.[26] Among women, AI has been associated with abnormal

anal cytology[27, 28] yet little data exist on rectal carriage of other STI pathogens in women, largely because female ano-rectal sites are rarely sampled and tested.

Globally, with the exception of communities where condoms are actively promoted and accessible for gay men and other MSM, almost all AI between women and men, as well as between men, is unprotected.[29] When women are the receptive partner in AI, the power dynamics involved may be different than between two men. For example, women may be more prone to engage in anal sex in cultures, contexts and regions where virginity is especially prized and contraception not easily accessible.

We must consider the possibility that UAI, even when practiced rarely, may in fact be a significant source of HIV transmission in many contexts.

Dangerous silences

Gay men and other MSM in North America, Western Europe and other industrial countries have made incredible strides in raising awareness, influencing policies and advocating for prevention programs that target their disproportionately impacted communities. However, all too often the seemingly inseparable connection between AI and Western gay and MSM has meant critical aspects of the pandemic in developing regions are overlooked and under-researched.

Globally, almost all anal intercourse is unprotected

By focusing almost exclusively on gay men, MSM, and the West when developing policy related to AI in the context of HIV prevention programming, we neglect to identify the prevalence of AI between women and men as well as the HIV prevalence among, and indeed, the mere existence of, gay men and other MSM in Asia, Africa and other parts of the developing world. This neglect costs lives. In its ground-breaking report *Off the Map*, the International Gay and Lesbian Human Rights Commission decried the wall of silence that surrounds AIDS and same-sex practices in Africa.[30] The situation in developing countries outside of Africa is often much the same regarding the collective blind eye turned toward MSM and anal sex practices between women and men.

Precious little research has examined the role of AI in HIV transmission in developing countries. However, studies in Senegal, Ghana, Kenya and Sudan indicate that rates of HIV prevalence among MSM are significantly higher than in the general population.[31,32] This has also been demonstrated in most countries of Latin America, and in several countries and cities in Asia.[33,34]

The illegality of AI in many countries and jurisdictions, the strong taboo and homophobia associated with anal sex, and the imprecise language we use to describe populations and behaviours conspire to render these realities invisible. We tend to conflate sex acts with identity through the use of imprecise, misleading language. Phrases like "heterosexual transmission" mask the fact that women and men who identify as heterosexual engage in AI. This lack of clarity, honesty

and specificity negates that a significant portion of the pandemic is likely driven by UAI in regions broadly characterized as being "driven by heterosexual HIV infection." In this construct, heterosexual HIV transmission automatically translates to vaginal intercourse. While identity, sexual orientation and sexual practices may be related, they are not always so clearly delineated. "HIV infection via unprotected vaginal intercourse" would be a more accurate phrase than "heterosexually acquired HIV infection".

These are more than innocuous semantics; language matters. Inaccurate language impacts quite concretely on program design and delivery; on research design, particularly for microbicides; on stigma faced by communities, including gay men and other MSM; and, on the deceptive absence of other populations that engage in AI, including heterosexual men and women, lesbians, and bisexuals across the globe.

Phrases like "heterosexual transmission" mask the fact that women and men who identify as heterosexual engage in anal intercourse

What we need to know

In order to improve prevention programs and develop tools that would reduce the risk of HIV transmission for women and men who engage in AI, we desperately need more research in the following areas:

- Standardized incidence and prevalence data on AI between women and men, as well as between men, from all regions of the world, including developing countries
- Greater qualitative data to understand the context for AI across cultures
- Improved methods of data collection to maximize confidentiality, and thus the reliability of responses
- More information on the behaviours associated with AI, e.g. use of condoms, lubricants, douches
- Estimates of the role UAI plays in the HIV pandemic, including but not limited to developing countries, among gay men and other MSM in developing countries, and among women and men in the context of so-called "heterosexual epidemics"
- Mathematical modeling that would assess the potential impact of rectal microbicides on the pandemic, including but not limited to that in developing countries, and among various populations, including women and men who engage in AI.

2 The state of rectal microbicide research

Rectal microbicide research is more robust at the end of 2007 than it has ever been. While the world's first rectal microbicide safety trial is under way, two more Phase I trials are in the planning stages. In addition, several research projects devoted to rectal microbicide–related topics are ongoing or have been recently completed, including projects that seek to establish a pipeline of potential products to test as rectal microbicides, to determine which formulations might work best rectally, to describe current behaviours and practices related to anal sex, to develop applicators and delivery systems that are appropriate for rectal use, to establish the baseline parameters that could be assessed in rectal trials, to facilitate the regulatory pathway and to establish the rectal safety profile of sexual lubricants.

The U-19 Microbicide Development Program (MDP)

While there are several groups that have been advocating and actually undertaking preliminary studies of rectal health, rectal toxicity from topical agents like N9, rectal physiology and reaction to enemas and receptive sex, there were no coordinated efforts to develop rectal microbicides until 2004. In August of that year, a 5-year grant from National Institutes of Health's National Institute of Allergy and Infectious Diseases (NIH/NIAID) was awarded to a consortium of researchers and institutions to develop a pipeline for testing the safety and efficacy of topical microbicides used rectally. This large grant was funded under the NIH's unique Integrated Preclinical/Clinical Program (IPCP), designed to support innovative, important translational research (bench to bedside, as it were). The primary site for this award was UCLA with collaborative institutions (and lead researchers) of Johns Hopkins University, University of Washington in Seattle, NIH itself, University of Pittsburgh/Magee Women's Research Institute, St. George's Hospital and Medical School in London and the Health Protection Agency at Porton Down (near London).

Inaccurate language

impacts quite concretely on program design and delivery; on research design, particularly for microbicides

The grant has five projects which approach the rectal microbicide issue from different angles and are coordinated to feed their derived data and information into each other to make the final whole greater than the parts. The projects are (i) preclinical and macaque trials which look at different compounds for safety in the cells line and then in the explant system. Then, with favourable agents, evaluate safety and possible efficacy in non-human primates; (ii) a novel trial involving nearly 900 participants in Baltimore and LA to identify behavioural perceptions, symptoms and signs associated with rectal health, in general, and what might be associated with RAI in men and women, HIV-negative and HIV-positive. This trial will have a subset of volunteers testing different potential applicators or "carriers" of rectal microbicide drugs to see what form they would find more acceptable when the real manufacturing process begins; (iii) a group

that is focused on developing formulations or carriers that will hold the rectal microbicide drugs, that will be designed specifically for the rectal compartment (in contrast to trying to adapt vaginally-formulated products); (iv) human trials of the effects of different kinds of enemas on causing injury to the fragile lining of the rectum and conduct tests designed to identify where the new rectal-specific formulations might actually distribute in real life; and finally, (v) two human Phase I trials of vaginally-formulated microbicides used rectally. These are the first true rectal microbicide Phase I trials.

As indicated by an asterisk (*), the following sections are part of this U-19 Microbicide Development Program: sections 2.1, 2.3, 2.4, 2.5, 2.6, 2.7 and 2.10.

2.1 The world's first rectal microbicide safety trial: testing UC-781*

In early 2007, the University of California, Los Angeles (UCLA) began actively enrolling for the world's first rectal microbicide safety trial. This is a Phase I randomized, blinded, placebo-controlled safety and acceptability study of the UC-781 vaginal microbicide gel formulation applied rectally in HIV-1 seronegative adults.[35]

In early **2007** **UCLA** began actively enrolling for the world's first rectal microbicide safety trial

The trial is sponsored by CONRAD in partnership with the NIH/NIAID.

Participants are exposed to either one of two concentrations of UC-781, a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a placebo, in a single dose followed later by a 7-day exposure. The UC-781 gels and the universal placebo gel are the same as in vaginal trials.

The trial objectives are:

- To evaluate the safety and acceptability of 0.1% and 0.25% UC-781 vaginal microbicide gel versus placebo when applied rectally.
- To determine whether use is associated with rectal mucosal damage.
- To determine the pharmacokinetics of UC-781 vaginal gel administered rectally in a subset of participants. This will help to guide future trials by providing an indication of how much drug is absorbed, and give further guidance when planning a trial among HIV-positive participants to measure potential resistance.

There are 36 HIV-negative men and women with a history of RAI participating in the study, divided into the three arms. Six of them are part of the pharmacokinetics study. Over a period of eight weeks, participants have five visits to the clinical trial site. This includes three flexible sigmoidoscopic exams, a procedure that involves placing a tube about the size of a finger (with light, water and air sources) into the rectum to visually examine and collect small amounts of tissue (biopsy) through

a channel in the scope. This is the same exam that, in the past, was recommended for all people for colon cancer screening. Biopsy samples are taken at 10 and 30 cm from the anal opening.

In contrast to biopsies taken from skin (or other areas that have nerve endings that detect pain), the inner lining of the gut/intestines does not have these pain nerve endings. So, biopsies are not really felt nor are they painful to obtain. Sometimes, a fair amount of air can be used in order to "open up" the colon enough for the scope to be slowly advanced. This distends the intestine, like when one has to pass gas, and can feel "uncomfortable". But it is very rarely painful in someone who does not otherwise have an underlying disease process in the gut.

In addition, throughout the trial, subjects also undergo testing for HIV, a range of STIs and pregnancy as well as standard measures of safety such as Complete Blood Cell counts and chemistry panels. Stool samples and rectal secretion samples are also taken for research testing.

