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Sex Transm Inf 2008;84;413-417
doi:10.1136/sti.2008.031328

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Rectal microbicides: a new focus for HIV prevention

I McGowan

Rectal microbicides are needed for individuals who engage in unprotected anal intercourse (UAI). It is apparent that UAI occurs at a significant level in both men who have sex with men (MSM)¹⁻³ and heterosexual women.⁴⁻⁶ Unfortunately, the rectal compartment is highly vulnerable to HIV transmission. A single layer of columnar epithelium separates the lumen from the lamina propria. The lamina propria is populated with a broad range of target cells including macrophages, dendritic cells and highly activated CD4 T lymphocytes expressing the CCR5 and CXCR4 HIV-1 co-receptors.⁷ It is likely that the immunology of the rectal mucosa is at least partly responsible for the 10–20-fold increased risk of HIV transmission associated with anal^{8,9} compared with vaginal^{10,11} intercourse. The purpose of this article is to provide an overview of the challenges and complexities of rectal microbicide development.

The development of topical microbicides over the past decade has focused on the prevention of HIV transmission associated with vaginal intercourse. Approximately 16 products have been evaluated in phase 1/2 safety studies and seven microbicides have advanced to phase 2B/3 effectiveness studies.¹² Despite promising results in animal challenge experiments, the field still lacks proof of concept that a vaginal microbicide might reduce HIV transmission in humans. One possible explanation for the disappointing results from previous studies is that the first generation products (either surfactants (eg, nonoxynol-9) or fusion/entry inhibitors (eg, carraguard)) lacked the potency required to prevent HIV transmission. In some cases products may have had the potential to induce low-grade mucosal inflammation that might actually facilitate HIV acquisition.^{13,14} However, the microbicide research community remains optimistic that vaginal microbicides may have the potential to reduce HIV transmission. This optimism is focused on the recent development of the antiretroviral class of microbicides. These products are extremely

potent and appear to have a very good safety profile.¹⁵ They may finally provide the field with the proof of concept that microbicides have the potential to be a critical component in the HIV prevention armamentarium.

As the vaginal microbicide development pipeline has matured there has been increasing interest in the parallel development of rectal microbicides. The first priority has been to define the safety of vaginal microbicides when placed in the rectal compartment and the second priority has been to develop rectal-specific products that might have the potential to prevent HIV transmission associated with anal intercourse.

The rationale for conducting phase 1 safety assessment of vaginal microbicides in the rectal compartment is based on increasing recognition that women in the developed^{16,17} and developing¹⁸ world engage in anal intercourse.¹⁹ It is therefore assumed that vaginal microbicides, once available, will also be used rectally and it will be important to know whether a safe vaginal microbicide will also be safe in the rectal compartment. Guidelines for the preclinical and clinical evaluation of vaginal microbicides have been well defined^{20,21} and provide a foundation for rectal microbicide development. Preclinical evaluation of vaginal microbicide safety and efficacy in cell lines, tissue explants and animal models²²⁻²⁴ are conducted before initial phase 1 studies in humans. A typical phase 1 vaginal microbicide study might enroll 20–40 participants who would usually receive the candidate vaginal microbicide or placebo once or twice a day for 2 weeks.²⁵⁻²⁷

PRECLINICAL ASSESSMENT OF RECTAL MICROBICIDES

There are limited preclinical data evaluating microbicide safety in the rectal compartment and the majority of data focus on nonoxynol-9. The nonoxynol-9 data have provided important insights concerning the intestinal mucosal response to microbicide-induced injury. Phillips and Zacharopoulos²⁸ demonstrated that the rectal application of nonoxynol-9 in mice resulted in rapid exfoliation of intestinal epithelium within 10 minutes of product

exposure. The changes were transient and histological examination of the intestinal biopsy samples collected at 1 h post-nonoxynol-9 exposure appeared normal. The study also demonstrated a nonoxynol-9 dose-dependent increase in murine susceptibility to anorectal herpes simplex infection. Similar dramatic intestinal exfoliation has been documented in macaques rectally exposed to nonoxynol-9.²⁹ However, other candidate microbicides including Buffergel, Savvy and VivaGel appeared to be safe in the macaque rectal model.³⁰⁻³²

