Rectal microbicide development

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Purpose of review
Individuals practicing unprotected receptive anal intercourse are at particularly high risk of HIV infection. Men who have sex with men (MSM) in the developed and developing world continue to have disproportionate and increasing levels of HIV infection. The past few years have seen important progress in demonstrating the efficacy of oral pre-exposure prophylaxis (PrEP), vaginal microbicides, and treatment as prevention, but there has also been significant progress in the development of rectal microbicides. The purpose of this review is to summarize the status of rectal microbicide research and to identify opportunities, challenges, and future directions in this important field of HIV prevention.

Recent findings
Recent phase 1 rectal microbicide studies have characterized the safety, acceptability, compartmental pharmacokinetics, and pharmacodynamics of both UC781 and tenofovir gels. The tenofovir gel formulation used in vaginal studies was not well tolerated in the rectum and newer rectal-specific formulations have been developed and evaluated in phase 1 studies.

Summary
Complex phase 1 studies have provided important data on candidate rectal microbicides. Tenofovir gel is poised to move into phase 2 evaluation and it is possible that a phase 2B/3 effectiveness study could be initiated in the next 2–3 years.

Keywords
HIV prevention, microbicides, rectal

INTRODUCTION
The field of vaginal microbicide development began as researchers in women’s health and contraception contemplated whether a virucidal gel could be developed that would have activity against sexually transmitted diseases including HIV-1 [1]. Nonoxynol-9 (N9) had demonstrated these properties in laboratory experiments [2] and was rapidly advanced into effectiveness studies. In addition it was also evaluated as a potential rectal microbicide [3,4]. Unfortunately, N9 was not found to be satisfactory as a vaginal microbicide [5] and was not further developed as a rectal microbicide. However, these early studies set the framework for how future microbicides were evaluated, and emphasized the importance of characterizing safety and acceptability in phase 1 studies. Following the early N9 studies, the field focused, without much success, on surfactant and polyanion vaginal microbicide candidates [6]. During this period there was no research on specific rectal microbicides. However it was clear that men who have sex with men (MSM) were interested in the concept of rectal microbicides and would be willing to enroll in clinical trials evaluating the safety and effectiveness of these products [7,8]. It was also apparent that sexual lubricant use, a possible model for rectal microbicide use, was common among MSM [9]. Other important early studies included exploring product formulation preferences in MSM [10,11] and assessment of the acceptability of different volumes of rectal gels [12]. The HIV Prevention Trials Network (HPTN) 056 study provided data on the variability of rectal mucosal safety parameters that might be measured in future rectal microbicide studies [13] and set the stage for the first rectal microbicide phase 1 studies evaluating antiretroviral products.
Pre-exposure prophylaxis

KEY POINTS

- Unprotected receptive anal intercourse (URAI) in both men and women continues to be a significant driver of the HIV-1 epidemic.
- Proof-of-concept studies in nonhuman primates suggest that an antiretroviral rectal microbicide might be effective in HIV prevention.
- Complex phase 1 rectal microbicide studies allow collection of key data including pharmacokinetics/pharmacodynamics early in product development and provide an efficient mechanism for product selection.
- An expanded safety phase 2 rectal microbicide domestic and international study of tenofovir 1% gel will start in 2012.

REVIEW

The purpose of this review is to summarize the status of rectal microbicide research and to identify opportunities, challenges, and future directions in this important field of HIV prevention.

The biology of HIV infection associated with anal sex

Unprotected receptive anal intercourse (URAI) between HIV-serodiscordant partners is an extremely efficient way of transmitting HIV infection, and this risk is likely to be significantly increased in situations in which one or both of the partners have STIs such as rectal gonorrhea or herpes simplex infection. In addition, the extremely high viral loads seen during primary HIV infection will further exacerbate the risk of HIV transmission [14]. As a consequence, it is estimated that the risk of HIV associated with heterosexual URAI is 1.7% per act, whereas it is only 0.08% during unprotected vaginal intercourse [15]. This situation is partially due to the rectal environment. A single layer of columnar epithelium and a preponderance of activated CD4+ T cells expressing the CCR5 co-receptor [16] provide a uniquely vulnerable environment for HIV acquisition.

