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Rectal Microbicides: Can We Make Them and Will People Use Them?

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Abstract The results of the CAPRISA 004 and iPrEx HIV prevention studies have demonstrated that topical or systemic use of antiretroviral agents can significantly reduce the risk of HIV acquisition associated with unprotected vaginal or anal sexual intercourse. However, the effect size in these studies was relatively modest and product adherence was generally poor. These observations suggest the need for new approaches to HIV prevention, especially for high risk MSM. Rates of lubricant use are high in MSM practicing receptive anal sex. Consequently, the development of an antiretroviral rectal microbicide gel may provide a safe and effective means of preventing HIV infection with an intervention that is likely to have high acceptability among the target population. The purpose of this article is to describe the challenges and progress in the development of rectal microbicides for HIV prevention.

Keywords HIV · Microbicides · Rectal · HIV prevention

Introduction

Microbicides are products that are designed to be applied to the vaginal or rectal mucosa with the intent of preventing or at least significantly reducing the acquisition of sexually transmitted infections (STIs) including HIV [1]. The original impetus for vaginal microbicide development was to provide women with options for HIV prevention in settings where their partners were unwilling to use condoms [2]. Years later, the need to also develop a rectal microbicide (RM) became clear, given that a significant proportion of men do not consistently use condoms during anal sex with men or women [3, 4], and that there has consequently been little or no decline in the rates of new HIV infections, particularly in men who have sex with men (MSM) [5]. Unprotected receptive anal intercourse (RAI) is the sexual behavior with the highest per act risk of HIV acquisition, conferring perhaps 10–20 times more risk than unprotected vaginal intercourse [6, 7]. Furthermore, there is increasing epidemiological evidence that women as well as men in both the developed [4, 8, 9] and developing world [10–12] practice RAI, and that a number of men in Sub-Saharan Africa practice RAI while also having sexual relationships with women [13, 14]. Clearly, RMs should be seen as an important HIV prevention technology for all individuals who practice RAI, and not just for MSM.

The development of a safe and effective RM is still in its early stages; however, there are many reasons to believe RMs can be a valuable part of an HIV prevention portfolio. One advantage of RMs is that their use would require only minimal behavioral modification, since sexual lubricant use is already a common component of RAI [15]. Indeed, formative studies have suggested that MSM are willing to participate in RM clinical trials [16, 17] as well as use these products should they become available [18]. Another positive aspect of RMs is that they would offer an alternative to condoms, which some see as a barrier to intimacy, pleasure, and satisfaction [19]. Finally, RMs have the benefit of giving receptive partners the capacity to protect themselves without depending on a partner's condom use.

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Vaginal Microbicide Development

Vaginal microbicide development began approximately 20 years ago as an outgrowth of the topical contraceptive field [2]. The intent was to develop a spermicidal gel that had activity against STIs including HIV. The first vaginal microbicides candidates, such as nonoxynol-9 (N-9) and cellulose sulfate, had broad spectrum in vitro activity against bacterial and viral STIs and some also had contraceptive efficacy. Unfortunately, when these products were evaluated in HIV effectiveness studies, they did not reduce HIV acquisition, and in one trial actually seemed to increase the risk of HIV infection [20].

The microbicide research community has subsequently focused on antiretroviral microbicides such as tenofovir gel. In July 2010, the Centre for the AIDS Programme of Research in South Africa (CAPRISA) 004 study team reported the first proof of concept for tenofovir vaginal gel, which was associated with a significant reduction in HIV acquisition in South African women [21]. In this randomized double-blind, placebo-controlled trial, women using tenofovir gel were overall 39% less likely to become HIV infected and 51% less likely to acquire herpes simplex virus (HSV-2) compared to the placebo group. Product effectiveness appeared to be linked to adherence since women who used the gel 80% or more of the time had a 54% reduction in HIV incidence, while women who used it less than 50% of the time had a 28% rate of protection. Furthermore, the effectiveness of tenofovir gel went from 50% after 12 months down to 39% after 30 months of use, but the difference in effectiveness was associated with lower adherence in the second year. These positive findings raise important questions about adherence and effectiveness, but have also renewed enthusiasm for microbicide development including both vaginal and RMs.

Rectal Microbicide Development

N-9 was the first vaginal microbicide to be evaluated for rectal safety [22]. This study, conducted in HIV positive and negative seroconcordant sexually active male couples, suggested that rectal N-9 was generally well tolerated although there was evidence of minor mucosal damage. The possibility that use of a microbicide, whether vaginal or rectal, might result in mucosal damage continues to be an area of concern within the microbicide field. It is conceivable that these mucosal changes may be asymptomatic but may still increase the risk of HIV infection. Moreover, these mucosal changes might be quite subtle. As one example, increased recruitment and activation of HIV target cells within the genital or rectal mucosa would not be identified through direct observation or microscopic assessment of tissue samples. Consequently, the initial focus of RM development has been to conduct rectal safety assessments of vaginal microbicides using increasingly sophisticated laboratory techniques [23, 24]. These have included collecting intestinal tissue samples from participants exposed to candidate microbicides and determining whether there is evidence of mucosal inflammation using a range of molecular biological and immunological techniques [24].