Despite concerns about the feasibility of developing a safe and effective rectal microbicide, two macaque studies evaluating cyanovirin and tenofovir have demonstrated significant protection from rectal challenge with SIV/SHIV. In 2003, Tsai *et al*³³ reported that adult male cynomolgus macaques that received a 2 ml dose of 1% or 2% cyanovirin gel 20 minutes before rectal exposure to SHIV89.6P were completely protected from infection. In contrast, all the animals receiving placebo or virus alone were infected. In the second study, Cranage *et al*³⁴ exposed Indian rhesus macaques to rectal challenge with SIV_{mac251/32H}. The macaques given tenofovir per rectum up to 2 h before virus challenge were protected from infection (n = 6) or had modified virus outcomes (n = 2), whereas all untreated macaques and three of four macaques given placebo gel were infected. One interesting observation from that study was that animals that were challenged with virus but remained uninfected developed T-cell immune responses to SIV. It is not certain if these responses would protect against future SIV challenge, but it illustrates the need for more collaborative research between microbicide and vaccine research groups. Microbicides might provide an important platform for mucosal vaccine delivery.

Preclinical evaluation of candidate microbicides for safety and efficacy has also been conducted using human intestinal explants.^{23,24} In these models, intestinal tissue explants are collected using endoscopy or are harvested from surgical resection specimens. The explants can be exposed to product and evaluated for toxicity using histological techniques and/or the MTT assay.²³ One limitation of intestinal explant safety assessment is that explants undergo profound architectural deterioration within 24 h of collection and so any meaningful histological assessment of toxicity can only be conducted within this time period. Intestinal explants have also been used

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to demonstrate the efficacy of antiretroviral microbicide candidates such as tenofovir, UC781 and TMC-120 (fig 1). In those studies intestinal tissue was exposed to the product *in vitro* and then virus was added to the model. Explants were then cultured for up to 2 weeks with repeated measurement of HIV-1 p24 in the culture supernatant.²⁴ Despite the limitations of the system, explants can provide important preliminary safety and efficacy data on a microbicide candidate before moving into more expensive animal models.

DESIGN OF PHASE 1 RECTAL SAFETY STUDIES

The first rectal safety studies evaluated nonoxynol-9. Tabet *et al*³⁵ described mild rectal histological changes in participants receiving up to 6 weeks of nonoxynol-9 or placebo gel. In contrast, marked epithelial exfoliation was seen after brief exposure to nonoxynol-9 in studies by Phillips and colleagues^{36 37} using rectal lavage and histology as endpoints. These contradictory results probably reflect the timing of sample collection. Epithelial reconstitution can occur within 1–8 h after exposure to nonoxynol-9.^{28 37} In the study by Tabet *et al*³⁵ samples were collected up to 12 h after nonoxynol-9 exposure but only 15 minutes in the studies by Phillips and colleagues.^{36 37} The implication of these early studies is that rectal safety should be assessed after acute (within 1 h) and chronic (at least 7 days) product exposure.

Histology and/or rectal lavage studies can be helpful in documenting severe microbicide-associated mucosal changes. However, there is increasing concern that repeated mucosal exposure to vaginal or rectal microbicides could induce subtle

