

## 2 The state of rectal microbicide research

### Summary

- The ground-breaking U-19 Microbicide Development Program (MDP) will end in 2010, and has included a number of important studies on rectal microbicides (RMs), including the world's first RM safety trial.
- Three new research projects will focus on RM research in the coming years: the Combination HIV Antiretroviral Rectal Microbicide (CHARM) Program and the Microbicide Safety and Acceptability in Young Men study in the U.S.; and, the Combined Highly-Active Antiretroviral Microbicides (CHAARM) Programme in Europe.
- Some of the next RM safety trials will be testing antiretroviral-based microbicides, including tenofovir (Viread™) gel and UC781 gel, and will be conducted through the Microbicide Trials Network (MTN) as well as the Integrated Preclinical Clinical Program for HIV Topical Microbicides (IPCP-HTM).
- amfAR–The Foundation for AIDS Research has supported many RM research projects throughout the world.
- A range of other projects have focussed on product acceptability, testing of candidates for rectal use, and the rectal safety of lubricants.

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

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

A number of independent studies and research projects have been conducted over the past two years, including: a half-dozen RM-specific projects funded by amfAR–The Foundation for AIDS Research

(see Section 2.7); basic research projects focussed on developing and testing new compounds to be used as candidate microbicides (see Sections 2.8 and 2.9); a study on product acceptability (see Section 2.10); and a study testing the rectal safety of sexual lubricants (see Section 2.11).

SECTION	RESEARCH PROJECT	YEAR
2.1	The Microbicide Development Program (MDP)	2004–2010
2.2	Combination HIV Antiretroviral Rectal Microbicide (CHARM) Program	2010–2014
2.3	Microbicide Safety and Acceptability in Young Men	2010–2013
2.4	Combined Highly-Active Antiretroviral Microbicides (CHAARM) Programme	2010–2014
2.5	RMP-02/MTN-006: Phase I rectal microbicide safety and acceptability trial of topically applied tenofovir compared with oral tablet	2009–2011
2.6	MTN-007: Phase I rectal safety and acceptability study of tenofovir gel	2010–2011
2.7	Biomedical, social, and behavioural research funded by amfAR	2007–2010
2.8	Aptamer microbicide development program	2005–2011
2.9	Evaluating rectal safety and efficacy of microbicides in macaques	2008–2009
2.10	Assessing user preferences for rectal microbicide formulations: Gel vs. suppository	2005–2007
2.11	Assessing the rectal safety of sexual lubricants	2009

As the field of RM research continues to evolve and expand, there is a stronger need than ever for additional resources (see Section 3) and for better coordinated efforts to plan for the future through the development of a Global Rectal Microbicide Development Plan (see Section 5.2).

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

## 2.1 The Microbicide Development Program (MDP)

Principal investigator: Peter Anton

Institution: University of California, Los Angeles (U.S.)

Funder: U.S. National Institutes of Health (NIH)


Years: 2004–2010

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

Some MDP studies are not described below, including a study of rectal applicator acceptability and a challenge experiment using explants to assess products using a combination of antiretroviral drugs.<sup>1</sup>

## 2.1.1 Prevention of infection in primates when pre-treated rectally with tenofovir gel


MDP-associated researchers in the UK investigated whether rectally-applied tenofovir gel had any protective efficacy in a rectal challenge experiment with macaques.<sup>2</sup> Of 20 macaques, nine animals received tenofovir gel rectally up to two hours prior to virus challenge with SIV, four macaques received placebo gel, and four macaques remained untreated. In addition, three macaques were given tenofovir gel two hours after virus challenge. Remarkably, eight of nine given the tenofovir gel two hours prior to being exposed to SIV were completely protected (using a variety of measures of infection) whereas all untreated and three of four placebo animals were infected. There also was a strong positive association between the concentration of tenofovir in the blood plasma 15 minutes after rectal application of the gel and the degree of protection, providing a potential surrogate for future trials to test. Importantly, in a finding similar to the results from the first Phase I trial in humans (see Section 2.1.7), colorectal explants from macaques treated with tenofovir *in vivo* resisted infection when exposed to SIV *ex vivo*. These results indicate that colorectal pre-treatment with antiretroviral drugs, such as tenofovir, has potential as a strategy for the prevention of HIV transmission in a clinical setting.



