



**Advancing New Ideas in AIDS Research:  
The Synthesis and Strategy (SAS) Conference on  
Rectal HIV Transmission**

**Hosted March 2009  
by amfAR, The Foundation for AIDS Research**

## Introduction

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More than 25 years since the HIV/AIDS epidemic was first identified, sexual transmission continues to be the leading cause of HIV infection worldwide. Of the more than 33 million people currently infected with HIV, around 90% of cases are believed to be due to sexual transmission. Of these, at least 80% of infections are estimated to have arisen from heterosexual contact.

However, it remains unknown how many of these sexual transmission can be attributed to anal intercourse. Among men who have sex with men (MSM) with no other known HIV risk factors, it is likely that the vast majority of infections occur as a result of unprotected anal intercourse. Even in MSM with other HIV risk factors (such as injection drug use), some proportion of HIV infections is likely due to anal intercourse. In addition, some unknown and largely overlooked fraction of heterosexual HIV transmission is due to anal intercourse. In fact, it is widely recognized that more women than men engage in receptive anal intercourse. Clearly, then, anal intercourse makes a significant contribution to the spread of HIV, although its extent has not been precisely measured.

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

In March 2009, amfAR convened these researchers to discuss their research. The meeting had several purposes: to review amfAR-funded research findings and discuss their implications; to place these findings in the context of the field at large; to identify remaining knowledge gaps; and to develop strategies on several fronts to promote this field of inquiry.

This summary of the meeting's proceedings documents the progress made in this area as well as the challenges of understanding and trying to mitigate rectal HIV transmission. It also aims to engage other stakeholders who did not attend the meeting, including researchers, policy makers, funding agencies and other interested parties.

For their participation in the meeting, amfAR is thankful to:

- Dr. Alex Carballo-Diequez of the New York State Psychiatric Institute and Columbia University in New York, New York;
- Dr. Charlene Dezzutti of the University of Pittsburgh, Magee-Womens Research Institute in Pittsburgh, Pennsylvania;
- Dr. Anna Foss of the London School of Hygiene and Tropical Medicine in London, United Kingdom;

- Edward Fuchs PA-C, representing Dr. Craig Hendrix of Johns Hopkins University in Baltimore, Maryland;
- Dr. Carolina Herrera of St. George's, University of London in London, United Kingdom;
- Dr. Marjan Javanbakht of the University of California, Los Angeles in Los Angeles, California;
- Dr. Hongjie Liu of Virginia Commonwealth University in Richmond, Virginia;
- Dr. Joanne Mantell of the New York State Psychiatric Institute and Columbia University in New York, New York;
- Jim Pickett of the AIDS Foundation of Chicago in Chicago, Illinois; and
- Dr. Roberto Speck of the University Hospital of Zurich in Zurich, Switzerland.
- Dr. Rowena Johnston, vice president, amfAR and director of research, convened and led the meeting.
- Dr. Jeffrey Laurence, senior scientific consultant for programs for amfAR, participated in the meeting as a discussant.

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## How common is anal intercourse and what factors are associated with it?

- Men who have sex with men and women engage in more behaviors associated with HIV infection compared to men whose sex partners are all women
- Women with male and female sex partners engage in behaviors that place them at elevated risk for HIV compared to women whose sex partners are all men
- There is a need for more counseling and education regarding anal intercourse at STD clinics

Although estimates of the relative risk vary, it is well known that anal intercourse is a far more efficient mode of HIV transmission than vaginal intercourse. Because of the stigmatized nature of the behavior, though, there is a dearth of reliable data concerning the extent to which anal intercourse is practiced among heterosexuals, and which factors are associated with it.



amfAR fellow **Dr. Marjan Javanbakht**, working from the University of California, Los Angeles, set about rectifying the lack of information by collaborating with clinics that treat clients with sexually transmitted infections (STIs) in the Los Angeles area. She collected data from new clients visiting 14 public STD clinics in Los Angeles County for over 18 months. Roughly two-thirds of the clients were male, the same proportion was under the age of 35, and African Americans constituted the largest racial/ethnic group (45 percent). Roughly 90 percent of all clients identified themselves as heterosexual.