immunological changes in the vaginal or rectal mucosa that might increase the risk of HIV transmission.¹⁴ Increased expression of mucosal inflammatory cytokines could lead to the recruitment of target cells to the local mucosa and these changes would probably not be detected using conventional histological techniques. As a consequence, it will be necessary to develop immunological biomarkers of microbicide safety. A first step in this process is the characterisation of the biological variability of putative mucosal safety biomarkers. Markers that demonstrate extreme variability will be unhelpful as safety biomarkers in microbicide studies. McGowan *et al*³⁸ recently published a study that investigated the biological variability of safety biomarkers in the intestinal mucosa. Intestinal biopsies were collected from 16 participants on three occasions over a 4-week period in the absence of any microbicide exposure. Tissue was collected at 15 and 30 cm from the anal margin and evaluated for biological variability of a broad range of parameters including histology, mucosal cytokine gene expression, rectal immunoglobulins and mucosal T-cell phenotype. The study demonstrated that tissue from both sites was essentially equivalent and that the most stable parameters included mucosal cytokine expression and T-cell phenotype. Both of these parameters could therefore have utility in the evaluation of potential microbicide toxicity within phase 1 rectal safety studies.

The first microbicide product to undergo phase 1 rectal safety assessment with this broader range of safety biomarkers is the non-nucleoside reverse transcriptase inhibitor UC781. In the study, which is being conducted at the

University of California at Los Angeles, participants are screened to exclude anorectal sexually transmitted infections and then baseline mucosal samples are collected. After a one-week period to allow mucosal healing, the participants receive a single dose of UC781. Within 30 minutes of microbicide exposure, the participants undergo mucosal assessment to assess acute mucosal responses to UC781.³⁹ After a second recovery period, seven daily doses of UC781 are administered followed by final mucosal assessment. The range of safety parameters evaluated in the study includes intestinal histology, rectal lavage for epithelial exfoliation, intestinal cytokine gene expression, mucosal mononuclear T-cell phenotype, rectal immunoglobulins and fecal calprotectin. A unique feature of the study is the evaluation of intestinal tissue explants, exposed to UC781 *in vivo*, to resist HIV infection *in vitro*.⁴⁰ This design feature allows for the preliminary assessment of microbicide efficacy as well as safety before potentially proceeding to much larger clinical effectiveness studies.

Future rectal safety studies are likely to optimise tissue collection and the choice of mucosal safety endpoints. Currently, phase 1 studies, such as the UC781 study described above, require the use of flexible sigmoidoscopy to collect intestinal tissue. If samples can be collected within 5 cm of the anal verge, then it would be possible to use anoscopy to collect the samples needed for safety assessment. This change in sampling strategy would allow for cheaper, less invasive study designs that could be conducted in sites without the need for gastroenterology services. Determining the differential utility of immunological safety endpoints may require including positive controls in the study design. One such study design would be to assign participants randomly to receive the test product, a placebo, or nonoxynol-9. Clearly, the participants would need to avoid UAI throughout the study. However, this approach would allow a rapid optimisation of the choice of mucosal safety parameters to be included in future phase 1 studies. There are no regulatory guidelines for the conduct of phase 1 rectal safety studies, but there appears to be a growing consensus that any vaginal microbicide moving into effectiveness studies requires a phase 1 rectal safety study.

Sexual lubricants are widely used by MSM⁴¹ and have even been considered as potential rectal microbicides because some products appear to have *in vitro* efficacy against HIV.⁴² Unfortunately, sexual

