

Rectal Microbicides: Investments & Advocacy



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This report was prepared on behalf of
the International Rectal Microbicide Working Group
by Cindra Feuer

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Technology should be the friend of all people, not solely a tool of the dominant group. We must demand that the full resources of our nations be committed to the development of new prevention technologies such as rectal microbicides that will allow us another way to care for each other and keep each other healthy.

—Eric Rofes, professor, author, and advocate for men's health

Women's need for protection against sexually transmitted pathogens, like the need for contraception, varies greatly from one individual to another, and can change over the course of a lifetime. The availability of both a rectal and vaginal microbicide will ensure that women have options, should they need them, for protection against HIV and other STDs. For this reason, an investment in research on rectal microbicides is essential.

—Geeta Rao Gupta, leading global authority on women's development

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1. Introduction

Research into rectal microbicides has been underfunded by both private and public sectors, despite the potentially large market for microbicides, and an urgent, international need for additional prevention tools, beyond condoms, for men and women who engage in anal intercourse. Political marginalization and scientific challenges have sidelined investment into what could be a promising new prevention technology. The need for a biomedical prevention intervention is underscored by the world's climbing HIV infection rates.

This report serves two purposes: Firstly, it tracks rectal microbicide research expenditures in order to determine the resources needed to accelerate progress in research and development. Total rectal microbicide investment, charted from 2000 onward, is compared with an estimated required sum to bring a rectal microbicide from the bench through to licensure. Secondly, this report provides advocates, policy makers, and scientists with a reference from which to pose recommendations and measure progress.

1.2 About the International Rectal Microbicide Working Group

The International Rectal Microbicide Working Group is a coalition of advocates, policy makers and scientists from five continents working to advance the research and development of rectal microbicides. The Group also promotes new prevention technologies beyond microbicides, exploring pre-exposure prophylaxis, lubricant safety, and sexual harm reduction.

2. Methodology

2.1 Data Retrieval

Rectal Microbicides: Investments and Advocacy is an unprecedented attempt to compile and publish comprehensive data on global expenditures for rectal microbicide research. The annual reports of the HIV Vaccine and Microbicide Tracking Working Group (WG) of UNAIDS, AVAC, International AIDS Vaccine Initiative, and Alliance for Microbicide Development, *Tracking Funding for Microbicide Research & Development*, chart vaginal and rectal microbicide spending, but do not differentiate between the two distinct research areas. In this report, we use the WG document as a reference from which to gauge rectal microbicide spending.

Data are collated from public and private sectors, and supplemented by interviews with a range of experts in the microbicide field. Most of the information is based on self-reporting by recipients and representatives of the funding sources. Survey inquiries include:

- a) confirmation of past, current, and future funding for rectal microbicide research;
- b) annual disbursements of research from 2000 onward; and
- c) institutions receiving or disbursing the allocated funds (to avoid double counting).

While basic science and clinical research on vaginal microbicides are crucial to the eventual development of a rectal microbicide, this survey tracks research focused on rectal mucosal transmission, rectal acceptability and safety markers, rectal explant studies, and behaviors associated with anal sex. Vaginal microbicide studies (preclinical and clinical), although useful as supportive research for the development of rectal microbicides, are not included in this analysis of rectal microbicide funding.

Projected costs needed to bring a rectal microbicide through to licensure were determined in consultation with microbicide researchers.

2.2 Data Limitations

Currently, the European Commission (EC) does not apportion specific funds for rectal microbicide research; however, there may be investments in vaginal microbicides that are used towards rectal microbicide investigations. In a survey of both European government representatives and researchers, none were able to identify direct European funding lines specifically for rectal microbicide research from either the EC or individual countries. Some EC funding may exist, although it proved too elusive to track in this report.

Only one of the two private companies identified as involved in rectal microbicide research quantified their in-kind contributions, as the commercial sector is often unwilling to reveal investments or returns to the public. Therefore, estimates provided in this document for the commercial sector may be underreported.

3. The Context of Rectal Microbicides

3.1 Role of Anal Intercourse in HIV Transmission

Overall rates of HIV transmission are still increasing, indicating that far greater attention to prevention, including new methods and technologies, is needed to decelerate the epidemic. Latest global figures show that in 2005 there were an additional 5 million new infections, and the number of people living with HIV hit its highest level at an estimated 40.3 million¹.

A range of data suggests that a significant proportion of transmission might be attributed to anal sex. Studies show that up to 30% of the heterosexual population in many cultures engage in anal intercourse (AI)^{2,3,4}. **Given the greater total numbers of heterosexuals than homosexuals, it is estimated that the total volume of heterosexual unprotected AI is up to fivefold that of males who have sex with males (MSM)⁵.** The prevalence of female AI is projected to be even

1. Joint United Nations Programme on HIV/AIDS (UNAIDS) and World Health Organization (WHO). UNAIDS/WHO AIDS epidemic update. 2005.

2. Mosher WD, Chandra A, Jones J. Sexual behavior and selected health measures: men and women 15–44 years of age, United States, 2002. *Adv Data*. September 2005; (362): 1-55.

3. Caceres C, Oss V, Marin B, Hudes E, et al. Young people and the structure of sexual risks in Lima. *AIDS*. 1997; 11((suppl. 1)): S67–77.

4. Ramjee G GE. Prevalence of HIV among truck drivers visiting sex workers in KwaZulu-Natal, South Africa. *Sex Transm Dis*. 2002; 29: 44–9.

5. Rohr B, Gross M, Mayer K. Rectal microbicides that protect against HIV infection, report from the Workshop Creating a Research and Development Agenda. Baltimore, Maryland, June 7–8, 2001.

greater in societies where contraception is unavailable and virginity is prized. Ultimately, it's difficult to know the exact extent of anal intercourse because it is taboo in many societies and data are not recorded.

While transmission of HIV has shown to be 10- to 100-fold more efficient through anal than vaginal intercourse,^{6,7} studies show that women engaging in AI seldom succeed in having their male partners use condoms⁸. Likewise, a recent South African study shows that among heterosexual men, anal sex was associated with being HIV-positive; those who engage in the behavior are nearly twice as likely to be infected as their male counterparts reporting only vaginal sex⁹.