Of the 24,614 men in the study, slightly more than 90 percent reported having sex with women, most of them exclusively, but around 5 percent reported sex with both men and women. Compared with men who only had sex with women, those who also had sex with men reported substantially higher rates of anal intercourse. Roughly three-fifths of these men had engaged in anal intercourse, compared to about 10 percent of men whose only sex partners were women. Men with female and male sex partners also more often engaged in behaviors that are associated with HIV infection, including exchanging money or drugs for sex, having anonymous sex, injecting drugs or having sex with an injecting drug user, or having sex with a partner known to be HIV positive. These men also had higher rates of several, STIs, including HIV, than men who had sex with women exclusively. For both groups of men, having an HIV positive sex partner was an important predictor of engaging in anal intercourse.

Almost 14,000 women took part in the study, with roughly one percent reporting sex exclusively with women, and about six percent reporting sex with both men and women. Women whose only sex partners were men reported lower rates of anal intercourse than women who had sex with both men and women. Women who reported bisexual behavior also reported higher levels of HIV risk behavior than women whose only sex partners were men, including exchanging money or drugs for sex, anonymous sex, incarceration, injecting drugs or having sex with an injection drug user, and having sex with a partner known to be HIV positive. Bisexual women reported higher rates of psychoactive substance use but had roughly equivalent rates of STIs. The greatest predictor of engaging in anal intercourse for women was exchanging money or drugs for sex.

For both men and women, rates of anal intercourse were higher in those who reported bisexual activity than in those who reported only heterosexual activity. On a worrisome note, those engaging in anal intercourse were also more likely to engage in other behaviors that put them at greater risk for HIV, such as exchanging money or drugs for sex, and having sex with a partner known to be HIV positive.

While the overall rate of anal intercourse found here among heterosexuals was not trivial, at around 10% in the past 90 days, the real rate may be even higher, due to participants' reticence about reporting their behaviors in these face-to-face interviews. Future studies investigating rates of anal intercourse and other HIV risk behaviors may generate more valid data if conducted anonymously. In the mean time, it is clear that STD clinic clients who report anal intercourse need increased rectal screening for STIs, as well as counseling regarding the risks of anal intercourse.

### **To what extent does anal intercourse contribute to the largely heterosexual HIV epidemic in Southern Africa?**

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- Knowledge concerning the relative risk of anal intercourse is low in this setting
- Self-report of anal intercourse is relatively uncommon, and condom use during anal intercourse is low
- Men and women report different motivations for participating in anal intercourse

More than in any other region of the world, the HIV epidemic ravaging southern Africa is spreading via heterosexual intercourse. The often unspoken assumption is that this heterosexual intercourse is vaginal, but formulating the most effective prevention interventions will rely critically on understanding the extent to which HIV may also be spreading via anal intercourse.

To shed more light on the situation, amfAR grantee **Dr. Joanne Mantell**, working from the New York State Psychiatric Institute and Columbia University, collaborated with colleagues at the HIV Center and the University of Cape Town School of Public Health and Family Medicine to design and conduct a culturally sensitive study of clients seeking treatment for STIs at three clinics in Cape Town, South Africa. The assessment was conducted to illuminate attitudes about anal intercourse, and the extent to which it is influenced by partners and events.



During three months in 2007, almost 2,000 individuals were interviewed. As in the Los Angeles study described above, roughly two-thirds of participants were male, but subjects in this study were on average younger, at about 27.5 years. The vast majority was black/African, and a very small number described themselves as colored (a term used in South Africa to describe people of mixed heritage), Indian or white.

There were troubling trends in knowledge of HIV as well as risk behaviors. Almost one in ten participants erroneously believed that anal intercourse poses a lower risk for HIV acquisition than vaginal intercourse. Despite the very high prevalence of HIV in South Africa, only one in seven participants reported using a condom regularly during vaginal intercourse with their main partner, and even those reporting other partners used condoms in only one-third of sexual encounters.

As for anal intercourse, a relatively small proportion of participants—about six percent—reported engaging in the behavior, and only 28 percent of those participants reported using condoms. Women and men both reported that the decision to engage in anal intercourse was initiated more often by the male partner. However, men believed women made that decision more often than women believed they did. Those who identified themselves as not-black were more likely to engage in anal intercourse, while those who identified anal intercourse as a high risk behavior were less likely to engage in it.