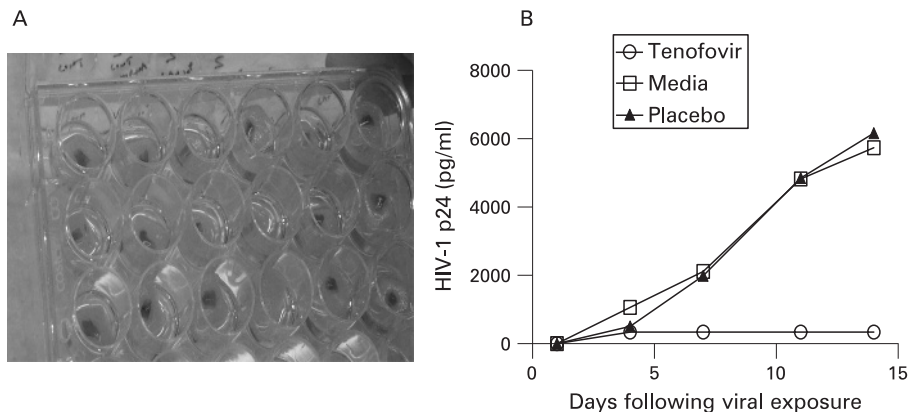


Figure 1 Colorectal explant model. (A) Intestinal explants are created from surgical resection specimens or endoscopic collection of intestinal biopsies.^{23 24} Explants are treated with the candidate microbicide and subsequently exposed to HIV-1. (B) HIV-1 p24 is measured in supernatant collected over a 2-week period to determine whether the microbicide has antiretroviral activity. In this experiment tenofovir is shown to be highly effective in preventing HIV infection.

lubricants may also have the capacity to induce rectal damage. This has been well documented for nonoxynol-9-containing lubricants, but may also be seen with other commercially available products that do not contain nonoxynol-9.⁴³ There is a clear need for wider evaluation of the safety profile of sexual lubricants as well as increased health education around this issue. Studies conducted in 2001–3 among MSM in San Francisco documented that 26–67% had used nonoxynol-9-containing products, often in the absence of condoms.^{44 45}

RECTAL-SPECIFIC MICROBICIDES

In order to move towards rectal microbicide effectiveness studies it will be necessary to conduct formative research to facilitate the development of rectal-specific microbicides. There seems little doubt that MSM would use such products. MSM commonly use sexual lubricants to facilitate anal intercourse,⁴¹ are interested in participating in rectal microbicide trials⁴⁶ and would use products if commercially available.^{45 47} Formulation is likely to be an important component of rectal microbicide development. Microbicides could be formulated as gels, suppositories, or douches.⁴⁸ To date, the majority of work has focused on a microbicide gel formulation. Carballo-Dieguez *et al*⁴⁹ recently conducted a rectal microbicide volume escalation study. Participants were asked to insert increasing volumes of a rectal microbicide surrogate (5–50 ml FemGlide; Trumbull, Connecticut, USA) on three consecutive days. When an unacceptable volume was encountered, the participants moved to evaluate the previously tolerated volume during anal intercourse. Using this approach, the investigators were able to demonstrate volume acceptability of up

to 35 ml in couples engaging in anal intercourse. One practical problem is that the majority of gel formulations are hyperosmolar (table 1). It is known that hyperosmolar products can induce epithelial damage,⁵⁰ clearly an undesirable characteristic for a rectal microbicide. Rectal douches might be another useful vehicle for microbicide delivery. In one US study,⁵¹ 53% of HIV-negative and 96% of HIV-positive men douched before rectal sex. This might not be safe if the douche is hyper or hypo-osmolar, but it does provide a potential mechanism to deliver microbicide products to the more proximal regions of the colon.

Ensuring that the right amount of product is present in the correct anatomical region for an adequate period of time lies at the heart of developing an effective microbicide. Imaging studies including magnetic resonance imaging have been used to define vaginal microbicide product distribution⁵² and similar studies have been initiated in the rectal compartment. Hendrix *et al*⁵³ used magnetic resonance imaging, single-photon emission tomography, computerised tomography and endoscopic pharmacokinetic sampling to characterise carefully the distribution of a semen simulant and microbicide candidate in participants undergoing simulated anal intercourse with an artificial phallus. The semen simulant was a 1 : 1 combination of hydroxyethylcellulose gel (K-Y Jelly) and saline designed to have the same viscosity of coagulated semen. K-Y Jelly was used as the microbicide surrogate. Over a 4-h period the semen surrogate introduced into the rectum showed significant retrograde movement into the descending colon. In 12% of single-photon emission tomography studies, the semen simulant migrated as far as the splenic flexure, approximately 60 cm from the anal verge. This observation has led to scepticism about the feasibility of delivering an adequate volume of microbicide to protect regions potentially at risk of HIV transmission. Such pessimism is probably premature and more recent studies have suggested less seminal migration.⁵⁴ Also, imaging studies are somewhat artificial and do not provide definitive proof as to where viral transmission occurs. In addition, gastroenterologists routinely prescribe topical products (gels, enemas, foams and suppositories) that are able to deliver 5' aminosalicic acid to the left side of the colon in patients with ulcerative colitis.^{55 56} Hopefully, pharmacological experience with the design and delivery of 5' aminosalicic acid products can be

used in the development of rectal microbicides.