Because women make up the majority of receptive anal partners, they, like MSM, are in need of a rectal HIV-prevention method. The same requirements for the discovery of a vaginal microbicide can be applied to the need for rectal protection: until a woman can negotiate condom use with her partners, she will need protection that she herself can control with or without her partners' knowledge or participation.

Women are particularly vulnerable to infection. In sub-Saharan Africa, where two-thirds of HIV infections occur¹⁰, women aged 15–24 years are three times more likely to be infected than men¹¹. The numbers underscore the need for vaginal microbicide research, to which the majority of microbicide expenditures is allocated. While some of these women are probably infected through anal sex, it is difficult to assess the role of AI in infection. Millions of women have neither the power in their sexual relationships to insist on abstinence, fidelity, or condom use, nor the social and economic resources to leave partners who put them at risk. Thus, putting a woman-controlled prevention tool into the hands of these women is the motivation driving most microbicide research.

Investments in rectal microbicides have been scant for several reasons, including the field's perceived relevance only to MSM. As we learn more about the incidence and prevalence of heterosexual AI, this misconception will be easier to refute; however, MSM still represent a

6. Vittinghoff E, Douglas J, Judon F, McKim D, MacQueen K, Buchinder SP. Per-contact risk of human immunodeficiency virus between male sexual partners. *American Journal of Epidemiology*. 1999; 150(3): 306–11.

7. Kalichman SC, Rompa D, Luke W, Austin J. HIV transmission risk behaviours among HIV-positive persons in serodiscordant relationships. *Int J STD AIDS*. October 2002; 13(10): 677–82.

8. Rohr B, et al.

9. Lane T, Pettifor A, Pascoe S, Fiamma A, Rees H. Heterosexual anal intercourse increases risk of HIV infection among young South African men. *AIDS*. 2006; 20(1): 123–25.

10. Joint United Nations Programme on HIV/AIDS (UNAIDS) and World Health Organization (WHO). UNAIDS/WHO AIDS epidemic update. 2005.

crucial population in need of interventions. Although the total incidence of unprotected AI is higher in heterosexuals, the prevalence of AI among MSM is higher. Compounding the risk to MSM are the elevated rates of HIV in this population in some regions. For example, MSM made up 44.3% of new infections in the U.S. in 2004¹². High rates of STIs and HIV infections testify to the fact that only one prevention tool for sexual activity—the condom—is insufficient.

Findings from a Gay Men's Sex Survey in 2002 in the U.K. showed that 48.8% of all men who had sex with men had had unprotected anal intercourse in the past year¹³. Even more concerning is that 14.6% of HIV negative (at last test) or untested men said they definitely, or probably, had unprotected anal sex with a man they thought was HIV-positive in the past year. In other countries, including Canada, Australia, and Scotland, increases in risk behaviors, STIs, and HIV incidences have been documented among MSM^{14 15 16}.

Several surveys have measured gay men's interest in microbicides. In a U.S. cohort, the majority of the men indicated a willingness to participate in microbicide studies¹⁷. An Internet survey of 10,000 MSM in the U.K. showed that most would use a microbicide¹⁸. According to a San Francisco study, however, only 25–35% of gay men said they would be interested in using microbicides if they weren't as effective as condoms¹⁹.

Because of this apprehension, it should be emphasized that microbicides, when available, should be used with condoms (if possible) for additional safety; however, even a microbicide that is less effective than condoms could give people who can't or don't use condoms a way of reducing their risk of infection—certainly a safer option than using nothing at all.

Efforts are needed to overcome the taboo and stigma around AI, and the denial and homo-phobia that are barriers to ensuring strong efforts to address the health needs of women, gay men, and MSM.

11. Kim J, Watts CH. Gaining a foothold: tackling poverty, gender, inequality and HIV in Africa. *BMJ*. 2005; 331: 769–72.
12. Centers for Disease Control and Prevention, Division of HIV/AIDS Prevention-Surveillance and Epidemiology, Special Data Request. November 2005.
13. Hickson F, Weatherburn P, Reid D, Stephens M. Out and about. Findings from the United Kingdom, gay men's sex survey 2002. Sigma Research. 2003. <http://www.sigmaresearch.org.uk/reports.html>.
14. HIV/AIDS Epi Updates, May 2005; Surveillance and Risk Assessment Division, Centre for Infectious Disease Prevention and Control, Public Health Agency of Canada, 2005.
15. Van De Ven P, Prestage G, French J, et al. Increase in unprotected anal intercourse with casual partners among Sydney gay men in 1996–98. *Aust NZ J Publ Heal*. 1998; 22: 814–18.
16. Hart GJ, Williamson LM. Increase in HIV sexual risk behaviour in homosexual men in Scotland, 1996–2002: prevention failure? *Sex Transm Infect*. October 2005; 81(5): 367–72.
17. Gross M, Buchbinder SP, Celum C, Heagerty P, Seage GR 3rd, Rectal Microbicides for U.S. Gay Men. Are clinical trials needed? Are they necessary? *Sex Transm Dis*. 1998; 25(6): 296–302.
18. Reid D, Weatherburn P, Hickson F, Stephens M, Hammond G. On the move, findings from the United Kingdom, gay men's sex survey. Sigma Research. 2003. <http://www.sigmaresearch.org.uk/reports.html>. Accessed April 3, 2006.
19. The study by Carballo-Diéguez was based on a secondary analysis of data from the third phase of the Urban Men's Health Study (UMHS-3). Catania J, Paul J, Pollack L, Fisher L, Folkman S, Osmond D. UMHS III Sexual trauma and HIV risk behavior of Gay Men. <http://www.caps.ucsf.edu/pdfs/2004portfolio/UMHS3.pdf>. Accessed April 7, 2006.

3.2 The Potential Impact of a Rectal Microbicide

Utilizing mathematical modeling, a team from the University of California–Los Angeles (UCLA) recently evaluated the potential impact of rectal microbicides on reducing HIV transmission. Using the MSM bathhouse setting for analysis, it found that even if microbicide use was fairly modest (30–50%), microbicide efficacy would only need to exceed 30% in order to have a significant impact in spreading secondary infections. A 50% effective microbicide, used in 50% of sex acts would reduce the number of new infections at disease invasion in the bathhouse by 13%²⁰. More importantly, this model suggested that a microbicide with greater than 30% efficacy would significantly reduce the number of secondary HIV infections in the bathhouse.