In a more detailed survey of a sample of those who reported anal intercourse, men and women expressed a range of experiences and motivations for engaging in the behavior. Men wanted to have anal intercourse to demonstrate dominance over their partner, while women wanted to please their partner. Men experienced orgasm more frequently than women during anal intercourse. Most women reported pain during anal intercourse, and most participants reported that they did not use condoms during anal intercourse.

It is interesting to note that while relatively few participants reported engaging in anal intercourse themselves, when asked whether they knew others who engaged in the

behavior, the kind of question commonly believed to reveal the respondents' own behaviors, fully one-third claimed to know others who have anal intercourse. Perhaps because HIV prevention messages in South Africa emphasize the risks associated with penile-vaginal intercourse, most participants underestimate the risk of anal intercourse in spreading HIV. Incorporating accurate information about anal intercourse into these messages has the potential to lower HIV transmission.

## What social network factors influence the risk of HIV in men who have sex with men?

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- A large proportion of MSM in this setting engage in commercial sex
- These MSM identified doctors and certain members of their social networks as particularly influential in perceived norms of sex behavior
- A new prevention intervention for MSM has been designed on the basis of these findings

Men who have sex with men are at particular risk for HIV acquisition because of their greater likelihood in engaging in anal intercourse. MSM in many regions of the world face additional obstacles including increased stigma and in some cases even legal sanctions against same-sex relationships. These challenges increase the difficulty of providing prevention and educational services to the very people at the greatest risk of HIV infection.



amfAR grantee **Dr. Hongjie Liu**, from Virginia Commonwealth University, delved into these issues in Shenzhen, China, a region bordering Hong Kong that is home to an estimated 60,000 MSM. Because MSM in Shenzhen are often not open about their sexuality, Dr. Liu first recruited 12 MSM into his study and asked each of these men to recruit three peers into the study. Each successive new wave of recruits in turn recruited more peers, until there were 350 participants in the study.

Using sophisticated statistical analyses, Dr. Liu estimates that approximately 9 percent of all MSM in Shenzhen are “money boys”, male sex workers who sell sex to MSM. Money boys exhibited a greater number of HIV risk behaviors, being more likely than other MSM to have had, in the previous six months, at least six anal sex partners and/or to have had sex with female sex workers. They were also more likely than other MSM to have had non-commercial sex with women.

The MSM in this study identified their HIV/STI doctors as trusted sources of information and support. Dr. Liu was interested in identifying other sources of tangible and emotional support for these men, with the ultimate goal of finding ways to implement innovative HIV prevention interventions. In most cases, the members of support networks named by the MSM in this study were male, highly educated, young, and single.

Interestingly, the impact of these relationships on the attitudes and behaviors of the MSM depended on whether they were sexual in nature. Unlike men whose strong social support came from social network members who were not sex partners, men whose social support came from their sex partners believed that high levels of condom use were the norm. Perceptions of peer norms generally strongly influence one's own behaviors to conform. Thus Dr. Liu sees the potential for an HIV prevention intervention that strengthens people's sense that condom use is the norm.

Dr. Liu is parlaying these initial findings into a subsequent amfAR-funded project intended to educate MSM both about behaviors that increase the risk of HIV infection and the ways to lower that risk, especially increased condom usage. He has designed a program that utilizes text messages sent by HIV/STI doctors to MSM participating in the study, testing whether the MSM find this form of intervention acceptable, and objectively assessing whether it reduces rates of HIV and other STIs.

### **Can we learn more about rectal HIV transmission in an animal model?**

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- The lack of a small animal model that closely mimics HIV infection in humans is a limiting factor in understanding transmission
- The BLT mouse currently appears to constitute the best model
- There is still no mouse that can be infected rectally with HIV under conditions similar to those during anal intercourse

Humans are almost unique in their ability to be infected with HIV. A wide variety of African and Asian monkeys and apes can be infected with a related virus called SIV, or simian immunodeficiency virus. This virus, however, differs from HIV sufficiently that scientists are unsure how many observations made with SIV can be generalized to HIV. The ability to infect small lab animals such as mice with HIV would not only provide an opportunity to learn more about the mechanisms underlying the heightened susceptibility of the rectum versus the vagina, but may also serve as a means to discover new ways to prevent rectal HIV transmission.



amfAR grantee **Dr. Roberto Speck**, working at the University Hospital of Zurich, set about genetically engineering mice that could be infected with HIV. Scientists have devised a number of ways that the immune system of a mouse can be modified to more closely resemble that of a human. When these humanized mice are injected with HIV intravenously, the virus replicates and there is a loss of immune cells similar to what happens in humans. The mice can also be treated with antiretroviral therapy, which reduces the ability of the virus to replicate, and at autopsy these mice manifest an immune system populated with human cells and cell surface markers.