Epidemiology of HIV infection associated with unprotected receptive anal intercourse

Recent epidemiological studies have confirmed that URAI is a common practice among MSM in the Americas and Europe [17,18], but have also clearly identified at-risk MSM in the developing world [19] as well as women across the globe [20,21]. Unfortunately this prevalence of URAI also appears, at least in MSM, to be associated with high prevalence and incidence of HIV infection as well as other STIs. These observations emphasize the need to develop new prevention strategies, including rectal microbicides, in populations at risk of HIV infection through URAI who are unable or unwilling to use a condom.

The rectal microbicide pipeline

In theory, the rectal microbicide pipeline could be derived from the vaginal microbicide pipeline. However, the majority of rectal microbicide candidates have only been evaluated in preclinical studies and the only products to have been evaluated in clinical studies are the non-nucleoside reverse transcriptase inhibitor (NNRTI) UC781 [22**] and the nucleotide inhibitor tenofovir [23**]. The first generation of antiretroviral rectal microbicides only contained one active pharmaceutical ingredient (API), but there is increasing interest in evaluating combination products with two, three, or even four APIs [24,25*]. The majority of research has been conducted on nucleotides (tenofovir) or NNRTIs [UC781 and dapivirine (TMC120)]. However, recent studies have also evaluated L’644, a fusion inhibitor, which demonstrated postexposure activity in both colorectal and cervical explants, as well as activity against reverse transcriptase resistant isolates [26*]. Protease inhibitors are also being considered as candidate rectal microbicides [27*,28*]. Potential rectal microbicide candidates are listed in Table 1, together with their current stage of development.

Formulation considerations

Qualitative and clinical studies have suggested that acceptable rectal microbicide formulations could include gels, suppositories, or douches [10,11]. Gels were considered more acceptable than suppositories [11] and a volume escalation of a placebo gel demonstrated that up to 35 ml of gel with the physical properties of Femglide (transparent and odorless) was acceptable to the majority of participants [12]. The first rectal microbicide clinical trials evaluated the rectal safety of gels that were being developed as vaginal microbicides. These products had a number of characteristics that were suboptimal for a rectal microbicide. They were extremely hyperosmolar and had an acid pH. Hyperosmolar products are known to induce mucosal damage [38,39**] and may be associated with increased risk of acquiring STIs [40*]. Rectal use of the vaginal formulation of tenofovir 1% gel was associated with gastrointestinal adverse events including diarrhea, bloating, urgency, and abdominal pain [23**]. Consequently, efforts are under way to
develop rectal-specific microbicide formulations that are iso-osmolar with a neutral pH \[41,42\]. Initial preclinical evaluation of a reduced glycerin formulation of tenofovir (RG-TFV) 1% gel suggested that the new gel induced less mucosal damage than the original formulation but was equally effective in explant models of HIV infection \[31\]. The RG-TFV 1% also appeared to have improved in-vivo safety and acceptability in phase 1 studies \[37\].

**Preclinical evaluation of rectal microbicides**

The preclinical and clinical evaluation of candidate microbicides encompasses steps that are required by regulatory authorities such as the US Food and Drug Administration (FDA) as well as guidelines developed by groups working within the field of microbicide development \[43,44\]. The role of preclinical evaluation is to characterize product safety, stability, and effectiveness, and to determine whether products should be advanced into phase 1 clinical trials. Buckheit and Buckheit \[45\] have recently published updated recommendations for the preclinical development of both rectal and vaginal microbicide candidates that places greater emphasis on evaluating products in the context of relevant biological fluids and in human tissue systems. In-vitro colorectal explant models play an important role in evaluating the safety and efficacy of rectal microbicides \[29,30\] and have been evaluated for use in multicenter studies \[46\]. Nonhuman primate (NHP) models have also been used to evaluate product safety and efficacy \[32,47\]. Cyanovirin, tenofovir, and the NNRTI MIV-150 have all protected against rectal challenge with simian immunodeficiency virus (SIV) and SHIV \[33,34,35\]. In addition, a zinc acetate carrageenan gel has been shown to protect against rectal challenge with herpes simplex virus (HSV)-2 \[48\]. Humanized murine models of HIV infection \[49\] have been used to evaluate vaginal microbicides \[50\] and are also being used to evaluate rectal microbicides (Garcia-Martinez JW, personal communication). One note of caution has been raised about the suitability of