UCLA researchers believe that even a moderately effective rectal microbicide would be of benefit in MSM bathhouse scenarios as well as in other high-risk environments that include heterosexual AI.

The cost savings to the global health system of averting HIV infections with rectal microbicides has yet to be mathematically modeled; however, it can be inferred through vaginal microbicide cost modeling that the savings would be in the billions when rectal microbicide use reduces the burden of care and treatment required of health systems²¹. The prevention of HIV infection through rectal microbicides will also reduce workplace illness and loss of productivity, resulting in indirect financial savings.

3.3 Sociocultural Challenges

Microbicide research is a new field with less than 15 years of study. In relation to its potential, the field is underfunded. Large pharmaceutical companies that usually fund new drug development have shied away from microbicide research, as they have with vaccines, because they see it as too much financial risk for too little profit. As a result, the task of microbicide development has

20. Breban R, McGowan I, Topaz C, Schwartz E, Anton P, Bowler S. Modeling the potential impact of rectal microbicides to reduce HIV transmission in bathhouses. *Mathematical Biosciences and Engineering*. In press.

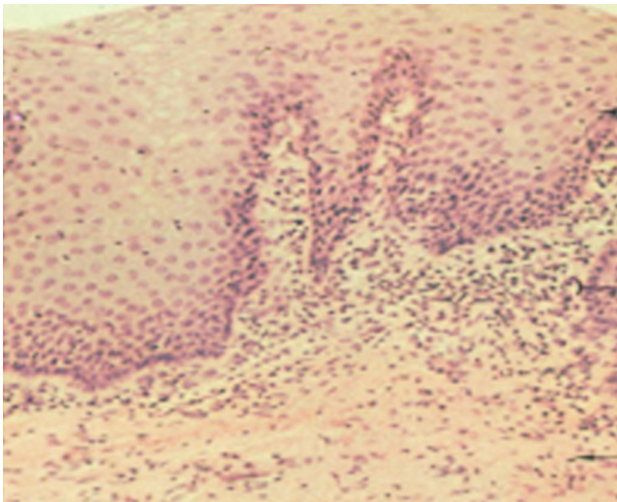
21. The Economics of Microbicide Development: A Case for Investment. Rockefeller Foundation.

fallen to scientists at nonprofit organizations, universities, and small biotech companies—all of which rely on government grants and foundation contributions to keep their research going. Progress has been slow due to inadequate funding from donor governments and from traditional multilateral institutions.

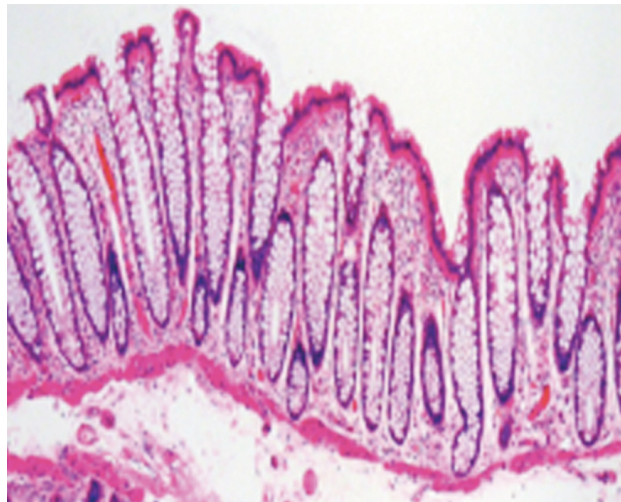
Homophobia and stigma have slowed down the progress of necessary research on the prevention of rectally acquired infections. In the U.S. and elsewhere, investment in rectal microbicides is difficult because civil society and policy makers are hesitant to talk about AI.

3.4 Scientific Challenges

Formulating a microbicide for rectal use is, for two reasons, more scientifically challenging than producing one for vaginal use. First, rectal tissue is far more fragile than most of the tissue lining the vagina. The vaginal epithelium is up to 40 cell layers thick. Rectal epithelium is composed of a single cell layer and is vulnerable to infection and trauma. The cells in the mucosa below the epithelium also contain many CD4 T cells with lots of necessary co-receptors, rendering them especially susceptible to HIV.



Vaginal Epithelium



Rectal Epithelium

The two illustrations reveal the significant differences between the vaginal and the rectal epithelium. On the (left) is a highly magnified picture of a sample of vaginal tissue. There are multiple layers, or strata, of epithelial cells. The vaginal epithelium is a stratified squamous epithelium designed to withstand the stresses associated with sexual intercourse. In contrast, the rectal epithelium (seen on the right) has a single layer of epithelial cells which makes it very vulnerable to damage associated with anal intercourse. To some extent, these differences may explain why it is much easier to acquire HIV infection through anal rather than vaginal intercourse.

Second, the colon is a tube that extends from the anus to the appendix, whereas the vagina is a closed pouch. The inside of the vagina can be completely coated with only about 3–5 ml of product. Since the rectal cavity isn't closed, it could require significantly more product to cover the rectal walls where they need protection. One of the key questions scientists are trying to answer now is exactly how much product it will take and what areas have to be covered to achieve the desired protective effect.

3.5 Research: Current and Past

To date, published rectal microbicide research has been limited. The only human trials for a specific product were for the spermicide nonoxynol-9 (N-9) in three separate studies in MSM^{22,23,24}. The studies by Phillips et al. demonstrated the potential for significant mucosal toxicity.

Since then, a promising study showed that cyanovirin, an HIV-cell fusion blocker derived from blue-green algae, prevents rectal transmission in the SHIV-infected macaque model²⁵. A more recent study showed that an oral tenofovir/FTC combination also prevents rectal SHIV transmission in macaques²⁶; however, there is still little known about the basics of HIV transmission in the rectum. Researchers are currently trying to determine which elements of the intestinal mucosa are the initial targets of infection, and which region of the colon needs safeguarding with a microbicide.

In a sobering discovery presented in 2004, scientists found that a semen simulate can travel two to three feet up the colon²⁷, which means a microbicide may be required to travel the same long distance to provide adequate protection. Although this represents a significant challenge, gastroenterologists routinely prescribe topical products to treat colitis associated with inflammatory bowel disease. These products, usually formed as foams, enemas, or suppositories, may provide a useful model for developing rectal microbicide formulations as they are designed to deliver drugs to the same region of the colon that might be most vulnerable to HIV infection.