Dr Speck did note some limitations in these mouse models, however. For example, when humans are infected with HIV there is a vigorous immune response aimed at destroying the virus, but in humanized mice the HIV-specific immune response is weak at best. In addition, there are fewer than expected human cells in the gastrointestinal tract of the humanized mouse, a finding that is especially pertinent to the topic of rectal HIV transmission. This is a significant drawback of these mice, because in humans the gut represents the region of the body most heavily populated with immune cells that are susceptible to HIV infection.

Not surprisingly, then, Dr. Speck found that there was no HIV infection in humanized mice that were inoculated with virus through the rectum. It appeared the virus was not able to cross the mucosal barrier lining the rectum and colon. In an attempt to enhance potential infection, Dr. Speck induced colitis, which increases inflammation of the tissues. In humans, inflammation enhances the ability of HIV to infect cells lying beneath the surface of tissues, but in humanized mice, this had little effect.

Of the various mouse models Dr. Speck looked into, he was most impressed with one known as BLT (denoting the reconstitution of the bone marrow/liver/thymus), in which human fetal liver cells are transplanted into immune deficient mice. This mouse was developed by Dr. Victor Garcia-Martinez, whose laboratory is currently receiving amfAR funding. Dr. Garcia-Martinez and his colleagues have reported that they were able to infect these mice rectally, although as Dr. Speck points out, this was achieved only after mechanical abrasion. The extent to which abrasion is necessary for HIV transmission during anal intercourse in humans is not known.

Ultimately, according to Dr. Speck, the optimal mouse model for rectal HIV transmission is still missing. The BLT mice are complicated and expensive to produce, which makes them poor candidates for study, but he remains hopeful that a better model can be found. The advantages of a good mouse model extend well beyond understanding rectal HIV

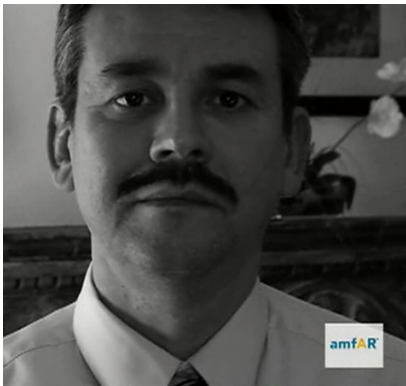
transmission – such a model could be used to test a variety of new treatment and prevention strategies, and to enhance our understanding of the barriers to a cure for HIV infection. The search continues.

## What happens in the human colon during anal intercourse?

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- Semen can cover a large area of the colon following ejaculation
- The effects of semen on these tissues is unknown
- Studies are needed to determine whether semen facilitates the passage of infected cells to underlying tissues

The fundamental differences between the colon and the vagina have important implications for understanding the events that occur during anal intercourse and how rectal HIV transmission can be prevented. The vagina is short and relatively closed with a thick lining of protective cells, while the colon is a long, open-ended canal with a thin and fragile layer of protective cells. Protecting the colon from HIV will require a thorough knowledge of how and where HIV crosses the thin protective barrier lining this organ.



amfAR grantee **Dr. Craig Hendrix**, working from Johns Hopkins University, is working closely with **Edward Fuchs** to understand the penetration of semen into the colon and the effects it has on the tissues it reaches. Older studies in rats and monkeys suggest that semen can disrupt the surface of the colon, increasing the likelihood that HIV and HIV-infected cells can reach and infect underlying cells more easily. Especially troubling are more recent studies that indicate that the widely used spermicide nonoxynol-9, commonly found in the

lubricant used on condoms and in other contraceptive products, profoundly disrupts the protective cell layer found in both the colon and the vagina. In fact, clinical studies have indicated that regular heavy use of nonoxynol-9 can significantly increase the risk of acquiring HIV.

The Hendrix laboratory has conducted several studies describing the distribution of semen within the colon after simulated ejaculation. They have demonstrated the potential for semen to travel at least 60cm up the colon, which means that a large surface area of those tissues is potentially exposed to semen each time anal intercourse occurs without a condom. While it is known that the movement - or even mere presence - of the penis within the rectum can cause tissue tears, what is less well understood is the extent to which semen

itself may denude the surface of the tissues lining the colon and thus render it more susceptible to infections, including HIV.