The trial includes several dozen tests and evaluations of safety, pharmacokinetics and acceptability, including:

- Epithelial sloughing – this determines if the product causes the surface of the mucosa to separate from the tissue.
- Histopathology – a microscopic review of the tissue to see if the product causes physical changes.
- Mucosal mononuclear cell phenotype (flow) – this tests whether the product changes the types or amounts of cells (CD4s, CD8s, other) or how activated ("turned on") they are in the mucosal tissue.
- Mucosal cytokine mRNA (tissue) – Mucosal cytokine/chemokine expression (substances linked to tissue inflammation) will be measured using the polymerase chain reaction (PCR) technique.
- Mucosal immunoglobulins – this measures possible changes in the levels of secreted antibodies the body sends into the gut area – an injurious drug might impact these protective levels.
- Fecal calprotectin – a measure of gut mucosal inflammation.
- Explant susceptibility to HIV infection – these are tests run on small pieces of mucosal tissue from the subjects to see if the product has an effect on the growth of HIV put on the tissue in the lab. It is hoped that the investigation might show that when the subject's biopsies have been exposed to the microbicide in vivo (in real life), the drug will also demonstrate inhibition of viral replication in the lab in the tissue (ex vivo).
- UC-781 blood levels to determine absorption from the gastrointestinal tract – this will give an indication of how easily this drug gets through and is absorbed into the blood for distribution to the rest of the body.

Dr. Alex Carballo-Diéguez

Columbia University (U.S.)

"For women, condom use for anal intercourse is much less frequent than for vaginal intercourse. Anal sex is part of the sexual repertoire of both men and women regardless of sexual orientation or identity. Rectal microbicides have the potential to serve as a much-needed prevention alternative to condoms."

- Behavioural questionnaire – this is a computer based survey of the sexual health and history of participants.
- Product acceptability questionnaire – this is a computer based survey of how people felt about the applicator and gel used in this particular trial.
- Acceptability interview – after completion of the trial, subjects complete an in depth interview including open ended questions about the product and applicator, future possible use of a microbicide as well as issues related to participation in the trial.

Some of the challenges to testing products rectally include dealing with fragile epithelia – single cell-layer thick – which can potentially be damaged through some of the study-related actions and tests themselves, such as the product applicator itself. This obviously poses significant challenges to measuring safety of the product being tested. In addition, rectal mucosa has increased absorptive potential and therefore potentially increased resistance profiles, compared to genital mucosa. It is a well-known and frequently used route of delivery of medications when patients can not take medications orally. Therefore, systemic (body) absorption of these topically applied products needs to be carefully considered. A number of the research parameters remain untested or unproven, including the safety indices for healthy subjects, and the suspicion that there are gender differences. This trial includes the most extensive list of rectal safety and mucosal immunotoxicity and mucosal injury measure yet utilized in a clinical trial in healthy subjects. It is hoped that results from this trial will help refine the list of necessary assays for future trials.

Results from the trial are expected in late 2008.

Dr. Pamina Gorbach

IRMA Steering Committee
UCLA (U.S.)

"I feel there is a critical need for a prevention method specifically for anal intercourse, a behaviour that carries an elevated risk of HIV transmission. As this is an indisputably common practice for many men and women, rectal microbicides offer a very promising new prevention option and I believe people will use them, and like them!"

Steve Wakefield

HIV Prevention Trials Network (U.S.)

"I am interested in IRMA because of a desire to connect with people who are willing to recognize that unprotected anal intercourse may still be the norm for both women and gay men."

2.2 Upcoming rectal microbicide safety trials: testing PRO 2000 and VivaGel for rectal safety

Two additional Phase I rectal safety studies are currently being planned for 2008.

The first study will evaluate the rectal safety of the vaginal formulation of VivaGel®. VivaGel is a polyanion dendrimer microbicide being developed by Starpharma Pty Ltd, an Australian biotechnology company. The product has already been studied in one Phase I vaginal safety study and two additional vaginal Phase I studies are currently ongoing. In addition, a penile tolerance study has been completed. A rectal safety study has already been conducted in monkeys and the 3% strength product seemed well tolerated. The rectal safety study will be conducted at UCLA and the University of Pittsburgh and is hoped to start in 2008. Enrolment will include HIV negative sexually abstinent men and women who have a history of practicing anal sex. This study will be sponsored by the Sexually Transmitted Infection – Clinical Trials Group that is sponsored by the NIH.

The second rectal safety study will be conducted on the other side of the Atlantic and is being sponsored by the United Kingdom Medical Research Council Microbicide Development Program (MRC-MDP). This study will evaluate the rectal safety profile of PRO 2000 (0.5% and 2%) in sexually active MSM. PRO 2000 is a polyanion microbicide being developed by Indevus Pharmaceuticals Inc in the U.S. The study will sequentially enrol HIV-negative and then HIV-positive MSM. The two concentrations of PRO 2000 are currently being evaluated as vaginal microbicides in a large Phase III effectiveness study being conducted in sub-Saharan Africa. The MRC-MDP hopes to start this trial in 2008.

2.3 Establishing baseline mucosal measures for rectal microbicide trials*

A critical question in rectal safety trials design is deciding what to measure. In late 2007, Dr. Ian McGowan and his team from UCLA published the results from a study that established, for the first time, the most stable parameters that could be used in studies of candidate microbicides used rectally. The study is published in the December 2007 edition of the Journal of Acquired Immune Deficiency Syndromes.[36]

Microbicide developers need to have a precise set of baseline measurements so they can accurately assess the impact of candidate microbicides in the rectum. Until now, without this baseline that describes what is "normal" in the absence of a candidate microbicide, a standardized comparison was not feasible. For example, the measures will help to assess the level of inflammation and cytotoxicity (cell-killing properties) caused by candidate microbicides.

This set of baseline measurements has already been done in vaginal and cervical tissues. They now exist for the rectum, which will allow for more standardized

testing, and improved comparability between rectal safety studies. This includes assessing the rectal safety of vaginal microbicides and rectal-specific microbicides once they are developed.

Sixteen volunteers participated in the study: four HIV-negative men who had been having (protected) AI at least once a week; four HIV-negative men who had not had AI for at least two months; four HIV-positive men not on antiretrovirals; and four HIV-positive men on antiretroviral drugs (ARVs) with viral loads under 50. All the HIV-positive men recorded having AI, protected or otherwise.

The volunteers were described by the researchers as "dedicated" because the study involved taking 20 tissue biopsies from two different sites, ten at each site, 10cm and 30cm from the anal entrance, three times within a month. (See section 2.1 for a description of this procedure, and an explanation for why it is not painful.) They also took samples of rectal secretions.

The team then evaluated the samples for signs of inflammation and immune response. There was almost no evidence of overt inflammation in any subject, which seems to indicate that AI in itself does not produce inflammation (men with conditions like diarrhea, herpes, gonorrhea and chlamydia that would cause inflammation were excluded from the study). However, different people seem to have different base levels of inflammation and immune responses, so measuring the impact of a candidate microbicide may be difficult without knowing these base levels.

The key findings of the study included recognizing that the level T cells and cytokines (inflammatory proteins often released by T cells) in the mucosa remained relatively stable from visit to visit. This is important as changes in T cell or cytokines induced by microbicides might make participants more vulnerable to HIV infection. Scientists can now use these data to track changes in rectal mucosa associated with microbicide application. Another useful observation was that there didn't seem to be much difference between tissue collected at 10cm and 30cm. This allows investigators to focus on sampling tissue at 10cm – an important step in reducing the complexity of rectal safety studies.

Future research in this area should include a larger number of participants as well as women, for whom results may be different.

Manju Chatani

IRMA Steering Committee
African Microbicides Advocacy Group
(Ghana)

"Rectal microbicides are an essential technology that could allow men and women to protect themselves, without fear, without shame, without taboo."

Dr. Ian McGowan

IRMA Steering Committee
University of Pittsburgh (U.S.)

"I see IRMA as a critical forum for advocating for rectal microbicide development. The high educational standards set by IRMA have resulted in increased respect for rectal microbicide development within the broader microbicide community."

2.4 Regulatory compliance in microbicide trials*

The regulatory issues faced by institutions performing clinical research have become increasingly more complex, placing greater demands on investigators for timely and complete compliance to federal and institutional guidelines. While regulatory approval helps ensure trials are conducted ethically, many investigators do not have an expert on staff that understands the regulatory issues involved in managing investigational research and the institution's obligations under the federal rules.

As part of the U-19 program a Regulatory Compliance and Subject Safety Core was created which provides an infrastructure of regulatory and technical expertise to facilitate management of and to maintain compliance with the regulatory responsibilities of the U-19 Projects while acting in an efficient and cost effective manner to facilitate conducting the clinical trial aspects of the three projects in the MDP, including the Phase I rectal microbicide safety trial. This is emerging as a standard structural component of any complex translational program involving human tissue samples.

2.5 Preclinical evaluation of HIV rectal microbicide candidates*

Through the U-19 Microbicide Development Program (MDP) centered at UCLA, Dr. Ian McGowan and collaborators at St. Georges Hospital and Medical School (headed by Dr. Robin Shattock) and Health Protection Authority, Porton Down (headed by Dr. Martin Cranage) propose to establish a pipeline for the preclinical development of highly active and safe microbicides to prevent rectal transmission of HIV infection. The project has four overall goals:

Aim 1 of this project is to define potential mucosal target cells for HIV infection and to characterize dissemination of migratory cells, with the potential to carry HIV, from rectal mucosa to other lymphoid tissue reservoirs.