<table>
<thead>
<tr>
<th>Table 1. Products that have been evaluated as candidate rectal microbicides*</th>
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</thead>
<tbody>
<tr>
<td><strong>Product</strong></td>
</tr>
<tr>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>Cellulose acetate; PRO2000; SP7013; Vena Gel; UC781</td>
</tr>
<tr>
<td>PRO2000; dextrin sulfate</td>
</tr>
<tr>
<td>Tenofovir</td>
</tr>
<tr>
<td>C34; T20; T1249; L’644</td>
</tr>
<tr>
<td>Tenofovir; emtricitabine; UC781; TMC120</td>
</tr>
<tr>
<td>Saquinavir</td>
</tr>
<tr>
<td>Maraviroc; Griffithsin; MIV-150; carrageenan; zinc acetate</td>
</tr>
<tr>
<td>BufferGel; nonoxynol-9; C31G; octylglycerol; polystyrene sulfate; cellulose sulfate; SP7013; Carraguard; UC781</td>
</tr>
<tr>
<td>Cyanovirin gel</td>
</tr>
<tr>
<td>Tenofovir gel</td>
</tr>
<tr>
<td>MIV-150 gel</td>
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<tr>
<td>UC781 gel</td>
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<tr>
<td>Tenofovir 1% gel [VF]</td>
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<td>Tenofovir 1% gel [RGF]</td>
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<td>Tenofovir 1% gel [RGF]</td>
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<td>Tenofovir 1% gel [VF, RGF, RF]</td>
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<td>Tenofovir 1% gel [VF, RGF, RF]</td>
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<td>Tenofovir 1% gel [RGF]</td>
</tr>
</tbody>
</table>

NHP, nonhuman primate; RF, rectal-specific formulation; RGF, reduced glycerin formulation; VF, vaginal formulation.

*Products that have been studied in colorectal explant systems, animal models, or humans.
Pre-exposure prophylaxis

tenofovir as a rectal microbicide. Garcia-Lerma et al. [51**] recently reported results of a NHP study in which the animals received oral GS7340, a tenofovir prodrug, before rectal challenge with SHIVSF162P3. Despite achieving high systemic and mucosal levels of tenofovir, GS7340 did not afford protection from infection with SHIVSF162P3. One possible explanation was that endogenous dATP in rectal lymphocytes competed with, and reduced the antiviral efficacy of, the nucleotide reverse transcriptase inhibitor [51**]. It remains to be seen whether the higher concentrations of tenofovir achieved through topical administration with a rectal microbicide will be sufficient to circumvent this phenomenon.

Clinical development of rectal microbicides

As with vaginal microbicides, the purpose of phase 1 rectal microbicide studies is to generate preliminary data on the safety, acceptability, pharmacokinetic, and pharmacodynamic activity of the candidate microbicide. However, in contrast to vaginal microbicide development, where there have been multiple phase 1 studies of surfactant, polyanion, and antiretroviral candidates, there have only been four phase 1 rectal microbicide studies conducted to date: HIV Network for HIV Prevention Trials [HIVNET-008 (N9 gel)] [3], Rectal Microbicide Program (RMP-01; UC781 0.1 and 0.25% gel) [22**,36], RMP-02/Microbicide Trials Network (MTN)-006 (oral tenofovir and tenofovir 1% gel (original formulation) [23**]), and MTN-007 (N9 gel, hydroxyethyl cellulose (HEC) placebo gel [52], and tenofovir 1% gel (reduced glycerin formulation) [37]. These studies are discussed in more detail below.

HIVNET-008

The HIVNET-008 study was designed to assess the safety of N9 when applied one to four times daily to the rectum and penis. Twenty-five HIV-negative and 10 HIV-positive, monogamous gay male couples were enrolled in Seattle, WA. Each partner was exclusively insertive or receptive while using N9 gel and served as his own control during placebo gel use compared with during N9 gel use. The study was conducted over 7 weeks. During the first week participants used the placebo gel. Thereafter, couples used the N9 gel and the frequency of use was escalated from once daily to two applicators twice daily in the final week of the study. Despite the frequency of administration, adverse events were generally mild and transient. No rectal ulcers were detected; superficial rectal erosions were noted in two HIV-negative participants. Abnormal or slightly abnormal histologic abnormalities of rectal biopsies were detected in 31 (89%) of receptive participants after N9 gel use compared with 24 (69%) of participants after 1 week of placebo gel use. Excluding participants who felt no need for an HIV prevention method, 58% said they would use N9 if approved for rectal use; 69% of receptive users reported rectal fullness and related side effects after insertion of the gel, and 68% reported applicator-related discomfort; 59% of insertive participants found the gel too sticky [4].