The research group is conducting a study among HIV-negative men to determine the effect of semen on rectal and colon tissues. Small biopsies of tissue will be collected, which will allow the researchers to determine if there are any microscopic indications of damage to the lining of the colon when it is exposed to semen, and whether the presence of semen results in increased permeability of the thin membrane lining the colon.

Ultimately, the group hopes to determine whether CD4+ T cells, commonly found in semen and potentially carrying HIV, are able to pass through the protective layer of the colon more easily after it has been exposed to semen. Clearly, this may represent an additional mechanism whereby HIV infection is facilitated following anal intercourse, and provides important clues as to what may be required in order to prevent infection, especially concerning the design of a rectal microbicide.

#### **What is a Microbicide?**

*A rectal microbicide, still under development, is a product that would be applied topically and would reduce the risk of acquiring HIV infection via anal intercourse.*

### **Can the gastrointestinal tract be protected from HIV infection?**

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- Preventing HIV transmission during anal intercourse may be even more challenging than for vaginal intercourse
- Regardless of the distance from the anus, colon and rectal tissues appear equally susceptible to HIV infection
- The ability of a microbicide to prevent rectal transmission, and whether this will be altered by semen, remains to be determined

According to a recent report, around 25 percent of MSM in the United States have had unprotected anal intercourse in the past 12 months. This points to a pressing need to protect this population from HIV, along with the even higher percentage of women who report engaging in anal intercourse without the use of a condom. Protecting the gastrointestinal tract presents even greater challenges than protecting the vagina, however, because of its large surface area, open-ended nature, thinner and more fragile tissues, and because the gastrointestinal tract is the largest immune organ in the body, providing a large number of immune cells for the virus to target.

In addition to studying the susceptibility of colon and rectum tissues, amfAR grantee **Dr. Charlene Dezzutti**, working at the University of Pittsburgh's Magee-Womens Research Institute, wondered whether the difficulties in protecting against HIV infection via this route might also be compounded by the presence of hemorrhoids. A significant portion of the population has hemorrhoids and doesn't necessarily know it. These regions of tissue are inflamed by swollen blood vessels, leading to the hypothesis that they may be an especially vulnerable site for HIV infection.



To assess the relative susceptibility to infection of tissue from various sites within the colon and to compare these to hemorrhoidal tissue, Dr. Dezzutti used pieces of tissue biopsied during colorectal surgery. Each piece of tissue was placed in an air-liquid setup designed to compare how easily each type of tissue could be infected. A roughly equal number of colon and hemorrhoid tissue pieces were exposed to HIV, and the extent to which productive HIV infection occurred was measured and compared.

Dr. Dezzutti found no significant difference between colon tissues located proximally versus distally from the anus in terms of the ease and productivity of HIV infection. Similarly, and somewhat unexpectedly, there was no significant difference between colon tissue versus that derived from hemorrhoids in terms of infection with HIV. This funding is in some ways so surprising that Dr. Dezzutti plans to delve further into this issue in her future studies.

In addition to determining the susceptibility of various colon areas, Dr. Dezzutti has begun to compare the safety and efficacy of various products that are being tested as microbicides. Using her air-liquid system of tissue pieces, her laboratory is measuring and comparing the ability of microbicides to prevent HIV infection. While the products appear to effectively lower the risk of HIV infection, there are other safety issues emerging that will require further investigation.

Dr. Dezzutti has also been interested in the effects of semen both on colon tissues and on the effectiveness of microbicides. On an encouraging note, she has not found any evidence that semen is toxic, and nor has she made any findings to suggest that semen enhances the ability of HIV to reproduce in colonic tissue. One of the major challenges facing the design of a microbicide for protection during anal intercourse, however, remains the relatively large and inaccessible nature of the tissue that needs to be protected.