Aim 2 will be to evaluate the efficacy of potential rectal microbicide candidates, alone and in combination against HIV infection using cell-based assays and explant cultures. Initial studies will focus on the three antiretroviral reverse transcriptase inhibitor (RT) compounds: PMPA, UC-781 and TMC-120 alone and when formulated as gels.

Aim 3 will be to evaluate the tissue biocompatibility of these rectal microbicide candidates, alone, and in combination, using cell based assays and intestinal explant cultures.

Aim 4 will be to evaluate the efficacy of candidate rectal microbicides against rectal challenge with SIV (in the case of PMPA) and infectious RT-SHIV (in the case of UC-781 and TMC-120) in the Rhesus macaque model of SIV/RT-SHIV infection.

These aims will distill and establish preclinical steps in rectal microbicide drug development which will then transition to exploratory safety evaluation of the same compounds in human studies.

2.6 Aptamer microbicide development program*

The aptamer microbicide development program is a unique collaboration between the University of Pittsburgh, the University of Oxford, UK, and a Belgian biotechnology company. The primary goal of the study is to develop aptamers with specific activity against viral STIs including HIV, HSV, and HPV.

Aptamers are sequences of nucleic acid that are specifically generated to bind to and hopefully render inactive viral targets. Randomly generated sequences of RNA are washed over fragments of the relevant viruses. RNA sequences that are shown to bind to the viral targets can then be captured and synthesized in sufficient quantities to allow evaluation of their activity in cell culture and tissue explant systems.

This program is currently focusing on generating HIV specific aptamers and evaluating them in anal, rectal, and cervical HIV infection studies. Theoretically, it might be possible to generate a multifunctional antiviral aptamer microbicide that might have activity against HIV, HSV, and HPV in rectal and cervical tissue. One of the challenges of working with RNA aptamers will be to modify the RNA so that it is stable in the rather hostile environment of the rectum and vagina.

2.7 Assessing rectal microbicide formulations*

Development of an effective rectal microbicide could be greatly enhanced by knowledge of the distribution of HIV in the rectum and into the surrounding tissues following sexual exposure, as well as the duration of the presence of HIV in these areas. Armed with this information, one could optimize the design of microbicides so that they outdistance and outlast HIV. It would also be beneficial to be able to measure the toxicity of a microbicide candidate, including toxicity duration. Advances in research have given us the ability to evaluate the effects of various formulations and active ingredients in much more sophisticated ways. Therefore we have the ability to move forward in attempts to define compartment-specific, mucosal-surface friendly and safe formulations in advance of broad clinical testing for efficacy.

A group of scientists from the MDP have developed methods to measure the distribution of products (gels and liquids) put into the rectum, simulate receptive AI, and to follow the movement of these products over time. They have applied these methods to study the luminal and tissue distribution of surrogates for cell-free and cell-associated HIV. Combining these methods, one can study the distribution of microbicide candidates simultaneously with the distribution of

Dazon Dixon Diallo

SisterLove (U.S.)

"Developing a rectal microbicide is important for a number of reasons: because more men and women engage in anal sex than are ready to admit it, because women who are not able to negotiate condom use for vaginal sex may be even less likely to do so for anal sex, and because of the potential for alliance-building between women and gay men if they advocate for things in conjuction with one another."

HIV surrogates. This information can be used to evaluate the adequacy of the microbicide distribution. These methods are being used in two related MDP studies – one study focuses on different kinds of enemas and the other is evaluating different kinds of gels.

It is important to better understand enemas because studies have shown that they are commonly used prior to AI (see section 2.11). Some kinds of enemas, including tap water enemas, have been shown to disrupt the lining of the rectum. Sexual lubricants are even more commonly used but less well studied. Like enemas, commonly used over-the-counter sexual lubricant gels may also disrupt the rectal lining (see section 2.12). Accordingly, both enemas and lubricants may contribute to the risk of HIV infection associated with AI. Conversely, because these products are so commonly used in association with AI, they could be excellent candidates for a microbicide drug delivery method if non-toxic enemas and gels could be developed. Therefore, if these formulations could be used to deliver effective microbicides, their implementation could involve little or no behaviour change. Rather, it would only involve a change in product selection, possibly at minimal additional cost.

In each of the MDP studies, the distribution over time of the enemas and gels is being studied to understand their suitability as microbicide delivery devices. This can be judged by comparisons of distribution with enema or gel and HIV surrogates. In addition, the rectal mucosa will be evaluated with several sensitive measures of toxicity to assess which enema or gel has the least effect on the health of the rectal lining and which may enhance HIV transmission. Finally, the acceptability of these enema and gel products is being extensively evaluated. The scientists believe that the combination of distribution, toxicity, and acceptability information will better inform the rational design of a rectal microbicide designed specifically for rectal application.

The enema comparison study was already underway in late 2007.
The gel study will begin in the second half of 2008.

2.8 Rectal microbicide formulation preference trial

Gels and suppositories are two possible rectal microbicide delivery vehicles. Through a rectal microbicide formulation preference trial funded by the National Institute for Child Health and Human Development, Dr. Alex Carballo-Diéguez explored user preferences.

The trial recruited 77 HIV-negative MSM who reported a recent history of inconsistent (or no) condom use for RAI to compare a placebo gel (35ml) delivered intrarectally with placebo rectal suppository (8g). The trial consisted of a cross over design in which men rated their product preferences after being assigned to use the gel in up to three occasions of RAI, and subsequently to use the

suppository in up to three occasions of RAI; or, alternatively, to try the suppository first and the gel second.

The results of the trial showed that more participants preferred the gel over the suppository (75% vs. 25%, p <.001), and so did their partners (71% vs. 29%, p <.001), according to the participants' report. Paired t-tests comparing gel vs. suppository showed more favorable ratings for the gel overall and also on attributes such as color, smell, consistency, feeling in rectum immediately after insertion and/or 30 minutes after insertion, and application process.

The gel resulted in less negative ratings than the suppository in terms of participants being bothered by leakage, soiling, bloating, gassiness, stomach cramps, urge to have bowel movement, diarrhea, pain or trauma. Participants also scored the gel more favorable than the suppository in terms of feelings during AI, sexual satisfaction using the product, partners' sexual satisfaction, liking the product when condoms were used and when condoms were not used.

Participants indicated a higher likelihood to use the gel than the suppository in the future if it were found to provide some benefit against acquiring HIV infection.

2.9 Rectal microbicide delivery device study

In January 2007, Dr. Alex Carballo-Diéguez received support from the American Foundation for AIDS Research (amfAR) to conduct a study in collaboration with PATH to develop a prototype of an inexpensive standard rectal microbicide delivery device (MDD) that could be used across rectal microbicide trials to ensure ease of use, comfort, and effective delivery of microbicide gel across a wide range of dose volumes to both men and women who have AI.

Prior studies had demonstrated that the applicator used to deliver a rectal gel was a crucial factor influencing rectal microbicide acceptability.

Following interviews with the nine experts in the field of rectal microbicide development (including IRMA members), specifications of a MDD were developed and sent to prospective manufacturers. At the time of this writing, manufacturers had bid to obtain the contract for the production of an MDD prototype and the contract was awarded to HTI Plastics. They have shared with Dr. Carballo-Diéguez's team an initial three-dimensional model and a final version was in development, with anticipated completion in the months ahead.

Lanre Onigbogi

University College Hospital Ibadan (Nigeria)

"Research ends up on dusty tables without advocacy."

Dr. Polly Harrison

Alliance for Microbicide Development (U.S.)

"We must know a lot more about rectal physiology and the best corresponding formulations than we do, if rectal microbicides are to be safe and eventually effective in helping prevent HIV."

2.10 Establishing rates of ano-rectal symptoms and signs among men and women who practice receptive anal intercourse*

As part of the U-19 MDP, Dr. Pamina Gorbach is leading a large epidemiological study of rectal health and behaviour among 896 men and women in Los Angeles and Baltimore to establish the prevalence of ano-rectal health conditions and practices. Half of this sample (450 individuals) will have recently practiced RAI. The sample will also be half HIV-positive individuals. All study participants are completing an extensive interview about the ano-rectal symptoms they are currently experiencing, their sexual behaviour including use of commercial lubricants and specific practices that occur along with RAI, and their practice of anal hygiene behaviours (including use of enemas, rectal douches, and high colonics). All study participants are then tested for STIs, and examined by a clinician and clinical signs recorded with a high resolution anoscope.

The findings of this study will establish prevalence of ano-rectal symptoms and disease and assess the relationship of sexual practices to ano-rectal symptoms and clinical diagnoses, including infections among 896 women and men before the introduction of study products such as rectal microbicides or placebos. This will help with the interpretation of reported ano-rectal symptoms and observed clinical signs in clinical trials of rectal microbicides. The findings from this study will serve as baseline measures of anal health to compare during clinical trials when randomization will be product vs. placebo. The study is expected to be completed by July 2009; it was one-third enrolled at the end of 2007.

2.11 The use of rectal douches among men who have anal intercourse

For HIV-negative men, douching may result in rectal mucosal damage that may facilitate the entry of HIV or other pathogens. In the case of HIV-positive men, whether rectal douching may exacerbate viral shedding needs to be investigated.

In a study from the HIV Center for Clinical and Behavioral Studies (U.S.)[37], researchers interviewed men who use the Internet to meet other men for intentional condomless AI ("bareback").[38,39] This study had three objectives. First, to report the prevalence of douching behaviours in a sample of men at high risk for HIV transmission. Second, to analyze whether rectal douching behaviour (e.g., age of onset, douching frequency, and number of pre-coital douching occasions) varied significantly by demographic characteristics (as had been reported for vaginal douching) and HIV status. Finally, to test whether pre-coital douching was associated with positive HIV status after controlling for unprotected receptive anal intercourse (URAI) occasions.