RMP-01

Thirty-six HIV-1-seronegative, sexually abstinent men and women were enrolled in Los Angeles, CA and randomized into a double-blinded, placebo-controlled trial comparing UC781 gel at two concentrations (0.10%, 0.25%) with a placebo gel (1:1:1). Safety and acceptability were primary study endpoints. Changes in colorectal mucosal safety biomarkers and UC781 plasma drug levels were secondary endpoints. Ex-vivo explant infectibility with HIV-1 was an ancillary study endpoint. Samples were collected at enrollment, after a single rectal dose of study product, and after seven daily doses. The majority of adverse events were mild. Product acceptability was high, including likelihood of future use. No changes in mucosal safety biomarkers were identified. Plasma levels of UC781 were not detected. Ex-vivo infection of biopsies using two titers of HIV-1p24 showed marked suppression of HIV-1 p24 in tissues exposed in vivo to 0.25% UC781 (Fig. 1). Ideally the product would have been advanced into phase 2 development but the Investigational New Drug (IND) sponsor (CONRAD; http://www.conrad.org/) terminated the UC781 development program.

RMP-02/MTN-006

Eighteen participants were enrolled from Pittsburgh, PA and Los Angeles, CA. All participants received a single 300 mg dose of oral tenofovir and were then randomized 2:1 to receive a single then seven daily doses of tenofovir 1% gel or the HEC placebo gel. Safety endpoints included clinical adverse events and mucosal safety biomarkers. Participants were assessed at enrollment, after single doses of oral tenofovir and study gel, and after seven daily doses of study gel. Blood and colonic biopsies were collected for pharmacokinetic analysis and ex-vivo challenge with HIV-1. No serious adverse events were reported. However, adverse events, especially gastrointestinal adverse events, were significantly increased with 7-day use of the tenofovir 1% gel. Only 25% of participants liked the tenofovir gel;
however, likelihood of use, if the product was somewhat protective, was high (75%). No significant mucosal injury was detected. Tissue TFV diphosphate (TFV-DP) $C_{\text{max}}$ 30 min after single rectal exposure was 112 times greater than single oral exposure, with tissue 7-day exposure five times greater than single rectal exposure. Single and 7-day exposure to rectal TFV was associated with significant suppression of explant infection. Increased adverse events suggested that the vaginal formulation of tenofovir 1% gel used rectally was not entirely well tolerated or fully acceptable, suggesting a need for improved formulations.

**MTN-007**

The study was designed to assess the safety, adherence, and acceptability of the reduced glycerin formulation of tenofovir 1% gel (RG-TFV 1% gel). An N9 arm was included as a positive control for the mucosal safety biomarker assays. Sixty-five participants (45 men and 20 women) aged 18–61 were recruited from Pittsburgh, PA; Boston, MA; and Birmingham, AL. Participants were randomized 1:1:1:1 to receive the RG-TFV 1% gel, a HEC placebo gel, an N9 gel, or to a no-treatment arm. Participants were evaluated at baseline, after a single dose, and after seven daily doses of study product. Systemic and mucosal safety, acceptability, and adherence were evaluated at all three visits. Comprehensive mucosal safety biomarker evaluation included histology, fecal calprotectin, epithelial sloughing, cytokine expression (mRNA and protein), microarray analysis, flow cytometry of mucosal T-cell phenotype, and rectal microflora. Acceptability and adherence were determined by computer-administered questionnaires and interactive telephone response, respectively. Product adherence was at least 94%. Adverse events were

![Graph of cumulative P-24 at day 14](image)

**FIGURE 1.** Suppression of HIV replication of HIV-1 in colorectal explants following in-vivo application of UC781 gel or placebo gel. UC781 gel (0.10 or 0.25%) or placebo gel was applied rectally to a total of 36 participants (12 per study arm). After approximately 30 min colorectal tissue samples were collected at 10 or 30 cm from the anal margin. Colorectal explants were challenged with HIV-1BaL and explant supernatant collected every 3–4 days out to day 14. Cumulative day 14 HIV-1 p24 at visit 2 (enrollment) and visit 3 (single dose exposure) are presented here. Significant inhibition of viral replication was seen with the 0.25% gel concentration but not the 0.10% gel. Adapted from Anton et al. [22**].
generally mild or moderate. There was no significant difference in the prevalence of adverse events across the four arms of the study. Likelihood of future product use (acceptability) was 86.7% (RG-TFV 1% gel), 93.3% (HEC gel), and 62.5% (N9 gel). Fecal calprotectin and epithelial sloughing did not alter during the study. In contrast, significant changes were seen in mucosal cytokine/chemokine expression, T-cell phenotype, and rectal microflora, which were mostly confined to the N9 gel arm. Overall the study suggested that the reduced glycerin formulation of 1% tenofovir was safe and well tolerated and should be advanced to phase 2 rectal microbicide development.