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

## 2.1.2 Enema comparison study for safety and acceptability

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



Products can be *iso-osmolar*, *hypo-osmolar* or *hyper-osmolar*. Iso-osmolar products have the same concentration of solutes (osmolarity) as normal cells, and thus have little effect on cells' integrity. Hypo-osmolar products tend to make cells swell up with water that can lead to cell collapse. Hyper-osmolar products have a higher concentration of solutes than normal human cells. Therefore, when in contact with mucosal membranes, they tend to "suck" away water from cells, making them dry up, and thus potentially increasing the risk of abrasion and HIV infection.

## 2.1.3 Rectal microbicide vehicle comparison study



“On a global basis there are more women exposed to HIV through rectal intercourse than men. Therefore, the development of a microbicide that works rectally will have a huge impact on the spread of HIV for both men and women.”

**Carolina Herrera**  
Scientist  
St. Georges, University of London  
London, UK

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

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

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

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

### I. Aqueous Formulations

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

### II. Lipid Formulations

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

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

As part of the rectal vehicle development efforts, the group also conducted condom compatibility testing for a large number of commonly used commercial lubricants. These studies found a wide range of properties in these products as well as potential associated problems. A new condom compatibility method was developed using a Texture Analyser, used to quickly screen new formulated products for condom compatibility.

### **Incorporation of UC781, in anticipation of making a rectal-specific formulation of UC781 as a RM:**

Incorporating UC781 in typical aqueous-based formulations is challenging because UC781 repels water and has limited solubility. This has been done successfully with the aqueous gel vehicle but presents a problem with the aqueous fluid, due to sedimentation. In contrast, the lipid placebo formulations are attractive since UC781 can be formulated as a solution, thereby maximising dissolution and drug delivery. UC781 showed significantly enhanced solubility in two lipid solvents but was not stable in either one. These data will be pivotal in selecting the carrier formulation for UC781 (and later, tenofovir) that will be most appropriate for human testing.

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

This study recruited 896 men and women in Los Angeles and Baltimore (U.S.). From 2006–2009, study participants completed computer-administered self interviews about rectal sexual behaviour, hygiene, and anorectal symptoms, and underwent high resolution anoscopy (HRA) to detect rectal and anal clinical signs. Half the men sampled practiced receptive AI (RAI) in the past month and half the women in the past year. Frequencies of behaviours, reported symptoms, and HRA-noted clinical signs were recorded and analysed.<sup>3</sup>

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

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

## **2.1.6 Rectal lubricant use and risk for rectal STIs**

Sexual lubricants are commonly used during RAI among men and women. Since there remains the possibility that lubes on their own may alter or increase vulnerability to rectal sexually transmitted infections (STIs)—possibly via mucosal irritation—information on this issue is critical to the development of rectally used, drug-containing lubricants. This association was examined within the study described in Section 2.1.5. Participants completed computer-administered self interviews about sexual and hygiene behaviour, and were tested for rectal STIs (gonorrhoea and chlamydia). 302 of the 896 participants reported RAI in the past month (men) or year (women). The study evaluated frequencies for lube use before last RAI and associations with demographics, HIV status, and other behaviours.

Overall 76% reported lube use before last RAI and 8.3% tested positive for a rectal STI (5.6% of women and 10.2% of men). 11.7% of lube users were positive for a rectal STI vs. 4.5% who did not use lube ( $p < 0.05$ ). Lube use was significantly associated with rectal STI after controlling for gender, HIV status, city, condom use, and number of sex partners in the past month.

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

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

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



“Developing a rectal microbicide is a way of empowering our fellow human beings to act in a responsible, safe way to protect themselves and their loved ones.”