A multiethnic sample with overrepresentation of HIV-negative MSM who had URAI in the previous year was recruited exclusively through the Internet. Participants were 105 MSM (78 HIV-negative, 27 HIV-positive).

A total of 53% of HIV-negative and 96% of HIV-positive men douched in preparation for sex, most of them frequently or always, mainly for hygienic purposes. 27% of HIV-negative and 44% of HIV-positive douched after sex, partly believing douching protected from infections. Douching practices started around age 25.

Regression analyses found the association between HIV status and douching occasions persisted after controlling for demographic characteristics and number of URAI occasions. Rectal douching in preparation for sex is common among men who practice URAI. This population could benefit from alternatives to condoms, such as rectal microbicides. Given the popularity of pre-coital douching and its frequency, a harmless rectal douche that could deliver a rectal microbicide could have great acceptability.

Given that respondents practice rectal douching as a hygiene measure prior to sex, and considering the frequency with which the behaviour takes place, it is likely to be quite resistant to change, as has been reported to be the case among women who use vaginal douches. Furthermore, the association between douching and HIV-positive status that persists after controlling for number of URAI occasions highlights the need to pay attention to rectal douching as a possible contributing factor to HIV transmission.

However, not all rectal douches may have harmful effects. One study did not observe epithelium loss after PEG-ES enemas.[40] Therefore, it may be possible to develop products that achieve the hygienic purpose pursued by users while avoiding harmful effects.[41] Furthermore, if a harmless rectal douche could be used as the vehicle to deliver an effective microbicidal agent, it could be possible to achieve wide coverage of the rectal mucosa with a protective agent prior to intercourse. A douche that was expelled or absorbed by the mucosa while leaving the microbicidal agent in any place that may become exposed to HIV during or after intercourse could be more acceptable than the current gel formulations of microbicides which may require a significant volume of gel to be present in the rectum during intercourse.[42]

Rectal douching after sex also merits attention, given that it is reported by a quarter of uninfected men and almost half of those infected. Would post-coital douching wash away a microbicide while ineffectively removing pathogens? Future research in microbicide development should consider the formulation of a multipurpose product that can be effectively used as a microbicidal and as a douche, not only before, but also after sex. Alternatively, future behavioural prevention interventions among MSM should consider incorporating cautionary information about the potential harms associated with douching after sex.

Jeremy Kwan

IRMA Steering Committee
PT Foundation (Malaysia)

"Providing access to rectal microbicides is a step toward securing and guaranteeing the bright future of our younger generation, which is the future of the world to come."

Rick Jones

IRMA Steering Committee
Global Network of People Living with HIV/AIDS (Netherlands)

"It is imperative that morality not get in the way of protecting human beings and life; people of every sexual orientation have practiced anal sex since the begining of time. The time for bigotry is over. We need to help those who are not infected stay that way."

Rectal douching may increase the susceptibility to HIV and other sexually -transmitted infections by sloughing the anal epithelium.[43] As a prime population to benefit from the availability of HIV prevention alternatives to condoms, such as rectal microbicides, it is vital to decrease sexual hygiene practices that may render the microbicide ineffective. For example, a potential harm reduction approach to minimize the sloughing of the anal epithelium may be to inform MSM on the risks of using soapsuds and water enemas and/or to increase the accessibility and marketing of PEG-ES enemas.[44]

Future studies exploring what hygienic practices precede or follow AI and the effect that they may have on the action of a microbicide are necessary.

2.12 Assessing rectal safety of sexual lubricants

The connective tissue of the rectum is protected by a single layer of epithelial cells. Lymphocytes and macrophages, potential target cells for HIV, reside in this connective tissue. There is overwhelming evidence that a break in the epithelium provides a conduit for HIV to make contact with target cells in the connective tissue. Breaches in the epithelium can therefore increase the risk of HIV infection. Unfortunately, rectal tissue is so fragile that the epithelium can be breached relatively easily. Thus, if a microbicide or sexual lubricant were to cause trauma during AI, it could increase susceptibility to HIV infection. As many men and women use sexual lubricants during AI, it is important to assess their safety for rectal use and to advise people about their relative safety. Determining the safety of sexual lubricants is not an easy task.

There are hundreds of different sexual lubricants available on the market. In addition to these, other substances are used as sexual lubricants, especially in the developing world where people cannot afford to purchase sexual lubricants. Given that clinical studies of rectal safety are expensive, time consuming and can only be conducted by a few expert clinicians, a clinical study of all products is impractical. In addition, clinical assessments were developed to identify major problems, and thus, these assays may not be sufficiently sensitive to detect minor breaches in the epithelium.

The Population Council has employed in vitro and mouse assays to determine the safety of sexual lubricants. The advantage of these assays over clinical studies is that they are far less time consuming and expensive so a number of lubricants or microbicides can be examined relatively easily. Although the assays can be done relatively fast, it is not possible to determine how relevant the assays are to what actually happens during AI. Also, as is the case with clinical assays, it is not clear if the methodology is sensitive enough to detect minor trauma.

Three assays are used to study rectal safety at the Population Council. The first is a simple cytotoxicity assay where they study the concentration of a lubricant that causes cell death in human colorectal cells in vitro. The second is a mouse infection assay. Although mice are not susceptible to HIV infection, they can be infected with herpes simplex virus 2 (HSV-2) following rectal administration. The third assay involves counting the number of epithelial cells that are sloughed following rectal administration of a lubricant in mice. The Population Council developed this assay because they previously observed that products containing Nonoxynol-9, which enhance HSV-2 infection, also cause sloughing of the epithelial cells lining the rectum.

So far, the Population Council has used these assays to study four different sexual lubricants. Two of the lubricants, KY Plus and DELUBE (now off the market) were considerably more cytotoxic, caused more cell sloughing and enhanced HSV infection as compared to saline controls.[45] They are currently using these assays to study additional sexual lubricants and are hopeful that their findings will help advise users which lubricants may be safest for use during rectal intercourse.

IRMA continues to monitor this research and to urge timely dissemination of the results.

2.13 Collecting data on rectal use of products and anal intercourse in vaginal microbicide trials

Currently, most vaginal microbicides trials collect behavioural data by asking participants whether they have engaged in AI. This information can be an important component of determining the reliability of trial results, and help to identify potential safety concerns related to rectal use of the products. However, the type of data collected varies greatly from trial to trial.

First, various trials ask questions at the point of screening, at enrolment and/or during follow-up visits in the course of the trial.

Second, depending on the trial, participants are asked about AI in a variety of ways. This can include whether they have ever engaged in AI, whether they have ever engaged in UAI, whether they have engaged in either unprotected oral or anal sex, whether they used a condom the last time they had AI, or the frequency in which condoms were used when having AI.

Third, the time frame used in the questions about AI also varies greatly, ranging from whether they ever engage in AI, or in the past week, in the past 4 weeks, in the past 30 days, in the past 3 months or since their last visit, depending on the trial.

Tiago Neves

Advocate (Portugal)

"The day a vaginal microbicide is available, people will be using it for rectal intercourse."

Obviously, the data collected vary considerably, making comparisons between trials difficult.

Participants are counselled against using the product rectally, since it has not been designed or tested for rectal safety. However, in some cases, participants may still use the product for AI. In these cases, gathering information on rectal use may help to identify any potentially serious adverse events.

In trials where candidate vaginal microbicides do not prove efficacious, gathering information on AI could allow researchers to identify UAI as a possible factor in cases where, despite randomization, one trial arm has higher rates of AI than another.

2.14 Biomedical, social and behavioural research funded by amfAR

amfAR, The Foundation for AIDS Research, is one of the world's leading nonprofit organizations dedicated to the support of AIDS research, HIV prevention, treatment education, and the advocacy of sound AIDS-related public policy. Since its founding in 1985, amfAR has been associated with important HIV/AIDS research, having invested nearly $250 million in its programs and awarding grants to more than 2,000 research teams worldwide.

In early 2007, amfAR awarded nearly $1 million to eight research projects aimed at increasing understanding and prevention of rectal HIV transmission.

The 8 projects are:

1. ***Development of a standard rectal microbicide delivery device***
   Dr. Alex Carballo-Dieguez
   Research Foundation for Mental Hygiene, Inc. (U.S.)
2. ***Social Networks and their role in HIV transmission between Chinese MSM and Women***
   Dr. Hongjie Liu
   Wayne State University (U.S.)
3. ***Exploring epithelial injury in regions of the rectum and colon most susceptible to HIV infection following intercourse***
   Dr. Craig Hendrix
   Johns Hopkins University School of Medicine (U.S.)
4. ***Anal sex practices among South African women and men***
   Dr. Joanne Mantell
   Research Foundation for Mental Hygiene, Inc. (U.S.)

Bridget Haire

IRMA Steering Committee
Australian Federation of
AIDS organizations (Australia)

"Microbicides, which are designed for receptive partners, could put power into the hands (and rectums and vaginas) of those who tend to be disempowered."

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

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

7. ***Anal intercourse, STIs, and HIV among men who have sex with men and women***
Dr. Marjan Javanbakht, Dr. Peter Anton and **Dr. Pamina Gorbach**
University of California, Los Angeles (U.S.)

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

"While support for the development of vaginal microbicides has thankfully grown over the past few years, these amfAR grants will help fill the persistent gaps in our understanding of rectal HIV transmission. They will help us understand how to formulate and deliver a rectal microbicide that can and will be used by diverse populations around the world who are at risk of rectal HIV transmission."