## How do immune cells respond to anal intercourse?

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- HIV infection in cells of the colon sets off a cascade of immune responses and changes in gene expression
- These changes depend on the type of HIV that has infected a cell
- Several microbicide products currently being tested may also affect immune responses and gene expression

Because the gastrointestinal tract is the largest immune organ in the body, and because immune cells are the target of HIV infection, it is critically important to characterize the immune responses of the colon and rectum to the virus, to semen, and to any microbicide products that may be used rectally. Because of the various functions of the colon and rectum, the immune cells in these tissues tend to be in an activated state, thus rendering them more susceptible to HIV.



amfAR fellow **Dr. Carolina Herrera**, working at St George's University of London, set about conducting an in-depth analysis of cell types found in the colon and rectum, as well as changes in immune hormone secretion and gene expression that occur when these tissues are exposed to HIV and/or candidate microbicide products. While one type of immune cell, lymphocytes, have been intensively studied and are thought to be the main targets of HIV infection, she discovered that monocytes (another type of immune cell) also bear the two key receptors most often required for HIV infection. These cells often mature into macrophages, a type of cell that can harbor HIV infection much longer time than lymphocytes and are thought to be one of several barriers to eliminating HIV through immune system defenses or with antiretroviral therapy.

In collaboration with the laboratory of Dr. Tom Hope, Dr. Herrera also used sophisticated microscopy techniques to trace how HIV travels through colorectal tissues over time. In some cases, mucus within the gastrointestinal tract traps viral particles, but in other cases, within six hours, virus particles can penetrate as deep as 39 microns into tissue, putting them within reach of target cells. When the virus infects these target cells, different immune hormones (cytokines) can be activated, depending on which of the two main types of HIV has infected them.

These two types are defined by their use of either CCR5 or CXCR4 as a co-receptor for infection. To enter cells, HIV must first attach itself to a cell surface protein called CD4, and then, depending on which of the two types of HIV it is, the virus binds to another cell

surface protein, either CCR5 or CXCR4. Dr. Herrera found that viruses that use CCR5 versus CXCR4 differed in their ability to induce the release of several specific cytokines. In particular, infection by viruses that use the CXCR4 receptor to infect cells results in higher levels of several cytokines that have been implicated in modulating HIV spread than infection by CCR5-using viruses. Because cytokines play an everyday role in communicating with and modulating the behavior of other cells, understanding how their levels are increased may have important implications for understanding how HIV affects and ultimately subverts its environment.

In addition to the effects on cytokines, Dr. Herrera found that HIV strains that use CCR5 versus CXCR4 can differentially increase or decrease the extent to which a variety of cellular genes are expressed. This intriguing finding remains to be fully explored. More than one hundred genes are in question, and it is never easy to understand the relationship between any gene and a downstream outcome, such as a change in the functioning of a cell.

Finally, Dr. Herrera has discovered that several compounds that are undergoing testing as potential microbicides also affect gene expression as well as cytokine levels. The implications of these findings are as yet difficult to summarize, because of the innumerable ways in which each of these factors might interact to change infection outcomes. Dr. Herrera's research has revealed the complexity of the gastrointestinal environment in terms of its multitudinous responses to both HIV infection as well as to products being developed to prevent or mitigate it.

## **What characteristics should a rectal microbicide have?**

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- Lubricant is commonly used during anal intercourse
- Most lubricant users prefer a liquid consistency, water-based product dispensed by pump or pop-up lid
- By and large, males and females prefer similar characteristics in lubricants

While any rectal microbicide must necessarily include ingredients that prevent or reduce the likelihood of infection, no product will have any effect on the epidemic if it is not actually used. Key to ensuring a product's use is acceptability, defined as the willingness of the intended audience to use the product as described. Any number of factors can affect the acceptability of a rectal microbicide, including cost, ease of use, and perceived pleasantness of its texture, smell, or any other characteristics.

**Jim Pickett** of the AIDS Foundation of Chicago presented the findings of a survey conceived and conducted by him and other members of the International Rectal Microbicide Advocates. Their goal was to learn more about trends in usage and desires regarding characteristics in lubricants used during anal intercourse. Because such products potentially share many characteristics with rectal microbicides, it is important to know people's behaviors and attitudes towards them.



The survey was conducted online in six languages and ran for 29 weeks. It included almost 9,000 participants from more than 100 countries, of whom about 7 in 10 reported that they had engaged in anal intercourse in the past six months. About half of all respondents were under the age of 35, and the great majority were male. Although most responses came from North America, roughly 30 percent came from other regions.