The current generation of rectal safety studies has used vaginal applicators or syringes to deliver test product to the rectal compartment. Clearly, this approach is suboptimal. Vaginal applicators are not designed for rectal insertion and have not been found to be acceptable in rectal safety studies.⁵⁷ Carballo-Dieguez *et al*⁵⁸ have recently conducted a comprehensive interview-based qualitative assessment of the design requirements for a rectal applicator. This has led to the production of a prototype model that will hopefully be evaluated in future rectal safety studies.

Breban *et al*⁶⁰ have published a mathematical model that explores the impact of introducing rectal microbicides into a high-risk sexual zone for HIV transmission. The setting they chose was a bathhouse. Bathhouses are venues commonly found in Europe and north America where MSM congregate and often have sex with multiple partners.^{61 62} In this model, the authors varied microbicide effectiveness and frequency of use by the bathhouse clients. After making appropriate adjustments for condom use, it was possible to demonstrate that, with 30–50% use of a product that was 30% effective in reducing HIV transmission, a rectal microbicide could prevent HIV dissemination within the bathhouse environment.⁶⁰ Based on the macaque data, it should be possible to develop products with greater than 30% effectiveness, especially those products that incorporate antiretroviral compounds.

CONCLUSIONS

The past decade of vaginal microbicide development has generated significant experience in the logistical challenges associated with conducting microbicide effectiveness studies. Key issues are identifying populations with an adequate background annual rate of HIV seroincidence (usually considered to be approximately 3%), maintaining high adherence rates to study product and avoiding interruptions in administration of study product due to events such as unplanned pregnancy. These lessons can be directly transferred to the design of future rectal microbicide effectiveness studies. Identifying suitable populations for these studies will be critical. Fortunately, HIV vaccine and antiretroviral pre-exposure prophylaxis studies have already identified populations of MSM at risk of HIV acquisition secondary to UAI. It is important to include women who engage in

Table 1 Osmolarity of selected sexual lubricants and microbicides*

Product	Osmolarity (mOsm/kg)
Tap water	3
FemGlide	42
Semen	340
VivaGel	683
Gynol II (2% nonoxynol-9)	1182
Fleet enema	2127
WET Original/sterile water (1 : 1)	2215
K-Y Jelly	2424
Astroglide/sterile water (1 : 1)	3126
Tenofovir gel (1%)	3347
ID Glide lubricant	3429
PrePair lubricant	4026

*Adapted from Fuchs *et al* 2007.⁵⁹

anal intercourse in rectal microbicide development. However, it would be extremely challenging to identify women with the required seroincidence rates who have a history of UAI. A more practical problem will be to generate sufficient funds to conduct rectal microbicide effectiveness studies. A typical vaginal microbicide effectiveness study may enroll 4000–6000 participants with a budget of approximately US\$60–100 million. At present, the majority of rectal microbicide research has been funded by the US National Institutes of Health. Movement towards rectal microbicide effectiveness studies will require a broader portfolio of funders including the European Union and non-governmental agencies.

The International Rectal Microbicides Advocates (IRMA) group has lobbied extensively for increased funding support for rectal microbicide research. IRMA was founded in 2005 and already has over 600 members from 46 countries on six continents, a membership that reflects the global interest in rectal microbicide development. IRMA has recently published an overview of the rectal microbicide field, "Less silence, more science", which summarises the status of rectal microbicide research.⁶³

Future priorities in rectal microbicide research are to optimise the design of phase 1 safety studies, to develop rectal-specific formulations and to define the operational requirements needed to evaluate rectal-specific microbicides in effectiveness studies. These studies may not occur for another 5 years but the preparatory work needs to start now.