A number of additional rectal microbicide studies are ongoing or will start enrollment in 2012. The National Institutes of Health (NIH) in the USA has funded a project entitled ‘Microbicide safety and acceptability in young men’ that attempts to evaluate rectal microbicide safety, adherence, and acceptability in young ethnic minority MSM in Boston, MA; Pittsburgh, PA; and San Juan, PR. The study design has two stages: a clinical and behavioral evaluation (stage 1A) with an acceptability and adherence trial (stage 1B), followed by a phase 1 randomized, double-blinded, multisite, placebo-controlled safety trial (stage 2). The first 120 eligible participants who complete stage 1A and report unprotected RAI in the previous 3 months will continue on to stage 1B. During stage 1B, participants will be given condoms and a placebo gel to use during receptive anal intercourse. Over a 3-month period they will report the frequency of product use and be interviewed about the acceptability of the product. The first 24 participants who complete stage 1B will be eligible to participate in stage 2 where they will be randomized to receive an actual microbicide (RG-TFV 1% gel) or matched placebo. It is hoped that data from this study will provide unique insights into the acceptability, safety, and adherence of rectal microbicides in young MSM.

The Combination HIV Antiretroviral Rectal Microbicide or CHARM Program will develop and evaluate a combination antiretroviral rectal-specific product. Tenofovir and maraviroc are the two lead compounds and the ultimate goal is to develop a tenofovir/maraviroc combination product. Two phase 1 studies, CHARM-01 and CHARM-02, will start in 2012. CHARM-01 will assess the safety, acceptability, and pharmacokinetic/pharmacodynamic profile of three tenofovir gel formulations; the original tenofovir 1% gel used in vaginal microbicide studies, the RG-TFV 1% gel, and a rectal-specific TFV gel (Table 2). CHARM-02 will evaluate the safety, pharmacokinetics, and distribution of the same three gels. Similar techniques have been used to characterize the distribution of semen surrogates and microbicide products in the presence and absence of simulated receptive anal intercourse [53,54]. Collectively, these studies will provide unique data on the influence of formulation characteristics, including osmolality, and product safety, pharmacokinetics/pharmacodynamics, and distribution. The final rectal microbicide study to start in 2012 will be MTN-017, a phase 2 expanded safety study of the RG-TFV 1% gel used in MTN-007. The study will enroll 186 MSM and transgendered

### Table 2. Characteristics of the currently available formulations of tenofovir 1% gel

<table>
<thead>
<tr>
<th>Chemical name</th>
<th>Original VF% w/w</th>
<th>RGF% w/w (used in MTN-007)</th>
<th>RGF% w/w (to be used in CHARM-01)</th>
<th>RF% w/w</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycerin</td>
<td>20.00</td>
<td>5.00</td>
<td>5.00</td>
<td>2.50</td>
</tr>
<tr>
<td>Hydroxyethyl cellulose</td>
<td>2.50</td>
<td>2.75</td>
<td>3.00</td>
<td>0</td>
</tr>
<tr>
<td>Carbopol 974</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.50</td>
</tr>
<tr>
<td>Sodium carboxymethylcellulose</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>Methylparaben</td>
<td>0.18</td>
<td>0.22</td>
<td>0.22</td>
<td>0.18</td>
</tr>
<tr>
<td>Propylparaben</td>
<td>0.02</td>
<td>0.024</td>
<td>0.05</td>
<td>0.02</td>
</tr>
<tr>
<td>Purified water</td>
<td>75.23</td>
<td>89.936</td>
<td>89.66</td>
<td>94.78</td>
</tr>
<tr>
<td>Disodium edetate (EDTA)</td>
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<td>0.05</td>
<td>0.01</td>
</tr>
<tr>
<td>Citric acid</td>
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<td>1.00</td>
<td>1.00</td>
<td>0</td>
</tr>
<tr>
<td>PMPA</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
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<tr>
<td>Sodium hydroxide</td>
<td>As needed</td>
<td>As needed</td>
<td>As needed</td>
<td>As needed</td>
</tr>
<tr>
<td>Diluted hydrochloric acid</td>
<td>As needed</td>
<td>As needed</td>
<td>As needed</td>
<td>As needed</td>
</tr>
<tr>
<td>pH</td>
<td>4.5</td>
<td>4.6</td>
<td>4.5</td>
<td>7</td>
</tr>
<tr>
<td>Osmolality (mOsmol/kg)</td>
<td>3111</td>
<td>836</td>
<td>846</td>
<td>479</td>
</tr>
</tbody>
</table>