Alarmingly, condom use was low for both insertive as well as receptive anal intercourse. Fewer than half of the respondents reported always using a condom, and more than a quarter reported never using one. The majority appear to use lubricant when engaging in anal intercourse, but approximately one quarter of respondents indicated both that on at least one occasion in the past six months they had not used one and were willing to provide reasons. The most commonly cited reason was the use of saliva, followed by the lack of availability of lubricant. Other reasons included a preference for dry sex, the use of a lubricated condom, or being “in a rush”.

Respondents were also asked to describe their preferences for various characteristics in lubricants. Only small percentages of respondents expressed an active preference for flavor, color or smell – the great majority either preferred the absence of those characteristics or had no preference. More respondents preferred a liquid consistency than any other, but a thick consistency was also popular. In terms of the type of dispenser, most preferred that it have either a pop-up lid or be dispensed by a pump. Most preferred that the lubricant be water-based, but silicone-based was also a popular choice.

In terms of behavior, it was edifying to learn that more than half of respondents found that lubricant use does not interrupt sex. Even those who thought it did by and large claimed that the interruption was not bothersome. Other substances were frequently added to lubricant, most often saliva, water or vaginal fluid. These latter findings might potentially have implications for the selection of a rectal microbicide solvent.

Finally, a look specifically at the female respondents yielded some disappointing results regarding condom use, the rates of which were even lower than in male respondents, with almost half of all women reporting never using condoms. Other results seemed consistent

with the survey group at large, however. When lubricant was not used, similar reasons were cited, and women shared similar trends in preferences regarding the desired characteristics of lubricants. Overall, the survey provided valuable insights into the kinds of characteristics a developer of rectal microbicides might want to take into account in designing an acceptable product that will actually be used.

## How can we get a rectal microbicide where it needs to go?

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- The design of a microbicide delivery device may greatly influence willingness to use the product
- User-friendliness is enhanced when the tip is soft and rounded and the product can be fully dispensed using one-handed operation
- A prototype device will soon be available that can be used in clinical trials of rectal microbicides

The importance of devising a safe and effective compound to prevent rectal HIV transmission cannot be understated. Experience has taught us that the compound must not only be very effective at killing HIV, it must also leave the delicate tissues to which it is exposed intact. There is, however, another equally important challenge. The product must also be packaged in such a way that at the very least, users are not discouraged from using it. In fact, ideally, users would actually be drawn to applying the microbicide.



Rising to the challenge, amfAR grantee **Dr. Alex Carballo-Diequez** and team, working from the New York State Psychiatric Institute and Columbia University, collected the impressions of participants in previous trials involving the rectal application of microbicide products. Participants provided a great deal of information not only on which aspects of the various applicators they disliked, but also on which features they thought would enhance the likelihood the product would be used.

Critiques of dispensers included the variability of the amount of gel that is dispensed, the need to shake the dispenser, the release of air along with product, and the inconvenience of the cap. Many of the complaints focused on the design of the inserted tip, especially the inconvenience of sharp edges or inflexibility. Users also provided information concerning the desired shape and size of the dispenser.



Drawing on these findings to design a more user-friendly dispenser, Dr. Carballo-Diequez first established that users would tolerate up to 35ml (a little more than 2 tablespoons) of gel product, and then set about designing a device that could carry and dispense this volume. Preliminary discussions with stakeholders and an advisory panel of experts led Dr. Carballo-Diequez to conclude that the applicator should accurately deliver a full dose in a single action using one-handed operation, that it should accurately deliver a full dose with minimal waste, and that it should be small, painless, easy to use without looking, and should have minimal cost.

Through a bidding process he identified a company willing and able to manufacture prototype devices. While certain aspects of the design have yet to be fully optimized, the semi-final prototype incorporates a tip similar to that of a widely available enema, can be operated with one hand, has ergonomic features for ease of use, and can deliver a precise dose up to 10ml.

Dr. Carballo-Diequez is in the process of obtaining further funding from NIH to follow up on these first steps, and will continue to refine the device. Ultimately, the hope is that this product will be utilized in all clinical trials in which a product is being tested for rectal use. This will allow researchers to eliminate one source of confounding when comparing the efficacy and acceptability of different products across different clinical trials. It will be interesting to see whether modifications can be made to the device so that it can also indicate adherence, an issue that has dogged clinical trials of microbicides to date.