**Roy Wadia**  
Advocate, IRMA Steering  
Committee Member  
Mumbai, India

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

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

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

This study showed the UC781 gel to be safe and well tolerated when used rectally. Participants were highly compliant, all procedures were completed, and all 36 enrolled participants (26 men, 10 women) completed the trial. No significant differences were seen in mucosal injury assays between high dose (0.25%), low dose (0.1%), or placebo groups. A noteworthy result showed that explants exposed *in vivo* to 0.25% UC781 gel for 30 minutes demonstrated significant suppression of *ex vivo* explant HIV infection.<sup>4,5</sup> *Ex vivo* assessment of *in vivo* effects of microbicides is an exciting, potentially valuable new efficacy indicator for possible use early in the development process, prior to formal Phase IIb/III trials.

## 2.1.8 Acceptability of UC781 gel as a rectal microbicide

As part of the trial described above, acceptability was assessed using structured questionnaires and qualitative in-depth interviews.<sup>6</sup> Participants' reports suggest that a UC781 gel formulation is highly acceptable and comparable to a placebo gel. The gels received favourable ratings overall and on attributes such as colour, smell, and consistency. All of the participants reported high intentions to use a gel like the one they used in this study.

## 2.2 Combination HIV Antiretroviral Rectal Microbicide (CHARM) Program

Principal investigator: Ian McGowan

Institution: University of Pittsburgh School of Medicine (U.S.)

Funder: U.S. NIH

Years: 2010-2014

CHARM<sup>7</sup> will develop rectal-specific antiretroviral microbicides. These candidate microbicides will include tenofovir, UC781, and a combination of tenofovir and UC781.

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

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

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

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

## 2.3 Microbicide Safety and Acceptability in Young Men

Principal investigators: Ian McGowan and Alex Carballo-Diéguez

Institutions: University of Pittsburgh School of Medicine (U.S.) and Columbia University (U.S.)

Funder: U.S. NIH

Years: 2010-2013



“I am committed to embracing the possibilities of biomedical prevention: microbicides, vaccines, PrEP and PEP, though not blindly. It seems to me IRMA is the perfect context to do all of this, all the while challenging the authority and privilege of biomedical science in gay men’s sexual health!”

**Charles Stephens**  
Advocate  
Atlanta, U.S.

This study<sup>8</sup> will be conducted with an ethnically diverse sample of HIV-negative 18-30 year-old men who report engaging in RAI using condoms inconsistently or not at all. The ultimate goal is to test whether or not this highly vulnerable population could safely use the microbicide candidate UC781, and whether or not patterns of placebo use are indistinguishable from UC781 use, suggesting that the product would be used correctly and consistently in real-life circumstances.

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

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

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

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

Principal investigators: Charles Kelly and Robin Shattock

Institutions: King’s College London (UK) and St. George’s Hospital and Medical School, University of London (UK)

Funder: European Commission’s Seventh Research Programme Framework

Years: 2010–2014

The CHAARM project<sup>9</sup> will develop new microbicides, and combinations thereof, to help maintain a pipeline of promising candidates. Combining two or more microbicides in a single product may be more effective than using a single microbicide and, importantly, may reduce the likelihood of HIV becoming resistant to an antiretroviral product.

The project involves scientists with expertise in a wide range of different disciplines from 31 institutions in 12 countries, including eight member states of the European Union, as well as Switzerland, South Africa, the United States, and Ukraine. CHAARM will develop rigorous procedures for testing efficacy and safety using new model systems as well as identify new microbicides and combinations. The programme will include human studies to determine microbicide safety and will investigate biomarkers associated with health or damage at mucosal surfaces. It will also investigate formulation and potential scale-up of microbicide production.

The project aims to develop microbicides for both rectal and vaginal application. The exact nature of the work on RMs may change as the project evolves. At this point, these efforts may include: developing or progressing new products with an emphasis on combinations; using an integrated strategy for testing efficacy and safety *in vitro* in which cervicovaginal and rectal explants, as well as colonic and vaginal derived cell lines, will be used; conducting studies to investigate both gel and vaginal ring formulations, including rectal gel formulations; and conducting pharmacokinetic studies and performing challenge experiments of the most promising compounds in macaques (vaginal and rectal challenge).

For more information, please visit [www.chaarm.eu](http://www.chaarm.eu)

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

Principal investigators: Peter Anton and Ian McGowan

Institutions: UCLA (U.S.) and University of Pittsburgh School of Medicine (U.S.)