Funding: Funding was received from the United States National Institutes of Health to support the author's research programme in rectal microbicide development (5U19AI060614 and 5U01AI066734).

Competing interests: None.

Accepted 29 June 2008

Sex Transm Infect 2008;**84**:413–417.
doi:10.1136/sti.2008.031328

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Anal cancer prevention: how we are failing men who have sex with men

Ross D Cranston

Although receptive anal intercourse (RAI) is far from the sole preserve of men who have sex with men (MSM), the medical consequences of this sexual behaviour and resulting infection with human papillomavirus (HPV) are becoming increasingly apparent in this population. It is over 25 years since Daling *et al* reported on the increased rates of anal cancer in never married men with positive syphilis serology—their proxy for MSM.¹ These rates of up to 35:100 000 were similar to those of cervical cancer before the institution of routine cervical cytology screening, and much greater than the rate of 2:100 000 seen currently in the general population. Since then, MSM have borne the brunt of the HIV epidemic in Western society and, paradoxically, with the now widespread availability and impact of highly active antiretroviral therapy, we are now seeing rates of anal cancer in HIV positive MSM that are more than double those initially reported.² In contrast to other AIDS-associated malignancies, such as Kaposi's sarcoma, anal cancer rates continue to increase, a fact that clinicians, MSM and the HIV community at large seem, for the most part, unable or unwilling to address.

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THE ANAL CANAL

The anal canal is 3–4 cm long and is lined with stratified squamous non-keratinising epithelium. It extends from the anal verge to the anorectal transition zone where it meets the unicellular columnar epithelium of the rectum. For the most part, it is only the anal canal and not the rectum that becomes infected with HPV.

HPV

In the general population, anogenital HPV is the most common viral sexually transmitted infection. Supporting data from serological studies indicate that over 50% of sexually active North Americans have antibodies indicative of previous exposure to anogenital HPV.³ HPV is both highly infectious and easily transmitted as demonstrated in a recent study showing an almost 30% risk of HPV acquisition in women from their first sexual partnership.⁴ Despite this high prevalence, the natural history of HPV in women is for the most part benign. Most cervical HPV infections are asymptomatic with no clinical sequelae and are transient with the infection either “cleared” or becoming undetectable in over 90% of cases after 2 years.⁵

Since 2003, a test that allows real time diagnosis of HPV infection in women has been approved by the US Food and Drug Administration (FDA). This test uses

hybrid capture technology to differentiate 18 HPV types that infect the anogenital region into high risk or low risk groups.⁶ Risk phenotype refers to previously established associations of HPV type with cervical cancer. This also translates to the association of HPV type to cancer risk at other anogenital sites in women, such as the vagina, vulva and anal canal—just as it does in men for cancer of the penis and anal canal.

HPV INFECTION IN MEN

There is no FDA approved HPV test for men. This may be explained in part due to issues related to sampling technique and sampling site. For example, which site should be sampled when HPV infects glans, foreskin (if present) and shaft of the penis as well as the scrotum and perineum? HPV testing of the anal canal, in contrast to the penis, is a relatively straightforward procedure. Most anal HPV testing has been performed in a research context using PCR techniques that identify individual HPV types. Using this method it is apparent that MSM carry a high burden of HPV infection. The EXPLORE HPV sub-study of approximately 1200 HIV negative MSM in four North American cities showed that HPV is detectable in between 50 and 60% of men through a wide age range of 24–60 years, with rates of high risk HPV in the range of 20–30%.⁷ It is clear from the cervical literature that persistence of high risk HPV is a risk factor for progression to high-grade dysplasia and cancer; finding a high and persistent level of high risk HPV in the anal canal may be a critical contribution to unravelling why MSM are at such high risk of anal cancer. Furthermore, in HIV positive MSM, HPV infection is an almost ubiquitous finding