22. Tabet SR, Surawicz C, Horton S, et al. Safety and toxicity of nonoxynol-9 gel as a rectal microbicide. *Sex Transm Dis. Infect.* 1999; 26: 564–71.

23. Phillips DM, Taylor CL, Zacharopoulos VR, Maguire RA. Nonoxynol-9 causes rapid exfoliation of sheets of rectal epithelium. *Contraception.* 2000; 62: 149–54.

24. Phillips DM, Sudol KM, Taylor CL, Guichard L, Elsen R, Maguire RA. Lubricants containing n-9 may enhance rectal transmission of HIV and other STDs. *Contraception.* 2004; 70: 107–10.

25. Tsai CC, Emau P, Jiang Y, Tian B, Morton WR, Gustafson KR, et al. Cyanovirin-n gel as a topical microbicide prevents rectal transmission of SHIV89.6p in macaques. *AIDS Res Hum Retroviruses.* 2003; 19: 535–41.

26. Garcia-Lerma J, Otten R, Qari S, Jackson E, Luo W, Monsour M, et al. Prevention of rectal SHIV transmission in macaques by tenofovir/FTC combination [abstract]. Paper presented at: 12th Conference on Retroviruses and Opportunistic Infections. February 5–8, 2005. Boston, MA

27. Hendrix CW, et al. Imaging the distribution of a rectal microbicide gel and semen surrogate in the lower GI tract [abstract]. Paper presented at: International Conference on Microbicides. March 28–31, 2004. London.

Preclinical rectal microbicide development research includes the use of cell lines, intestinal explants (biopsies), and macaque studies of microbicide safety and efficacy. These investigations will enable the advancement of microbicide studies into exploratory human trials. These studies will optimize microbicide safety evaluation in humans; provide initial *ex vivo/in vitro* efficacy data; and yield information about distribution and bioavailability of rectal microbicides. The goal will be to assess the most cost-effective and predictive assays for use in future microbicide development.

Other preclinical research will target the behavioral correlates of AI as well as acceptability studies of candidate formulations. These studies are crucial to developing a product that people will find acceptable and actually use. The findings will help guide the selection of the formulation used in final human trials and will provide a rational basis for the development of other classes of rectal microbicides²⁸.

Microbicide compounds that are currently under study for rectal use (in addition to vaginal use) include topical formulations of antiretroviral drugs, including the nucleotide analogue reverse transcriptase inhibitor PMPA, a form of tenofovir, as well as TMC 120 (dapivirine), a second-generation non-nucleoside reverse transcriptase inhibitor. Another non-nucleoside reverse transcriptase inhibitor, UC-781, is poised for phase 1 clinical trials this year.

4. Investment in Rectal Microbicide Research

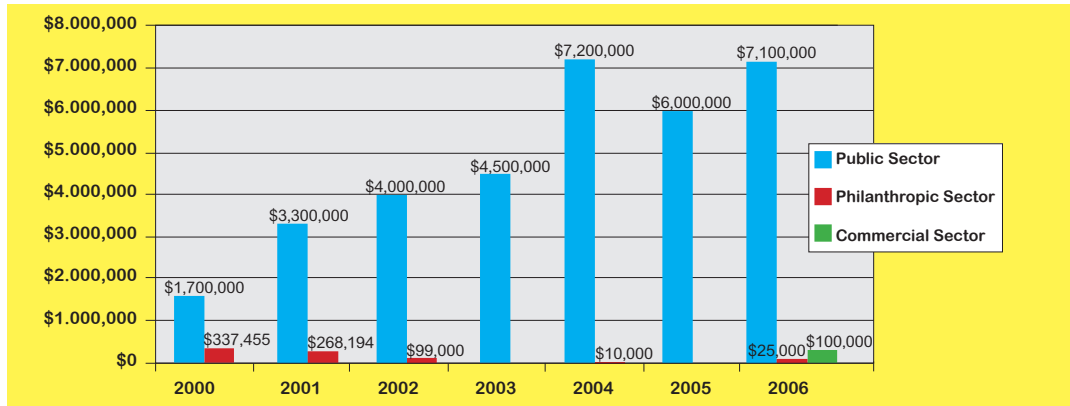
4.1 Total Investment

Between 2000 and 2006, total investments in rectal microbicide research show a small, steady increase in funding trends. Total public, private, and philanthropic spending was \$34 million. In 2006 estimated disbursements total \$7.2 million.

28. Global Campaign for Microbicides. Rectal microbicide presentation, November 2005. <http://www.global-campaign.org/download.htm>. Accessed January 7, 2006.

The U.S. public sector was the primary source of these funds, contributing \$33.1 million, 97.4% of overall monies contributed between 2000 and 2006. The philanthropic and commercial sectors accounted for \$839,649 of the spending. Member states of the European Union, other countries, and multilaterals show no evidence of specific rectal microbicide investments.

Rectal Microbicide Expenditures 2000-2006



4.2 Public Sector

In 2006, the public sector invested an estimated \$7.1 million. Overall public investment trends show an increase from \$1.7 million in 2000, but a drop in committed future funds. The National Institutes of Health (NIH) estimates \$5.5 million in expenditures for 2007.

Within the U.S. public sector, the primary sources of funding come from two health and research funding agencies: NIH, and the Centers for Disease Control and Prevention (CDC). NIH accounted for \$30.8 million of the U.S. public-sector funding between 2000 and 2006. CDC contributed \$2.3 million between 2001 and 2006, averaging \$453,400 in annual disbursements.

From 2000 to 2006, the U.S. public sector spent approximately 12 cents per capita on rectal microbicide R&D²⁹.

Nonoxynol-9 Spending

Nonoxynol-9, the spermicide, is the only compound tested rectally in human trials to date. The Population Council spent an estimated \$400,000, and studies from the University of Washington cost \$206,151, in 2000 and 1999, respectively, totaling \$606,151.