Funder: U.S. NIH

Years: 2009–2011

The RMP-02/MTN-006 trial<sup>10</sup> is a collaborative effort between IPCP-HTM and MTN. The study involves 18 participants and is evaluating the safety and early pharmacokinetic profile of vaginally-formulated tenofovir gel applied rectally in a single dose, followed by once-daily dosing for seven days, compared to a single oral dose of tenofovir. The study is designed as a Phase I rectal safety trial to support the vaginal microbicide application, should vaginal efficacy be demonstrated. As of this writing, the study is almost fully enrolled and should be completed in 2010.

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

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

Principal investigator: Ian McGowan

Institution: University of Pittsburgh School of Medicine (U.S.)

Funder: U.S. NIH

Years: 2010–2011

MTN-007<sup>11</sup> is a Phase I, randomised, blinded, placebo-controlled safety and acceptability study of rectally applied tenofovir gel. Participants will be randomised to receive a single dose of tenofovir gel, a placebo gel, or Nonoxynol-9 (N-9) gel—used as a positive control. One week later they will be given a seven-day supply of the study gel. Approximately 63 men and women at sites in the U.S. will participate in the trial, scheduled to start in late 2010.

## 2.7 Biomedical, social, and behavioural research funded by amfAR

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



“There is not much information on the risks involved in anal sex, and prevention messages simply ignore this. That means talk of universal access is empty talk as we do not address all the aspects that impact responses to HIV.”

**Martha Tholanah**  
Advocate  
Harare, Zimbabwe

In a report issued in early 2009, amfAR provided a review of its findings and discussed their implications, identified remaining knowledge gaps, and suggested strategies to promote this field of enquiry. For more information on these projects, which were funded in the 2007-2010 period, please consult *Advancing New Ideas in AIDS Research*.<sup>12</sup> The projects related to RM research and development included:

- *Development of a standard microbicide delivery device*, Alex Carballo-Diéguéz, Research Foundation for Mental Hygiene, Inc. (U.S.)
- *Exploring epithelial injury in regions of the rectum and colon most susceptible to HIV infection following intercourse*, Craig Hendrix, Johns Hopkins University School of Medicine (U.S.)
- *Rectal transmission of HIV-1 in genetically engineered mice with an immune system that mimics that of humans*, Roberto Speck, University Hospital of Zurich (Switzerland)
- *Colorectal responses to HIV-1 and modulation by microbicides*, Carolina Herrera and Robin Shattock, St. George's University of London (UK)
- *Understanding how HIV and rectal cells interact at the point of infection*, Dr. Charlene Dezzutti, Magee-Women's Research Institute and Foundation (U.S.)
- *Modelling the impact of a rectal microbicide*, Anna Foss, London School of Hygiene and Tropical Medicine (UK)

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

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

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

Dr. Anna Foss and colleagues at the London School of Hygiene and Tropical Medicine used detailed epidemiological and behavioural data from Bangalore and Lima—two settings in which the HIV

epidemic remains concentrated in high-risk groups, including gay men and other MSM—to parameterise and fit a compartmental epidemiological model. The joint transmission dynamics of HIV, syphilis, and genital herpes were simulated among three behavioural subgroups of gay men and other MSM, defined by their typical role during AI—insertive, receptive, or both. The potential evolution of the HIV epidemic was investigated with and without a five-year RM intervention. Various scenarios of RM availability, consistency of use, and per sex act efficacy against HIV were explored.

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

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

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

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

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

Further details<sup>13,14</sup> will be presented at the Microbicides 2010 conference in May 2010.

## 2.8 Aptamer Microbicide Development Program

Principal investigator: Ian McGowan

Institution: University of Pittsburgh School of Medicine (U.S.)

Funder: U.S. NIH

Years: 2005–2011

The purpose of this grant is to develop aptamers as novel candidate microbicides for the prevention of HIV-1, herpes simplex virus 2 (HSV-2), and human papillomavirus (HPV) transmission. Aptamers are RNA molecules that have been generated through a process that identifies and enriches molecules which show affinity for binding to components of viruses such as HIV. To date this project has focussed on the preclinical evaluation of HIV gp120 RNA aptamers in cell lines and the colorectal explant model.