— Dr. Rowena Johnston,
Vice President, Research, amfAR

Dr. Peter Anton
UCLA (U.S.)

"This work is so incredibly important. Every day we don't move forward, thousands more get infected. There is an ethical obligation here to advance the research and development of rectal microbicides, with good science and community awareness."

3 IRMA in action: key activities

IRMA activities are underpinned by a highly active, moderated global listserv, a website (www.rectalmicrobicides.org) featuring a wealth of information and resources, and regular teleconferences hosted by member organizations featuring presentations on cutting-edge rectal microbicide science. Ongoing advocacy includes mobilizing on issues such as the rectal safety of candidate vaginal microbicides and responding to false claims. Throughout most of 2007, the group developed, disseminated, and analyzed an international internet-based survey on lubricants used for AI (section 3.2).

3.1 Consensus statement on rectal safety of candidate vaginal microbicides

In May 2007, IRMA issued a statement calling upon the microbicide community to support rectal safety trials of candidate vaginal microbicides which have progressed to Phase III efficacy trials.

IRMA strongly supports the collection of rectal safety data for all candidate vaginal microbicides in efficacy trials to ensure information is provided to eventual users through appropriate product labelling and community education efforts.

The statement was endorsed by the African Microbicides Advocacy Group (AMAG), the Alliance for Microbicide Development (AMD) and the Global Campaign for Microbicides (GCM).

Specifically the statement urges:

1. Trial sponsors to fund rectal safety trials alongside all candidate vaginal microbicides in efficacy trials;
2. Donors to provide more resources for the field to conduct rectal safety trials;
3. Regulatory agencies to provide guidance describing reasonable rectal safety data needed to approve vaginal microbicides.

IRMA does not recommend halting or delaying the introduction of vaginal microbicides. IRMA believes the field should work diligently to ensure that gathering rectal safety data poses no delays to efficacy trials. Short rectal safety trials can be conducted in parallel to vaginal efficacy trials.

IRMA, AMAG, AMD and GCM have agreed to collaborate on the development of an "Advocate's Brief" focusing on rectal safety, and will collectively design and implement advocacy strategies connected with the statement in 2008.

The consensus statement is available at www.rectalmicrobicides.org.

3.2 International survey on lubricants used for anal sex

Over a period of 29 weeks, from February 14 to August 31, 2007, IRMA conducted an on-line survey on lubricants used for anal sex, which was hosted on www.surveymonkey.com. The purpose of the survey was to gather data on the types of lubricants people use, as well as preferred lube characteristics.

With 8,945 responses (nearly 78% were completed surveys) from 107 countries, this is the largest survey on anal sex ever conducted. Thanks to the work of volunteer translators from around the world, the survey was offered in six languages: English, French, German, Portuguese, Spanish and Turkish. It should be noted that despite having the survey translated in an additional four Indic and Dravidian languages (Hindi, Marathi, Telugu and Tamil), it was not possible to post the surveys for technical reasons.

The survey was promoted through various means. First, brief e-mail messages in various languages with three different target audiences (general, gay men/MSM, and women) were sent periodically through various topical, regional and community listservs, including those focussed on HIV, microbicides, gay men's health, women's health, and sexual and reproductive health. Second, a number of websites posted information and links to the survey, including sites targeted to gay men and MSM (e.g. LifeLube.org, Manhunt.net), barebacking, and rectal microbicides (i.e. IRMA). In addition, a number of individuals and organizations used the basic promotional messages to include notices in agency newsletters and websites. Finally, a number of specialized media outlets, both print and cyber, wrote articles about the survey. Many respondents were reached through old-fashioned word-of-mouth.

IRMA collaborated with colleagues at UCLA who conducted the data analysis.

The survey results provide valuable information relating to:

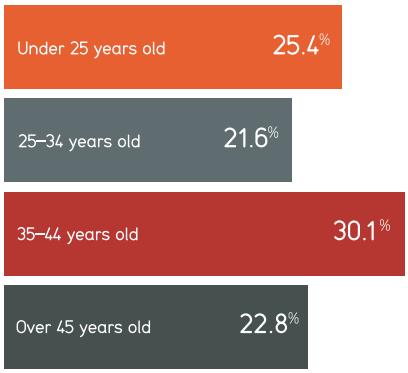
- the lubricants more commonly used for anal sex;
- how people use lubricants for anal sex;
- preferred lubricant characteristics; and,
- frequency of condom use during anal sex.

This information will be useful in helping advocates and researchers:

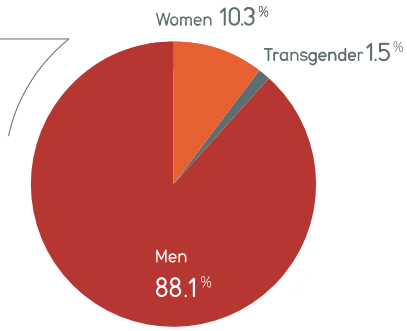
- decide which lubricants should be prioritized for safety testing;
- learn which lubricant characteristics are most acceptable and should be considered in rectal microbicide development and packaging;
- understand which methods may improve lubricant and condom access;
- gain insight into differences among regions, genders and age; and,
- contemplate anal sex practices as they relate to the sexual health of women and men in various regions.

Information on all survey respondents

Age: There was a fairly even distribution of age groups. Among those who indicated an age, 25.4% of respondents were under 25, 21.6% were 25-34, 30.1% were 35-44, and 22.8% were over 45 years old.

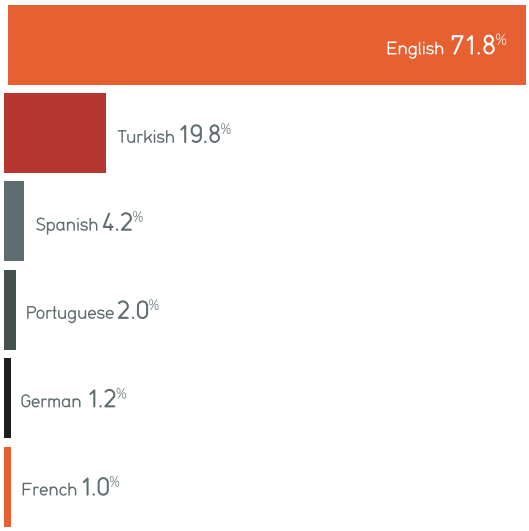


Gender: The vast majority of respondents were men, however over 900 women responded to the survey. Among those who indicated a gender, 88.1% were men, 10.3% were women and 1.5% were transgendered.



Regions: Most respondents indicated they were from North America and Europe. Among those who indicated a country, 63.9% were from North America (U.S. and Canada), 26.9% were from Europe (29 countries), 3.9% were from Latin America and the Caribbean (27 countries), 2.8% were from Asia (21 countries), 1.7% were from Oceania (Australia and New Zealand), 0.6% were from Africa (18 countries), and 0.2% were from the Middle East (8 countries).

Language: Most respondents answered the English survey, although surveys completed in Turkish represented a significant proportion of the responses. Over one quarter of all responses was in languages other than English: English (71.8%), Turkish (19.8%), Spanish (4.2%), Portuguese (2%), German (1.2%), and French (1%).

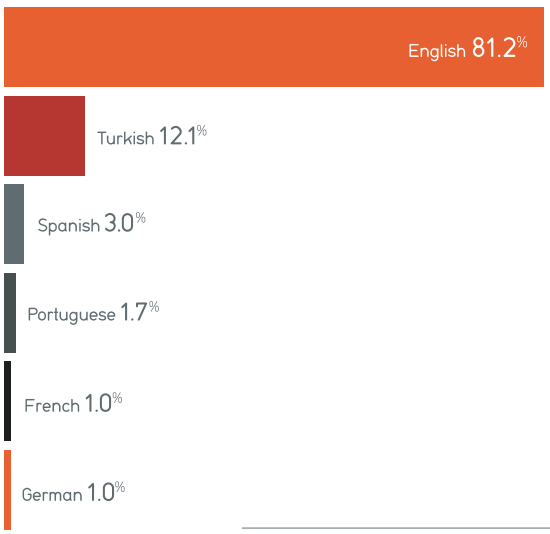


Survey results among respondents who reported having anal sex in the past six months

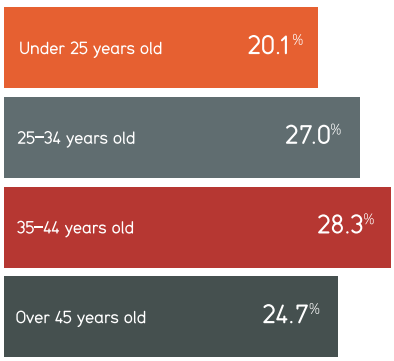
The majority of survey respondents (70.1%, or 6,273 people) reported having anal sex within six months prior to the survey. The following data looks at this group.