29. The World Bank. 2005 World Development Indicators. Washington, DC. 2005.

4.3 Philanthropic Sector

Philanthropic funding totaled \$739,649, around 2.2% of the total invested funds for rectal microbicide research between 2000 and 2006. The primary philanthropic investor identified was the American Foundation for AIDS Research (amfAR). The foundation does not have a dedicated rectal microbicide funding stream and therefore funding levels fluctuate between years. Rectal microbicide funding from amfAR includes direct support for research as well as meeting support.

4.4 Commercial Sector

The commercial sector has yet to contribute actual dollars; instead support is through in-kind donations, including time spent, pipeline compounds, and infrastructure. All the companies involved in R&D are funded through NIH. Out of the two private companies identified as contributors to rectal microbicide research, Gilead and Biosyn, only the latter revealed a dollar sum contribution, totaling \$100,000 in in-kind donations in 2006.

5. Discussion

5.1 Summary

This paper is a first-time effort to track and analyze total rectal microbicide expenditures. In generating estimates from the public and private sectors, we have chosen a very specific focus on rectal research, quantifying the relevant investigations into basic and behavioral sciences, and in animal studies (there are currently no human trials). Although rectal microbicide research will benefit greatly from research on vaginal mucosal transmission, pathogenesis, immunology, and clinical studies, we aim to separate out funding allocated strictly for rectal microbicide inquiry.

While vaginal microbicide development is a global research effort, with the main sources of financing to date coming from the U.S., Canada, Europe, and other countries such as Australia and Japan, investments in rectal research tilt heavily toward U.S. sources.

Data show that between 2000 and 2006, funding for rectal microbicide research totaled \$34 million, showing an increase from \$2 million in 2000. The growing funding for rectal microbicides reflects an overall global shift in greater financial allocations for HIV/AIDS.

NIH, the donor with the world's largest health research budget, gave \$6.6 million, .023% of its overall budget in 2006, while geographically, disbursements from Europe, other countries, and multilaterals were below detectable levels. The commercial sector has had little direct investment, and their support has largely been through in-kind donations, worth an estimated \$100,000. Philanthropic giving shows a downward trend.

CDC, through its own rectal microbicide program, *The Evaluation of Topical Microbicides in Men Who Have Sex With Men*, spent \$2.3 million from 2001 to 2006, almost matching its domestic vaginal microbicide expenditures over the same time period, which totaled \$2.4 million.

Although funding levels for rectal microbicides are well below those for vaginal candidates, both are dwarfed by investments in other health pursuits. There are a significant number of vaginal microbicide candidates in the preclinical and clinical stages of testing that do not have the funding to proceed further.

Comparisons of NIH investments outside of HIV prevention tools shed light on the priorities of the U.S. In 2005, \$1.7 billion was spent on bioterrorism, including \$1.1 billion to prepare an anthrax vaccine and \$200 million for a smallpox vaccine in 2006³⁰. Congress approved \$3.3 billion in 2006 for avian flu vaccine and drug research, after a \$7.1 billion request from the Bush administration³¹.

Looking ahead, the administration's proposed budget for U.S. fiscal year 2007 aims to cut AIDS research spending by \$15 million. If passed, less scientific research will receive funding, with fewer grants for new research. Congress doubled the NIH budget between 1998 and 2003, but the new budget means fewer than one in five NIH grants will be approved³², portending an even greater challenge to an already beleaguered rectal microbicide budget.

30. Wysocki B. Missing medicine—radical therapy: agency chief spurs bioterror research—and controversy. *Wall Street Journal*. December 6, 2005; A1.

31. McNeil D. States and cities lag in readiness to fight bird flu. *New York Times*. February 6, 2006.

32. American Foundation for AIDS Research. President's budget slights AIDS research [press release]. February 6, 2006.

This report shows rectal microbicide funding tilting heavily toward U.S. sources; however, there may be European funding unaccounted for. Because the European Commission's microbicide programs—European Microbicides Project (EMPRO) and Selection and Development of Microbicides for Mucosal Use to Prevent Sexual HIV Transmission/Acquisition (SHIVA)—do not specifically finance rectal microbicide research, it is possible that rectal research is carried out under EMPRO's microbicide rubric and that European funding may have gone undetected in this survey. Furthermore, the British government, through its Microbicide Development Programme, plans to perform a phase 1 rectal safety study of a microbicide by the end of 2006; however, specific investment totals could not be confirmed.

Advocates believe that if the U.S. took a leadership role and adequately invested in rectal microbicides, the research would be much further along. European researchers would be collaborating more with scientists from the U.S. and seeking funding from E.U. sources. Without this drive, Europeans will have to recognize the need and push for greater resources themselves.

Levels of European investment in vaginal microbicides are catching up with those of the U.S., due to global advocacy by the Global Campaign for Microbicides and the International Partnership for Microbicides, as well as a number of national, regional, and local efforts by NGOs and CBOs in different European countries. In 2000, Europe contributed only 2% of the global resources for microbicides, but by 2004 it had contributed 23%³³. Now that the E.U. is generally supportive of microbicides, it is possible that it will fund rectal research; however, at a national level, governments may prefer to fund public-private partnerships (PPPs) like the International Partnership for Microbicides or their own national research teams.

amfAR proved to be the largest philanthropic funder, totaling \$739,649 in grants between 2000 and 2006. Researchers believe that midway through 2007, rectal safety indices will have been discovered and candidates will be poised for fast track research. It is incumbent upon the philanthropic sector to support these efforts.

Beyond in-kind donations of around \$100,000, the commercial sector has yet to invest, as it is most likely waiting for proof of concept before taking on fiscal risks.

33. Ibid.

5.2 Reasons for Resource Lag

Experts are of many opinions as to why rectal microbicide research has been relegated to the shadows of HIV prevention. Researchers in the microbicide field are occupied with pushing through a potential vaginal microbicide candidate, as there are currently 16 in human trials, 5 in phase 2B and 3 efficacy trials, and over two-dozen others behind them in the pipeline.

Calculations show that to achieve a viable first-generation vaginal microbicide, annual funding for R&D needs to double to \$280 million annually over the next five years³⁴. The need for funding, scientific gains, and the goal of finding a proof of concept keeps researchers diligent in their pursuit of a vaginal microbicide, not leaving a great deal of time and resources for rectal microbicide investigations.