RF, rectal-specific formulation; RGF, reduced glycerin formulation; VF, vaginal formulation.
women in the USA, Peru, Thailand, and South Africa. Each participant will receive 8 weeks exposure to oral Truvada, daily RG-TFV 1% gel, and use of RG-TFV 1% gel before and after sex (analogous to the regimen used in the CAPRISA 004 vaginal microbicide study [55]). Apart from general safety and acceptability, a subset of approximately 30 participants in the USA and Thailand will undergo more intensive mucosal sampling for evaluation of mucosal safety biomarkers and pharmacokinetics/pharmacodynamics. If successful, it is hoped that MTN-017 will set the stage for a phase 2B/3 rectal microbicide trial in 2015.

Drug development does not occur in a vacuum and from the outset advocacy groups have played a critical role in rectal microbicide development. The International Rectal Microbicide Advocates group (IRMA; http://www.rectalmicrobicides.org/) has focused attention on rectal microbicide development including conducting community/internet-based studies on lubricant usage [56]. IRMA has also led efforts to define the need for rectal microbicides for men and women at risk of HIV infection associated with URAI in sub-Saharan Africa (http://www.rectalmicrobicides.org/ProjectARMreport2012.pdf).

CONCLUSION

Given the ongoing epidemic of HIV infection associated with URAI it is clear that there remains an urgent need to develop well tolerated and effective methods of HIV prevention that the target population will be willing to use. Although the iPrEx (Pre-Exposure Prophylaxis Initiative) study demonstrated the efficacy of pre-exposure prophylaxis (PrEP) in MSM [57], overall adherence in the participants receiving Truvada was estimated to be only about 50%. This suggests that a rectal microbicide, possibly used in addition to oral PrEP, might increase overall protection from HIV infection. The design of phase 1 rectal microbicide studies has evolved such that key data on safety, acceptability, and pharmacokinetics/pharmacodynamics can be generated at an early stage of product development. The development of rectal-specific formulations and combination antiretroviral products also increases the likelihood of developing a well tolerated and effective rectal microbicide.

Acknowledgements

None.

Conflicts of interest

Rectal microbicide research has been extensively funded through the National Institute of Allergy and Infectious Diseases, Division of AIDS (SUM1A068633 and SU19A082637), and the Eunice Kennedy Shriver National Institute of Child Health and Human Development, as well as the National Institute of Mental Health (SR01HD059533).

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

Pre-exposure prophylaxis


23. A comprehensive preclinical evaluation of the HIVRT inhibitor, UC781 gel. The article provides extensive details on phase 1 rectal microbicide clinical trial methodology and demonstrates the ex-vivo/in-vivo efficacy of UC781 gel in the colorectal explant system.


27. A preclinical evaluation of four fusion inhibitors: C34, T20, T1249, and L644. L644, a cholesterol-derivated version of C34, was the most potent fusion inhibitor and also active against RTI-resistant virus and appeared and provided protection even when used after viral exposure.


29. An interesting discussion on the potential use of protease inhibitors as candidate microbicides. Useful properties include low systemic absorption, a high genetic barrier to HIV-1 resistance, and potential activity against other pathogens including human papilloma virus (HPV) infection as well as HPV-associated dysplasia.


31. Stefanidou et al. present preliminary data on the protease inhibitor saquinavir as a candidate microbicide. Intriguingly, saquinavir was able to block infection in colorectal explants but was unable to do so in penile or cervical explants. Moreover, saquinavir appeared to be active when added to colorectal explants after infection. However, virus released from penile or cervical explants was unable to infect indicator T cells. Although saquinavir may be suitable as a single-agent rectal microbicide, it is likely that a combination would be needed for an effective protease inhibitor-based vaginal microbicide.


39. A successful demonstration of efficacy of the MIV-150/carrageenan gel developed by the Population Council. The study was conducted in adult Chinese rhesus macaques with a single high-dose SIV/HIV-1 challenge. All animals were protected when gel was applied 30 min of 4 h before viral challenge. These data support initiation of phase 1 human trials of MV-150.