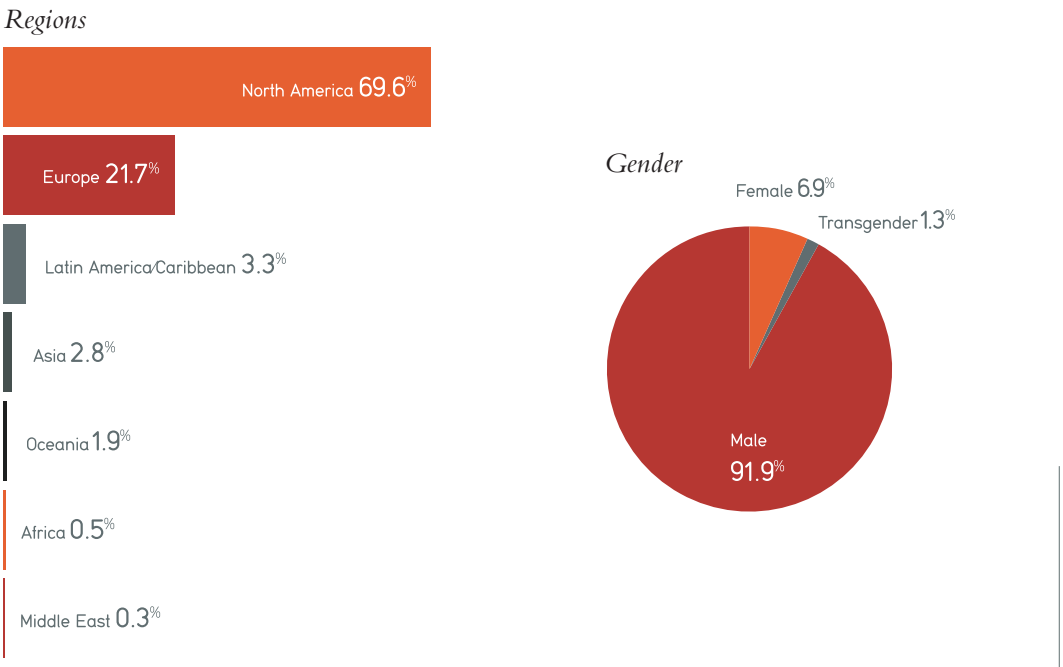
Demographics. There is a fairly even distribution of age groups across this cohort. However, the vast majority of respondents are North American males who responded in English. This is important to keep in mind when reviewing results from this cohort.

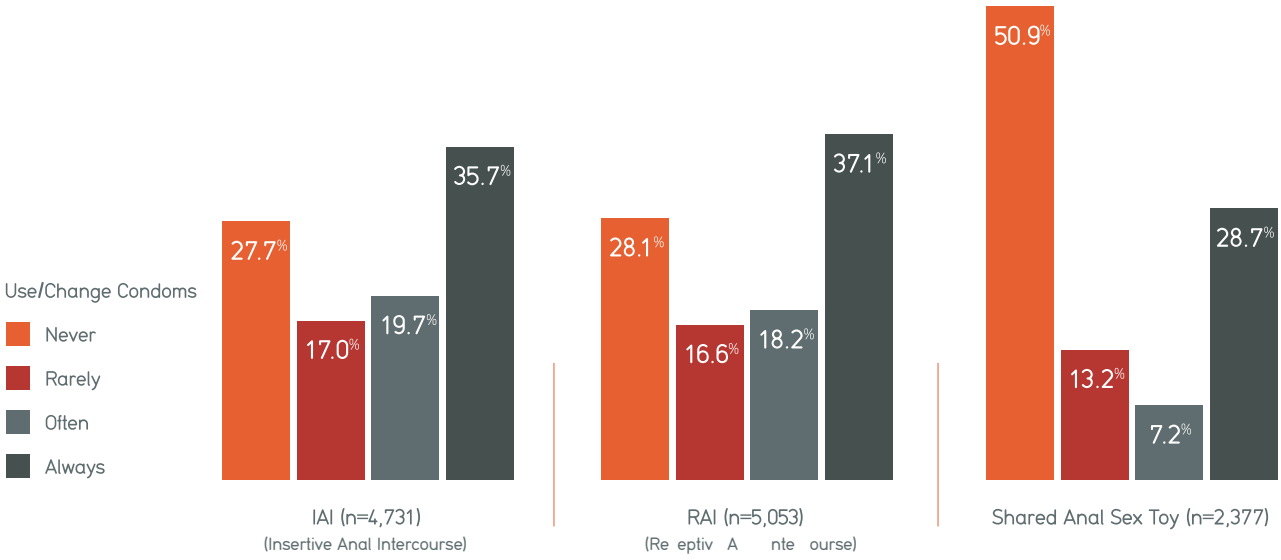
Language



Age







Condom use patterns. The patterns of condom use are quite similar when comparing receptive and insertive AI. Approximately 28% of respondents reported never using condoms, while approximately 35-37% of respondents always use condoms. Another 35-37% of people indicated either "rarely" or "often" using condoms. However, when asked about the frequency of changing condoms when sharing sex toys anally,

a greater proportion of people reported never changing condoms between users (nearly 51%), compared to "always" (nearly 29%) or either option of "rarely" and "often" (approximately 20% combined). Since no information on the nature of the relationship with sexual partners was requested (casual vs. main partner, for example), or whether the HIV serostatus of partners was known, it is difficult to draw definitive conclusions about the levels of HIV risk that respondents faced.

Non-Condom Using		Condom Using		Combined
Bottoms (N = 2264)	Tops (N = 2224)	Bottoms (N = 2545)	Tops (N = 2479)	
Astroglide*	Astroglide*	Astroglide*	Astroglide*	Astroglide*
Boy Butter	Crisco	Durex*	Durex*	Durex*
Crisco	Elbow Grease	Elbow Grease	Elbow Grease	Elbow Grease
Elbow Grease	Gun Oil	Gun Oil	Gun Oil	Gun Oil
Gun Oil	ID*	ID*	ID*	ID*
ID*	K-Y*	K-Y*	K-Y*	K-Y*
K-Y*	Liquid Silk	Liquid Silk	Pjur Eros	Liquid Silk
Liquid Silk	Pjur Eros	Pjur Eros	spit	Pjur Eros
Pjur Eros	spit	spit	Swiss Navy	spit
spit	Vaseline	Wet*	Trojan	Swiss Navy
Vaseline	Wet*		Wet*	Vaseline
Wet*				Wet*

Note: Lubricants listed alphabetically. Compilation of English responses only

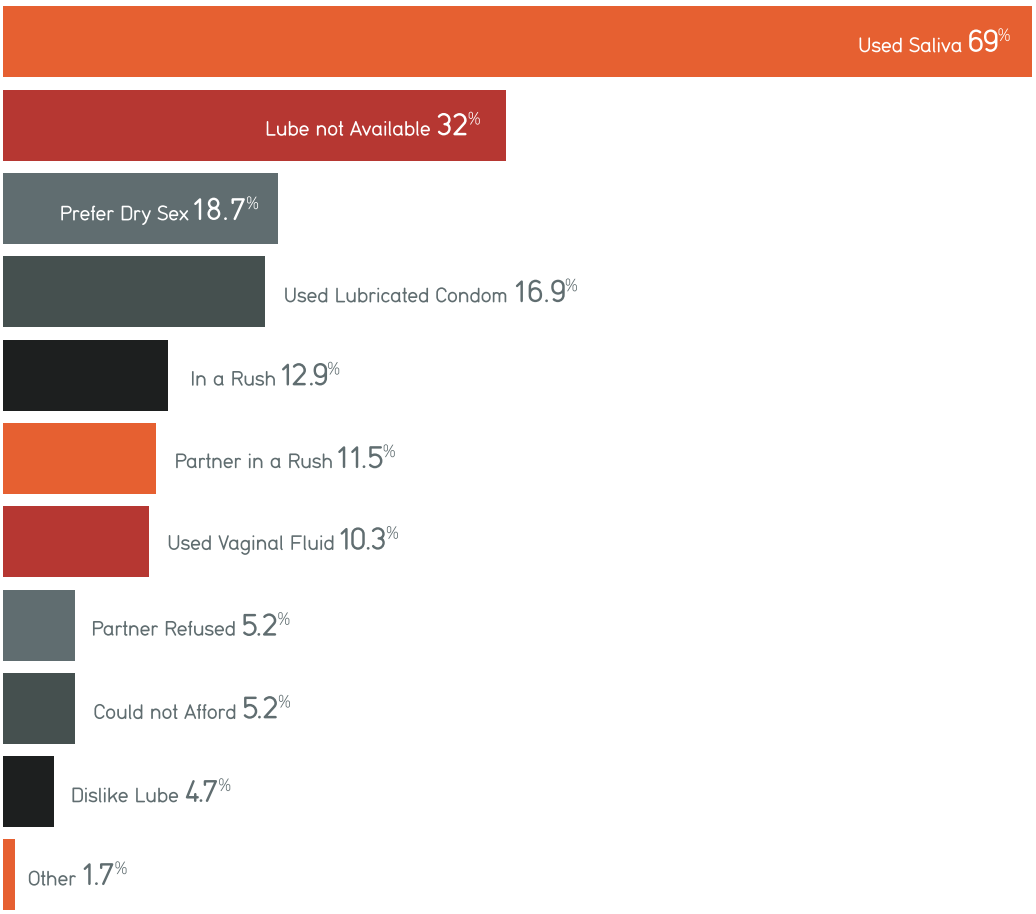
* Includes all formulations with this brand name

Lubes most commonly used.

Data analysis reveals that well over 100 different lubricants were named by respondents. Among these, the 15 most commonly named lubricants used for anal sex included, in alphabetical order: Astroglide (all types combined, including original), Crisco, Durex, Elbow Grease, Gun Oil, ID (all types combined, including Glide and Millennium), K-Y (all types combined), Liquid Silk, Pjur Eros, Probe, spit/saliva, Swiss Navy, Trojan, Vaseline and Wet (all types combined, including Wet original and Wet Platinum). The only notable differences among respondents who indicated they had anal sex as bottoms/receptive partners vs. tops/insertive partners, and using condoms vs. not using condoms were twofold: first, oil-based lubricants (Vaseline, Crisco) featured prominently among respondents who did not use condoms; second, respondents who did not use condoms were more likely to list spit/saliva as lubricant.