Additionally, experts reason that, historically, vaginal microbicide development was predicated on discovering a woman-initiated prevention tool to be used vaginally. As an afterthought, researchers realized that because microbicides would undoubtedly be used rectally, and probably without any efficacy basis—thus causing more harm—it behooved them to discover a rectally protective product. Hence, the lag in resources partially follows the lag in awareness.

In Europe, the first pledges for vaginal microbicides came from the U.K. as late as 2002. Rebekah Webb, European Coordinator of the Global Campaign for Microbicides, believes that Europe will have a stronger role to play in the future in both the creation of a vaginal and a rectal microbicide. **“Advocates are becoming passionate about rectal products now, because they perceive that vaginal microbicides are going to happen,” she says.**

A second reason for the research lag may be the complexity of the science: this may have worked to deter some investigators from applying for funding. The profound vulnerability of the rectal mucosa to HIV infection, uncertainty about the extent of drug delivery needed for protection, and ongoing concerns about the possibility of microbicides inducing mucosal damage have created some concern. In this setting, however, the positive results from the macaque rectal-challenge studies provide hope that the development of a safe and effective rectal microbicide, is in fact a realistic goal.

34. The Pharmaco-Economics Working Group of the Rockefeller Foundation Microbicide Initiative. The economics of microbicide development: a case for investment. <http://www.microbicide.org/microbicideinfo/rockefeller.shtml>. Accessed April 3, 2006.

The final reason for lack of applications and funding commitments are the sociocultural taboos that condemn a scientific pursuit based on anal-sex behaviors as discussed above in section 3.3, *Sociocultural Challenges*. The head of a biotech firm and a former rectal microbicide investigator, who wishes to remain anonymous because of dependency on U.S. government grants, says the primary obstacles are the politicians: **“There are scientific reasons that give cover, but behind it all, [scientists] are thinking politics are the biggest inhibitor.”**

As for the commercial sector, despite repeated efforts to engage their interest, no large pharmaceutical company is involved in microbicide R&D—vaginal or rectal. Instead, the task of development has fallen to nonprofit research institutes, academic scientists, and small biotech companies, all of whom depend on government grants to move their leads forward. Major pharmaceutical companies remain reluctant to get involved because of concerns over scientific regulatory uncertainty and competing opportunities to invest in products that are potentially more profitable³⁵.

Pharmaceutical companies cannot be relied upon to develop the first microbicide because they perceive that it is not in their economic self-interest to do so. The Boston Consulting Group analyzed the profit potential of vaginal microbicides. They confirmed that, in the short term, the potential economic return to investors on a first-generation microbicide is not sufficient enough to attract private investment—i.e., the expected revenue would not cover the development cost³⁶.

The incentive structure of the private market fails to drive investment in microbicides although they are a potentially a classic public-health good and an innovation predicted to yield enormous returns to society in terms of productivity and health benefits. However, in the longer term, the Boston Consulting Group found that microbicides would create enough of a market to attract private investors in second- and third-generation products³⁷. This analysis has been applied to vaginal microbicides; one can infer that the same will likely hold true for rectal microbicides.

35. The Pharmaco-Economics Working Group of the Rockefeller Foundation Microbicide Initiative. The economics of microbicide development: a case for investment. <http://www.microbicide.org/microbicideinfo/rockefeller.shtml>. Accessed April 3, 2006.

36. Ibid.

37. Ibid.

6. Cost Modeling for Rectal Microbicide Development

6.1 Projections and Gaps

Findings show that current total rectal microbicide research expenditures are \$7.2 million. It is estimated that it will cost approximately \$69.5 million to develop one rectal microbicide candidate over a 10–15 year period. Conservatively, the field probably needs five candidates developed over this period. This will require \$350 million, or roughly \$35 million a year to realize a comprehensive rectal microbicide program. Annual spending needs to increase fivefold to ensure timely discovery and development of a rectal microbicide.

Unfortunately, in the absence of specific regulatory guidance from authorities such as the United States Food and Drug Administration (FDA) or the European Medicines Evaluation Agency (EMA), it is not clear what portfolio of studies might be needed to file a New Drug Application (NDA) or European Marketing Authorization (MA).

To complicate matters further, the microbicide pipeline is extremely heterogeneous. If it is assumed that some vaginal microbicides can be evaluated as rectal microbicides, then it is likely that significant amounts of product data can be cross-referenced from completed vaginal Investigational New Drug (IND) studies. Some compounds may have minimal preclinical/clinical data whereas others have quite substantial data already collected.

Clearly, the quantity and quality of available IND data will influence the costs associated with moving products through to licensure. Another consideration that will drive cost is the question of which group or groups will conduct the studies needed to file an IND/NDA or MA. In reality, rectal microbicide studies are likely to be conducted within federally funded networks. This may reduce cost but increases the complexity of creating a model and reduces the degree of precision in generating an overall cost. The field of rectal microbicide research is still in its infancy, and it is probable that any compound being developed will need significant resources to optimize formulation as well as acceptability studies to determine the success or failure of the formulation research.

6.2 Model Parameters

For the purpose of this analysis, the following assumptions are made:

- The product is a small molecule that is stable at room temperature and can be made at 1 kg scale for negligible cost.
- A commercial sponsor would provide the active pharmaceutical ingredient.
- The chemistry, stability, and preliminary pharmacokinetics profiles have been completed.
- An investigator brochure is available with some preclinical toxicology.

This table summarizes the studies that might be required in order to file an Investigational New Drug together with their approximate costs.

Phase of Development	Specific Study	Participants	Approx. Duration	Approx. Cost
Formulation development	Development of one rectal formulation	20	1.5 years	\$2.5 million
Preclinical animal toxicology	Species 1 toxicology	N/A	6 months	\$150,000
	Species 2 toxicology	N/A	6 months	\$150,000
Phase 1 safety studies (N=3)	Sexually abstinent population (HIV-neg.)	40	1.5 years	\$750,000
	Sexually active population (HIV-neg.)	40	1.5 years	\$750,000
	Sexually abstinent population (HIV-pos.)	40	2 years	\$1 million
	Penile acceptability	10	6 months	\$150,000
Phase 2 safety	Extended exposure	200	2 years	\$4 million
Phase 2B/3 efficacy	Efficacy study	4000	4 years	\$60 million
Total Time / Cost			10–15 years	\$69,450,000

7. Advocacy

7.1 Strategy

Rectal microbicide research is underfunded, impeding scientific inquiry, as documented in this report. We must advocate for more research, but questions remain as to the most effective strategy: should the rectal microbicide community of advocates, policy makers and scientists in the U.S. continue to ride the status quo, applying for piecemeal NIH grants and continuing in the shadow of vaginal microbicide research and development?