## **What is the potential impact of a rectal microbicide?**

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- Reducing rectal transmission of HIV will have an unknown effect on levels of infection in communities, across countries, and internationally
- Knowing how microbicides of varying efficacies may change community levels of HIV could help guide product development
- Learning the potential number of infections averted will also play a valuable role in advocacy efforts

The advantages to an individual of the availability of a rectal microbicide are clear. What is not known, however, is the extent to which such a product might influence the course of an HIV epidemic at the community, national, or even international level. For an individual, only two outcomes are possible – the person is either infected with HIV or is not. In a large population of people, however, there are gradations of rates of infection, from low (less than one percent) to intermediate (one to five percent) or high (greater than 5 percent)

prevalence. In turn, the prevalence of HIV in a community can influence the likelihood of any particular individual becoming infected.

amfAR awardee **Dr. Anna Foss** was tasked with developing a model that would permit predictions regarding the impact of a rectal microbicide among MSM. The potential value of such modeling is wide-ranging. It can provide clues to how the product should be distributed, the possible advantages of targeting the distribution, the relative importance of different product characteristics, and how a rectal microbicide might compare to other prevention interventions in reducing individual and/or community infection rates.



Dr. Foss and her colleagues from the London School of Hygiene and Tropical Medicine will use detailed biological and behavioral data from MSM in Bangalore, India, and Lima, Peru. The study has several objectives: to anticipate trends in infections in these two populations; explore the transmission of HIV beyond MSM; estimate the potential of a rectal microbicide in reducing infections both in MSM as well as in their female partners; and predict the possible decline in condom use should a rectal microbicide become available.

Preliminary results have already described some of the complicating factors. MSM may primarily be the insertive or receptive partner, or may be versatile in their behavior. They may also be more or less infectious depending on the amount of virus in the body, which in turn can depend on the stage of infection and the presence of other STIs. For the sample of MSM in Bangalore who have responded compared to the sample of respondents in Lima, there seems to be a difference in terms of the number of sex partners they reported. The Bangalore sample were mostly high-risk MSM, many of whom reported selling sex, meaning that those who are predominantly receptive were over-sampled and that they reported very high numbers of partners. It is thought that there are many “hidden” MSM in Bangalore who are predominantly insertive and typically buy sex.

Ultimately, the model will provide data to shine more light on the potential advantages of this understudied intervention—in terms of specific target populations, and the number of infections that might be averted. This will arm us with research-based information to advocate for more research and policy support for the development of rectal microbicides.

## Next Steps

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In a report released in 2006, the International Rectal Microbicide Advocates stated that about \$7.2 million was spent on rectal microbicide research and development, about one-fifth of the estimated \$35 million required each year for the next 10 to 15 years. The report highlighted notable absences in funding streams – the European Commission, other countries, and multilaterals had not contributed directly to rectal microbicides in any way that could be traced, and commercial contributions were minimal. amfAR was the only philanthropic contributor.

Increased attention and resources could address several outstanding issues, which fall into four main categories:

- Developing a more complete understanding of behavioral issues.
  - Who engages in anal intercourse?
  - What contribution does anal intercourse make to the pandemic?
  - Which currently practiced behaviors might increase or mitigate HIV risk during anal intercourse?
  
- Improving understanding of how infection is established following anal intercourse.
  - What is the timing and sequence of infection events in the gastrointestinal tract?
  - Which time point and mechanism present the best opportunity for intervention?
  - Should infection route (vaginal vs. rectal) or HIV type (e.g., clades, receptor tropism) influence the design of a prevention intervention?
  
- Developing a plan to conduct clinical trials in the most efficient manner.
  - How can acceptability and adherence be optimally monitored?
  - How many products will need to be tested before a safe and efficacious rectal microbicide is found?
  - What will be the challenges in recruiting trial participants?
  
- Constructing a comprehensive policy and marketing plan to roll out once a product becomes available.
  - How can a microbicide be marketed to specific populations?
  - How will partial vs. full efficacy affect regulatory as well as marketing considerations?
  - How will legal and policy issues confound marketing and product availability in regions where anal intercourse is illegal and/or punishable by death?

Anal intercourse contributes a significant proportion of HIV/AIDS cases around the world. This pandemic cannot be effectively and comprehensively addressed until research on all routes of infection receives the funding, resources and attention required to reduce and ultimately eliminate new infections. This endeavor will depend on the combined efforts of researchers, advocates, political leaders and philanthropists to face this difficult but surmountable challenge.