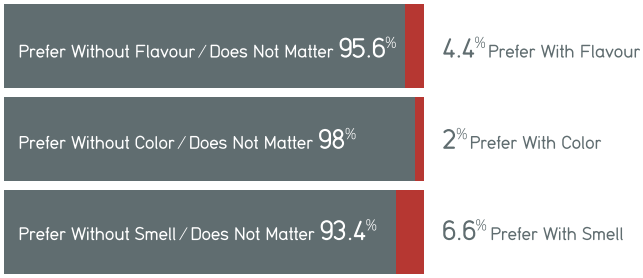
Reasons for not using lubricant.

Little more than a quarter of people who indicated they had engaged in anal sex in the past 6 months provided reasons why they did not use lube. The rest either indicated they did not have anal sex without lube, or they did not answer. The most common reasons given for not using lube were: used saliva instead (well over half of respondents), lube was not available (one-third), prefer dry sex, or used lubricated condoms. Overall, responses seem to indicate considerably high acceptability of lubes for anal sex, with "dislike lube" as the least common answer.



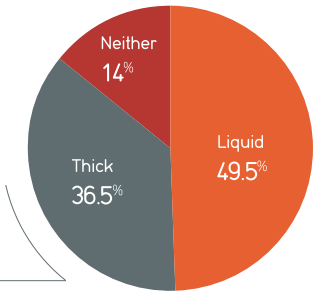
Lube characteristics: flavour, colour, smell.

A very small percentage of respondents stated a preference for lubes that have a flavour (4.4%), colour (2%) or smell (6.6%).



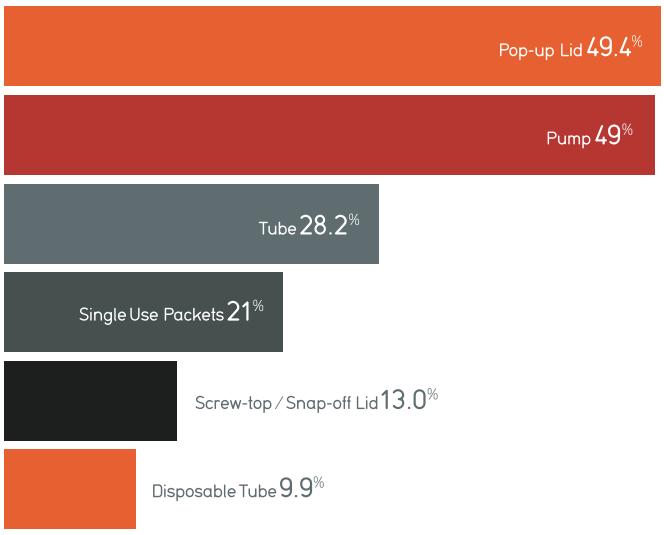
Lube consistency.

Half of respondents prefer a liquid lube; over one third prefer a lube that is thick. Given these proportions, a rectal microbicide formulated as a lube would probably be most acceptable if available in both thick and more liquid-style formulations.



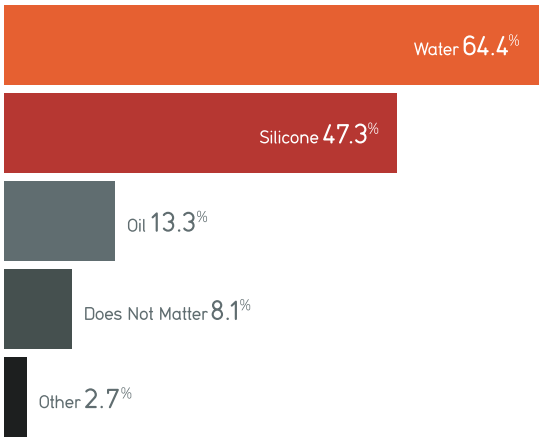
Lube dispensers.

A variety of lube dispensers are preferred by respondents, with nearly half the respondents preferring a dispenser with a pop-up lid or a pump, followed by tubes (over a quarter of respondents). One-fifth of respondents preferred single-use packets.



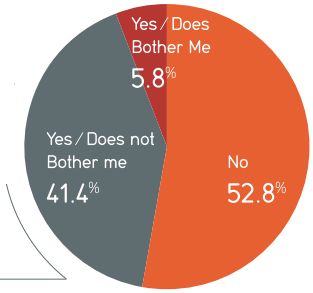
Lubricant base.

Both water-based and silicone-based lubes are preferred over oil-based lubes. Given these proportions, a rectal microbicide formulated as a lube would probably be most acceptable if available in both water-based and silicone-based formulations.



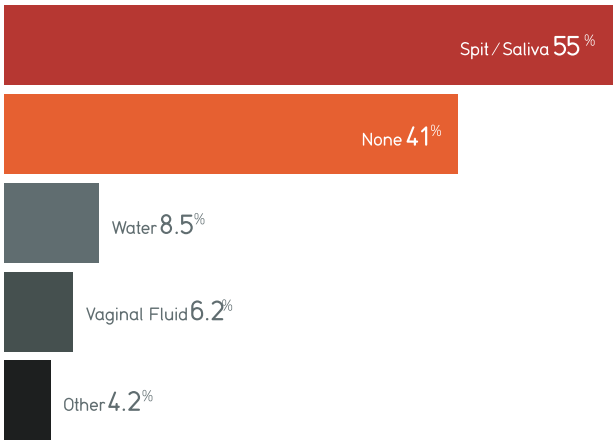
Applying lube: Does it interrupt sex?

Less than 6% of respondents felt that applying lube for anal sex interrupted sex and bothered them. The majority felt it did not interrupt sex (nearly 53%) and even if they did feel lube application interrupted sex, it did not bother them (over 41%). These data indicate a very high acceptability rate for lube.



Adding substances to lube.

The majority of respondents indicated they added another substance to the lube they used for anal sex, including spit/saliva (55%), water (8.5%) or vaginal fluid (6.2%).When testing lubes for safety and rectal microbicides for both safety and efficacy, this behaviour should be taken into account.



Conclusions.

Most respondents who engage in anal sex do not always use condoms, but many people use lubricants, providing an excellent opportunity for a rectal microbicide formulated as a lube to provide protection. Most respondents report use of commercial lubricants, suggesting rectal microbicides that are similar to existing lube products will be acceptable. Indeed, a rectal microbicide formulated as a lube would probably have a high acceptability rate, especially if it has no flavour, colour or smell, and is available in both thick and liquid consistencies, and with the option of a water or silicone base. When testing lubricant products for rectal safety and testing candidate rectal microbicides for safety and efficacy, researchers should consider the implications of other substances (saliva, water, vaginal fluid) added to the product.

Next steps.

IRMA will issue a full report of the survey data analysis by mid-2008. Sub-analysis will include a breakdown by age, gender, region and language. It will also include translation and analysis of qualitative data from all six languages, including a compilation of the most frequently named lubricants used for anal sex. These results will be disseminated to various target audiences (researchers, advocates, prevention educators, gay men, and women) using various means (fact sheets, teleconferences, published articles and the IRMA website as well as other web-based information).

Limitation of an on-line survey.

As stated by Rhodes and colleagues:
"The advantages of using the world wide web to collect behavioural data include rapid access to numerous potential respondents and previously hidden populations, respondent openness and full participation… and reduced research costs. Challenges identified include issues related to sampling and sample representativeness… and potential limitations resulting from the much cited "digital divide", literacy, and disability… Justifiable concerns regarding the use of the world wide web in research exist, but… the world wide web may be the only research tool able to reach some previously hidden population subgroups. Furthermore, many of the criticisms of online data collection are common to other survey research methodologies."[46]

IRMA expresses sincere gratitude to the thousands of people who responded to the survey.

3.3 Serving as a watchdog

In addition to promoting research to find a safe, effective and acceptable rectal microbicide, IRMA diligently works as watchdog to protect consumers against falsely marketed products. Working collaboratively in 2007, IRMA and GCM investigated the claims of a lubricant manufacturer in the United Kingdom called Kirklees Medical Limited. The company was making explicit claims on its website regarding the ability of its products to reduce the risk of sexually transmitted HIV infection with no proof of safety or efficacy. In an e-mail to IRMA from Kirklees Medical, a company representative stated that a Kirklees lubricant "is less than 50% effective against HIV in actual use between partners although it performed exceptionally well against other STIs."

GCM has maintained an Unproven Product Claims Watch for several years to raise awareness of products that are being presented to the public (without substantiating evidence) as effective microbicides and to advocate for the removal of such products from the market wherever possible. Knowing this, IRMA worked together with GCM, urging Kirklees either to provide peer-reviewed scientific

data supporting its anti-HIV/anti-STI claims or to cease making such statements. The Terrence Higgins Trust (THT), as a UK-based partner of both the GCM and IRMA, took the lead on generating this dialogue.

Once a complaint was registered by IRMA, GCM and THT with the UK's Medical and Healthcare Regulatory Authority (MHRA) in September 2007, Kirklees promptly removed some of the claims and misleading language from its website. However, as of press time, officials have yet to provide data demonstrating either (1) anti-HIV efficacy in vivo or (2) that long-term use of the product is safe over time (i.e. does not damage either vaginal or rectal epithelia in any way that might increase HIV risk).