Or, should the rectal microbicide community take a more directed approach and openly advocate for its own specially funded programs? Will scientists then be more willing to come forward and ask for what they need? “Greater strides in the development of rectal microbicides can be achieved by targeted grant funding,” says Osmond D’Cruz, a researcher at Parker Hughes Institute. **“At present, this area is just a side project of vaginal microbicides.”**

Others, however, caution that community advocacy efforts on behalf of rectal microbicides may wake a sleeping giant and thus threaten to create a backlash against all microbicide funding. After all, the U.S. funds 74% of global vaginal microbicide public investment³⁸.

Advocates are looking to the governments of Europe and Canada to accelerate their support for rectal microbicide research and development. Although it is possible for advocates and scientists to overtly talk about the need for rectal products without fear of political reprisals in certain countries, many advocates aren’t convinced that setting up a separate program for rectal microbicides is realistic, even in progressive settings.

“We’ve made progress in focusing policy maker attention on the need for microbicides,” says Anna Forbes, coordinator of the Global Campaign’s efforts in North American and Europe. “When people think of new prevention technologies, they tend to think of vaccines first, and we’ve had to do a lot of awareness raising to expand that view,” she adds. “The next move would be to get these governments to recognize the need for parallel rectal and vaginal tracks within the broad topical microbicide funding. That would be a huge step forward.”

38. <http://www.avac.org/#2> Ibid.

Specifically, advocates would like to see the European Commission (EC) begin to support rectal microbicides explicitly within basic science and clinical trial budget lines so that scientists could apply for funding; however, the EC needs to rethink the way it supports microbicides altogether and focus on taking the product all the way through development, instead of only supporting various stages separately.

Whatever the strategy, the securing of public funding for every stage of rectal microbicide

R&D must be a priority. In the U.S., to strengthen and accelerate all microbicide R&D at NIH, USAID, and CDC, advocates must work toward the passage of the pending Microbicide Development Act. In addition to enhancing funding, the Act could help the federal government coordinate microbicide programs and weed out inefficiencies and unproductive duplication of effort.

Private sector investment will be easier to secure once proof of concept is achieved.

7.2 Recommendations

The public and private sectors, donors and investors, international agencies, policy makers, health providers, advocates, and activists all have critical roles to play in ensuring the development of a rectal microbicide for those who need them most—women and their partners, as well males who have sex with males—a large cross-section of the world's population.

The International Rectal Microbicide Working Group recommends the following urgent actions in order to discover a rectal microbicide within a time frame proportionate to the urgency of its need.

Donors must:

- Provide a minimum of \$350 million for targeted rectal microbicide research funding over the next 10 to 15 years, or an average of at least \$35 million per year to build a comprehensive rectal microbicide research program.
- Provide transparency and an increase in institutional commitment to explicitly fund rectal microbicide development.
- Commit to supporting phase 1 rectal safety studies for all vaginal microbicide candidates being evaluated in phase 2B/3 efficacy trials.

International nongovernmental organizations must:

- Form a body to specifically track rectal microbicide development, to ensure funding, and to coordinate research, regulatory approval, and advocacy.

Researchers must:

- Recruit new scientists to the field and promote rectal microbicide research within the scientific community.
- Initiate ideas for grant proposals to create demand for funding.

Advocates must:

- Reach out to affected communities to educate and to promote rectal microbicide trial preparedness.
- Promote global, national, and regional surveillance efforts to determine percentage of HIV infections attributed to AI in order to better assess the need for rectal microbicide development.
- Raise awareness, educate, and mobilize communities to foment a stronger, more visible demand for rectal microbicides and to elevate the profile of microbicides among policy makers.
- Ensure linkages to the broader microbicide movement and to advocates working on other prevention technologies.

Regulatory agencies like the U.S. FDA, the EMEA, and others must:

- Create support and development guidelines to accelerate the study and licensure of rectal microbicides.
- Request that all New Drug Applications for vaginal microbicides include at least one rectal safety study as part of the submission package.

The U.S. Congress must:

- Pass the Microbicide Development Act, and other countries should consider similar legislation.