Compared to drugs like tenofovir, the HIV aptamers appear to have modest activity in the explant system. One possible explanation is that bacterial-associated enzymes present in the rectal compartment actually break down the aptamers and prevent them from working as microbicides. Characterising the mechanism of this process will have important implications for the development of future RNA-based microbicides.

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

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



“I can only imagine the beautiful world a complimentary product like a rectal microbicide would create for HIV prevention in women.”

**Morenike Ukpong**  
Advocate  
Ibadan, Nigeria

This study<sup>15</sup> developed a standardised protocol for an assessment of preclinical rectal safety and (chlamydial) efficacy assessment of topical microbicide candidates in a nonhuman primate model. It evaluated a total of 12 test compounds for rectal safety, and one compound for efficacy, against rectal chlamydial infection.

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

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

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

This study<sup>16</sup> assessed whether gay men and other MSM prefer a gel or a suppository as an RM delivery vehicle. Study participants included 77 HIV-negative gay men and other MSM with a recent history of inconsistent condom use during RAI who acknowledged being at risk of contracting HIV. In this randomised acceptability trial, participants compared 35ml placebo gel with 8g placebo rectal suppositories used up to three RAI occasions each.

Participants preferred the gel over the suppository (75% versus 25%,  $p=0.001$ ) and so did their partners (71% versus 29%,  $p=0.001$ ). The gel received more favourable ratings overall and on attributes such as colour, smell, consistency, and feeling in rectum immediately after insertion and/or 30 minutes after insertion, as well as during the application process. Participants reported favourably on the gel and did not report significant instances of leakage, soiling, bloating, gassiness, stomach cramps, urge to have a bowel movement, diarrhea, pain, or trauma. Participants also preferred the gel in terms of feelings during anal sex, sexual satisfaction, partners' sexual satisfaction, and liking the product when condoms were used and when condoms were not used.

The study concluded that a gel had greater acceptability than a suppository as a potential microbicide vehicle in this sample recruited from one of the populations most likely to benefit from RM availability.

## 2.11 Assessing the rectal safety of sexual lubricants

Principal investigator: Charlene Dezzutti

Institution: University of Pittsburgh (U.S.)

Funder: U.S. NIH

Year: 2009

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

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

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

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

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

- Using *in vitro* and mouse assays to determine cellular toxicity, increased risk of HSV-2 infection, and epithelial sloughing caused by lubricants<sup>17</sup>
- Testing the osmolarity of lubricants<sup>18</sup>
- Using slug mucosal irritation assays to evaluate mucosal irritation caused by lubricants<sup>19,20</sup>

The question remains: what do all of these studies tell us? We're not sure. We still don't know what assays should be used to determine the rectal safety of lubricants. Furthermore, even when studies find a wide range of values for their safety markers, we still don't know to what extent—if any—some of these markers might indicate a higher risk of HIV transmission.

Relatively high levels of cellular toxicity, mucosal irritation, cell damage caused by hyper-osmolar or hypo-osmolar products, inflammation, or epithelial sloughing could in theory increase the risk of HIV infection. However, this remains to be proven.

It is important to keep in mind that:

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

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

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

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

## Glossary

*IRMA thanks the Global Campaign for Microbicides for much of this glossary. Many of the following terms may be found in their "Microbicides Essentials Course," available at [www.hivpreventionresearch.org](http://www.hivpreventionresearch.org)*

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

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

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

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

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

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

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

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

**Challenge experiment:** A test where primates are exposed in a lab to SIV (the simian equivalent of HIV). Typically, some of the animals are given a test product beforehand, while others are not. Differences in

infection rates between the two groups can be attributed to the test product. Similar tests are sometimes done with human tissue explants and HIV.

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

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

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

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

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

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

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

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

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

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

**Lactobacillus:** A type of bacteria found in the vagina and gastrointestinal tract. A disruption of these bacteria can cause a change in the natural pH level of the vagina or rectum.

**Molecule:** The smallest particle of a compound that has all the chemical properties of that compound. Molecules vary widely in their size and structure.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

**Viscosity:** A measure of how fluid a substance is; how “thin” (like water) or “thick” (like honey) it is.