The text of the letter that was submitted to MHRA and other background materials are available at www.rectalmicrobicides.org, where updates on this matter are posted.

Caveat Rectum!
No product has yet been approved for use as an effective vaginal or rectal microbicide. Any product making such a claim should be reported immediately to regulators and advocacy organizations such as IRMA.

In order to raise awareness among advocates, IRMA and GCM have produced a fact sheet on the safety of sexual lubricants for vaginal and rectal use, which can be obtained from either group's website, www.rectalmicrobicides.org or www.global-campaign.org.

IRMA continues to advocate and to work with researchers to promote rectal safety testing of sexual lubricants (see sections 2.12 and 3.2 for more information on these activities.

3.4 Key resources on the IRMA website

The IRMA website, www.rectalmicrobicides.org., is hosted and maintained by the AIDS Foundation of Chicago (AFC). What follows are key resources most accessed by members and other visitors to the site.

Presentation slides and minutes from regular teleconferences.
IRMA, with the generosity of its organizational partners, hosts regular, free international teleconferences featuring speakers from around the world who are leading rectal microbicides research and advocacy efforts. All calls include a set of slides which participants can follow online. Minutes of the call are posted, and all materials are archived on the website.

Rectal Microbicides: Investments and Advocacy.
This report, released by IRMA in April 2006 at the Microbicides 2006 conference, was the first document to specifically track rectal microbicide research

and development expenditures. The report has recommendations for rectal microbicide advocates, researchers and funders.

Consensus statement on rectal safety of vaginal microbicides.
This statement calls upon the microbicide community to support rectal safety trials of vaginal microbicides which have progressed to Phase III efficacy trials. The statement was endorsed by AMAG, AMD, GCM, and IRMA.

Community education and awareness presentations.
IRMA members regularly present on rectal microbicide advocacy in their communities and at local, national and international conferences. These presentations are highlighted on the site and other advocates are encouraged to use them as examples and templates that may be adapted for various audiences and contexts.

Resources on rectal microbicides.
The website includes fact sheets, documents, reports, journal articles and links to other web-based resources on rectal microbicides.

Resources on other new prevention technologies.
Information on PrEP, vaccines, male circumcision and vaginal microbicides, among other new prevention technologies, are highlighted with links.

Advocate and researcher bios.
Rectal microbicide advocates and researchers from around the globe are regularly featured on the website. A short biography and a recent photo help connect members from distant locales, personalizing their experience and assisting IRMA in building and nurturing a virtual community.

News items and fresh resources.
Notices on recent developments in the field and new informational resources are all prominently posted.

Contact.
To sign up for the IRMA listserv or to communicate with IRMA for more information on how to become involved in rectal microbicides advocacy, internet users can utilize the contact portion of the website.

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4 Looking forward: goals for IRMA and the rectal microbicides field

IRMA's over-arching goals are:

- To advocate for accelerated research, development and access to safe, effective and acceptable rectal microbicides;
- To promote rectal safety studies on all viable vaginal candidate microbicides;
- To support, where appropriate, the research of other new prevention technologies, such as male circumcision, vaccines and oral prevention (PrEP), and to promote existing prevention methods such as male and female condoms as part of a range of prevention options;
- To serve as a central forum for exchange, debate, and networking on rectal microbicides; and,
- To convene diverse perspectives and scientific disciplines to improve understanding and action.

4.1 Ten rectal microbicide objectives to achieve by 2010

Over the next three years, from 2008-2010, IRMA will pursue the following ten objectives as a roadmap to achieving our goals:

Accelerated research

1. Develop a document (*Rectal Microbicide Research: Mind the Gap*) which would provide an overview of key areas requiring urgent attention to move rectal microbicides research forward.
2. Recruit new researchers to the field by promoting the work of IRMA, utilizing *Rectal Microbicide Research: Mind the Gap* and *Less Silence, More Science* as well as active engagement in scientific conferences.
3. Implement advocacy strategies to increase funding for rectal microbicide research five-fold, from U.S.$7 million/year in 2006 to a minimum of U.S.$35 million/year in 2010.
4. Implement advocacy strategies to diversify funding sources for rectal microbicide research, with a target of reaching 25% of global rectal microbicide research funding originating from non-U.S. government sources by 2010. Currently, more than 97% of rectal microbicide funding is from the U.S. government.

5. Use the results of the lubricant survey to encourage the testing of additional commercial lubricants for rectal safety, and disseminate the survey results to all vested audiences, including scientists engaging in acceptability and formulation work.

6. Advocate for increased research into global AI incidence, prevalence and behavioural contexts in which AI occurs.

Rectal safety of vaginal microbicides

7. Develop an *Advocates Brief* on rectal safety of vaginal microbicides, and implement advocacy strategies connected with the *Consensus statement on rectal safety of vaginal microbicides*, with AMAG, AMD and GCM.

Other new prevention technologies

8. Participate in collaborative efforts and other prevention research networks and listservs as means of ensuring visibility for rectal microbicides and to encourage greater integration and coordination of prevention research efforts.

Mentor aspiring rectal microbicide advocates

9. Increase IRMA's global reach, particularly in developing countries, by expanding means of participation in IRMA-related activities, including both electronic and non-electronic methods. This may include efforts to continue the development of the John Shaw Memorial Scholarship Fund which assists advocates in attending critical international conferences and exploring the possibility of developing a mentorship or buddy program in which more established advocates encourage and support new advocates.

Convene diverse perspectives

10. With key advocates, researchers, policy makers and funders, convene a forum for developing, monitoring, discussing and making decisions about the elements of a Global Rectal Microbicide Development Plan.

4.2 Global Rectal Microbicide Development Plan

As the world's first Phase I clinical trials evaluating the rectal safety of vaginal microbicides have gotten under way, the rectal microbicides field needs to consider the future course of research. The normal drug development pathway suggests that the next steps would be to move safe vaginal products into expanded rectal safety trials (Phase II), while concurrently developing rectal-specific formulations for Phase I safety trials, and moving those into expanded safety trials. A critical scientific question is determining whether a rectally safe vaginal microbicide would be effective in preventing, or at least reducing, HIV transmission associated with URAI. To date, the animal data suggest that this might be possible, but these data are very preliminary and should

not be over-interpreted. The overall goal of course, would be to move towards large-scale Phase III rectal efficacy trials of either vaginal or rectal-specific formulations.

While this research pathway will obviously take several years to develop, several questions come to mind which must be addressed. Primarily, the field should consider whether this research pathway is actually feasible and if so, articulate a Global Rectal Microbicide Development Plan.

First, who would fund such trials?

As trials get larger, their visibility is heightened. Given the current rectal microbicides research funding context, it is uncertain whether or not the field can continue to rely almost exclusively on U.S. government funding. Diversifying the funding base for rectal microbicides research overall is absolutely critical, and may be a role that Europe and some foundations will be willing to play.

Second, how will this research process be coordinated?

The entire process of moving products through research phases will require a high level of coordination among key players. Comparing and coming to an agreement on research methodologies will be tremendously useful.

Third, where will the field locate research sites?

Large-scale efficacy trials of candidate rectal microbicides will need to be conducted in settings where there is a high incidence of HIV driven by UAI. This will likely mean developing and building on trial sites to reach communities of gay men and other men who have sex with men, possibly in the U.S., Canada, Latin America, Western Europe, Australia, and South Africa.

Fourth, what will be the broader prevention research and advocacy context within which these trials would occur?

It is likely that by the time candidate rectal microbicides reach large-scale trials, other new prevention technologies may already exist, creating significant challenges for trial design in terms of the prevention package offered for participants. At the same time, with challenges there are opportunities, and an intriguing Phase III study would be to compare oral prevention versus topical prevention. Advocates are crucial to maintaining the political climate for sustained research funding and community support and engagement for trials. Their support for trials of specific products and approaches within a broader context of prevention research may fluctuate.

A Global Rectal Microbicide Development Plan, and perhaps more importantly, a forum for developing, monitoring, discussing and making decisions about the elements of such a plan, would allow better alignment and coordination in the field and across new prevention technology research.

Rectal Microbicides Advocacy...

Developing safe, effective and acceptable rectal microbicides as quickly as possible for the women and men who need them globally requires the concerted efforts of advocates, researchers, policy makers and funders from all parts of the world.

...Includes You

If you only have 5 to 10 minutes…

- Visit the IRMA website at www.rectalmicrobicides.org
- Read one fact sheet or news item on rectal microbicides from the website
- Sign up for the IRMA listserv through the website
- Pass along our web address and contact information to another advocate, researcher, policy maker or potential funder

If you only have 30 to 60 minutes…

- Dial-in to one of IRMA's regular free teleconferences featuring world leaders in the field of rectal microbicide research and advocacy
- Read some of the excellent resources on the website (*see section 3.4*)
- Download one of the prepared presentations and host a discussion with your co-workers or other group
- Talk to other members in your community about your interest in rectal microbicides

If you want to engage actively in shaping the rectal microbicide field…

- Join one of IRMA's working groups to help us meet our objectives (*see section 4.1*)
- Offer to join IRMA's Steering Committee
- Become your community's spokesperson for the research and development of safe, effective and acceptable rectal microbicides by enlisting organizational support, conducting ongoing presentations and strategically engaging the media with support and direction from IRMA
- Reach out to advocates, researchers, policy makers and funders and ask them to join IRMA, to create policy that illuminates the importance of rectal microbicides, and to provide financial support for research and advocacy activities

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