8. Literature Relevant to Rectal Microbicide Research

- Abner SR, Guenther PC, Guarner J, et al. A human colorectal explant culture to evaluate topical microbicides for the prevention of HIV infection. *J Infect Dis*. 2005; 192(9): 1545–56.
- Balzarini J, Van Damme L. Intravaginal and intrarectal microbicides to prevent HIV infection. *CMAJ*. 2005; 172(4): 461–64.
- Baron S, Poast J, Nguyen D, Cloyd MW. Practical prevention of vaginal and rectal transmission of HIV by adapting the oral defense: use of commercial lubricants. *AIDS Res Hum Retroviruses*. July 20, 2001; 17(11): 997–1002.
- Beer BE, Doncel GF, Krebs FC, et al. In vitro preclinical testing of nonoxynol-9 as potential anti-human immunodeficiency virus microbicide: a retrospective analysis of results from five laboratories. *Antimicrob Agents Chemother*. 2006; 50(2): 713–23.
- Breban R, McGowan IM, Topaz C, Schwartz EJ, Anton P, Blower S. Modeling the potential impact of rectal microbicides to reduce HIV transmission in bathhouses. *Mathematical Biosciences & Engineering*. In press.
- Carballo-Diéguez A, Stein Z, Saez H, et al. Frequent use of lubricants for anal sex among men who have sex with men: the HIV prevention potential of a microbicide gel. *American Journal of Public Health*. 2000; 90(7): 1117–121.
- Carballo-Diéguez A. Rectal microbicide acceptability: results of a volume escalation trial [abstract]. Paper presented at: 3rd IAS Conference on HIV Pathogenesis and Treatment; July 24–27, 2005; Rio de Janeiro.
- Cohen J. Microbicide shuts the door on HIV. *Science*. 2004; 306(15): 387.
- Coplan PM, Mitchnick M, Rosenberg ZF. Regulatory challenges in microbicide development. *Science*. 2004; 304(5679): 1911–12.
- D’Cruz OJ, Uckun FM. Dawn of non-nucleoside inhibitor-based anti-HIV microbicides. *J Antimicrob Chemother*. 2006; 57(3): 411–23.
- D’Cruz OJ, Waurzyniak B, Uckun FM. Antiretroviral spermicide WHI-07 prevents vaginal and rectal transmission of feline immunodeficiency virus in domestic cats. *Antimicrobial Agents and Chemotherapy*. 2004; 48(4): 1082–88.
- Foss AM, Vickerman PT, Heise L, Watts, CH. Shifts in condom use following microbicide introduction: should we be concerned? *AIDS*. 2003; 17: 1227–37.
- Fuchs E, Wahl R, Macura K, Leal J, Grohskopf L, Hendrix CW. Imaging the distribution and clearance of a rectal microbicide gel and semen surrogate in the lower gastrointestinal tract [abstract]. Paper presented at: American Society for Clinical Pharmacology and Therapeutics Annual Meeting. March 2, 2005. Orlando, FL.
- Garg S, Tambwekar KR, Vermani K, et al. Development pharmaceuticals of microbicide formulations. Part II: formulation, evaluation, and challenges. *AIDS Patient Care STDS*. August 2003; 17(8): 377–99.
- Global Campaign for Microbicides. Rectal microbicides fact sheet, All about rectal microbicides. www.global-campaign.org/download.htm
- Gross M, Holte SE, Marmor M, Mwatha A, Koblin BA, Mayer KH. Anal sex among HIV-seronegative women at high risk of HIV exposure. *J Acquir Immune Defic Syndr*. 2001; 24(4): 393–98.
- Gross M, Buchbinder SP, Celum C, et al. Rectal microbicides for US gay men. Are clinical trials needed? Are they feasible? HIVNET Vaccine Preparedness Study Protocol Team. *Sexually Transmitted Diseases*. 1998; 25(6): 296–302.

- Gupta GR. How men's power over women fuels the HIV epidemic. *British Medical Journal*. 2002; 324: 183–84.
- Gurney KB, Elliott J, Nassanian H, et al. Binding and transfer of human immunodeficiency virus by DC-SIGN+ cells in human rectal mucosa. *J Virol*. 2005; 79(9): 5762–5773.
- Harrison P, Lamourelle G, Rowley R, Warren M. Tracking funding for microbicide research and development: estimates of annual investments 2000–2005, August 2005. <http://www.avac.org/#2>.
- Hickson F, Weaherburn P, Reid D, Stephens M. Out and about. Findings from the United Kingdom, gay men's sex survey 2002. Sigma Research. <http://www.sigmaresearch.org.uk/projects21.html>.
- Khan W, Fuchs E, Parsons T, et al. Rectal microbicide gel vehicle distribution in the lower gastrointestinal tract using SPECT/CT and direct endoscopic sampling [abstract]. Paper presented at: 12th National Conference on Retroviruses and Opportunistic Infections; February 22–25, 2005; Boston, MA.
- Keller MJ, Klotman ME, Herold BC. Development of topical microbicides for prevention of human immunodeficiency virus and herpes simplex virus. *Am J Reprod Immunol*. May 2003; 49(5): 279–284.
- Mantell JE, Myer L, Carballo-Diéguez A, et al. Microbicide acceptability research: current approaches and future directions. *Soc Sci Med*. January 2005; 60(2): 319–30.
- Patton DL, Sweeney YC, Cummings PK, et al. Safety and efficacy evaluations for vaginal and rectal use of BufferGel in the macaque model. *Sexually Transmitted Diseases*. 2004; 31(5): 290–96.
- Patton DL, Cosgrove Sweeney YT, Rabe LK, et al. Rectal applications of nonoxynol-9 cause tissue disruption in a monkey model. *Sexually Transmitted Diseases*. 2002; 29(10): 581–87.
- Patton DL, Cosgrove Sweeney YT, Rabe LK, et al. The pig-tailed macaque rectal model: microflora and chlamydial infection. *Sexually Transmitted Diseases*. 2001; 28(7): 363–6.
- Phillips DM, Taylor CL, Zacharopoulos VR, Maguire RA. Nonoxynol-9 causes rapid exfoliation of sheets of rectal epithelium. *Contraception*. 2000; 62: 149–54.
- Rader M, Marks G, Mansergh G, et al. Preferences about the characteristics of future HIV prevention products among men who have sex with men. *AIDS Educ Prev*. April, 2001; 13(2): 149–59.
- Roehr B. Microbicides 2000: fashioning new tools to deter HIV transmission. *Journal of International Association of Physicians in AIDS Care*. 2000; 157–69.
- Rosengarten M, Murphy D. Making connections, HIV vaccines and microbicides: a social research agenda report. National AIDS Trust. www.nat.org.uk/documents/MakingConnections.pdf.
- Shattock RJ, Moore JP. Inhibiting sexual transmission of HIV-1 infection. *Nat Rev Microbiol*. October 1, 2003; (1): 25–34.
- Stephenson J. Microbicides: Ideas flourish, money to follow? *JAMA*. 2000; 283(14): 1811–12.
- Tabet SR, Surawicz C, Horton, S, et al. Safety and toxicity of nonoxynol-9 gel as a rectal microbicide. *Sex Transm Dis*. 1999; 26(10): 564–71.
- Tsai C, Emau P, Jiang Y, et al. Cyanovirin-n gel as a topical microbicide prevents rectal transmission of SHIV89.6P in macaques. *AIDS Research Human Retroviruses*. 2003; 19(7): 535–41.
- What's flowing through the microbicide pipeline. Approaches range from complex to simple. *AIDS Alert*. May 2004; 19(5): 52–4.
- Zuckerman RA, Whittington WL, Celum CL, et al. Higher concentration of HIV RNA in rectal mucosa secretions than in blood and seminal plasma, among men who have sex with men, independent of antiretroviral therapy. *J Infect Dis*. July 1, 2004; 190(1): 156–61.

To join the Working Group or for more information on our activities, contact:

Jim Pickett
AIDS Foundation of Chicago
411 South Wells Suite 300
Chicago, IL USA 60607
+1-312-334-0920
JPickett@aidschicago.org
www.lifelube.org