More recently, there have been attempts to develop microbicides whose properties are better suited for use in the rectal compartment. The majority of sexual lubricants and vaginal microbicides are extremely hyper-osmolar, meaning they are potentially more concentrated than body fluids. This property can result in reduced product acceptability and potentially mucosal damage [25]. Rectal specific microbicides will need to be iso-osmolar to minimize these problems. Clearly, the rectal compartment is very different from the vaginal compartment. One obvious difference is that the surface area required to be protected using an RM might be much larger than for a vaginal microbicide. Imaging studies of vaginal microbicide distribution have been conducted using radiological techniques such as MRI [26, 27] and similar studies are being conducted in rectal compartments [28]. RMs with varying rheological or flow characteristics are being evaluated in these systems to identify formulations that provide adequate coverage of the intestinal mucosa that might be exposed to infected semen. In addition, rectal specific microbicide applicators are being designed to optimize delivery of the microbicide to the rectal compartment.

Phases of Microbicide Development

Drug development including microbicide development involves a number of different stages. In the preclinical phase, new molecules are evaluated for safety and efficacy in cell lines and animal models. Compounds with an adequate safety profile are then advanced into Phase 1 safety studies where small groups of participants are exposed to the product in very controlled circumstances for relatively short periods of time. The participants in Phase 1 RM studies are usually at very low risk of HIV acquisition and are asked to be sexually abstinent. On completion of these studies, candidate microbicides are then evaluated in Phase 2 studies. Characteristically, Phase 2 microbicide studies are conducted in sexually active populations for three to six months and are designed to identify safety or acceptability issues associated with frequent use of the product. On completion of Phase 2, a candidate microbicide then advances into an effectiveness (Phase 2B/3) study. This is the final phase of testing and seeks to determine whether

the product can actually reduce HIV acquisition rates in at risk populations.

Phase 2B/3 evaluation of microbicides is the most arduous phase of assessment. Of necessity, the microbicide intervention has to be evaluated in populations who are already receiving a comprehensive HIV prevention package. The components of this package continue to evolve but would be expected to include diagnosis and treatment of STIs, frequent safer sex counseling, condom provision, and possibly male circumcision [29]. The net effect of these interventions is that the participants enrolled in Phase 2B/3 studies often develop a lower risk of infection than their peers not participating in the study, potentially reducing the overall HIV incidence in the study population and therefore the power to find a statistically significant result. As a consequence, Phase 2B/3 studies are usually large, long, and expensive.

Acceptability of Rectal Microbicides

Rectal microbicides will only play an important role in HIV prevention if the target populations find them acceptable and use them correctly and consistently [30–32]. Although there has been some discussion concerning whether acceptability studies should be postponed until efficacy of a product is demonstrated, others [32–34] have convincingly defended the wisdom of integrating acceptability research in early clinical phases of microbicide development. Morrow and Ruiz [33] state that Phase 1 trial participants "are an invaluable source of information regarding acceptability [for] they constitute the handful of individuals with actual product use experience and, thus, are in the best position to provide feedback on actual product characteristics and how these factors may influence individuals' willingness to initiate and maintain product use over time". They suggest that these trials assess a variety of factors, including product scent, color, and texture; clarity of instructions and ease of product preparation and application; qualities of product during and after use; frequency and timing of use; and related covariates, such as history of lubricant use, frequency of anal and vaginal sex, and relationship communication. Rosen et al. [35] and Morrow and Ruiz [33] propose the use of mixed methods (quantitative and qualitative) to assess the different factors. This advice is particularly sound in the case of small trials for which the utility of quantitative findings alone often has been limited [36–38].

Three recent papers have made important contributions to our knowledge of the acceptability of RMs. Importantly, the observations were based on interviews with participants who had actually used experimental rectal products rather than a theoretical discussion of product acceptability. An NICHD funded trial found that a sexually active cohort of middle aged MSM rated volumes up to 35 ml of gel acceptable for use during anal intercourse [39]. In a second study, MSM appeared to prefer microbicide gels rather than rectal suppositories [40]. Acceptability data from a Phase 1 safety study of UC781 gel, an antiretroviral microbicide gel, found the product to be highly acceptable and the majority of participants said that they would use such a product if it was commercially available [41].

Ongoing and Future Rectal Microbicide Trials

Information is currently lacking concerning microbicide acceptability in younger populations, particularly young adult males from ethnic minority groups and especially MSM with a history of unprotected RAI [42]. To address this issue, the National Institutes of Health (NIH) has recently funded a project entitled "Microbicide safety and acceptability in young men" that attempts to evaluate RM safety, adherence, and acceptability in young ethnic minority MSM in Boston, Pittsburgh, and San Juan. The study design has two stages (Fig. 1): A clinical and behavioral evaluation (Stage 1A) with an acceptability and adherence trial (Stage 1B), followed by a Phase 1 randomized, double-blind, multi-site, 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 RAI. Over a 3 month period they will report the frequency of product use and be interviewed about the acceptability of the product. The first 42 participants who complete Stage 1B with $\geq$80% adherence to product use will be eligible to participate in Stage 2 where they will be randomized to receive an actual microbicide (tenofovir gel) or matched placebo. Each participant will be evaluated for any adverse events after they apply a single dose of the gel in the study clinic, and again after they self-administer once-daily outpatient doses for 7 days. It is hoped that data from this study will provide unique insights into the acceptability, safety, and adherence of RMs in young MSM.

As can be seen in Table 1, RM development has not yet moved beyond Phase 1, although the NIH sponsored Microbicide Trials Network (www.mtnstopsHIV.org) hopes to conduct a Phase 2 rectal safety evaluation of tenofovir gel in 2012. Designing Phase 2B/3 studies to demonstrate the effectiveness of RMs may actually prove less challenging than it has with vaginal microbicides. This is because for effectiveness studies, it is necessary to find at risk populations with annual HIV seroconversion rates in excess of 3%. Vaginal microbicides studies have needed to

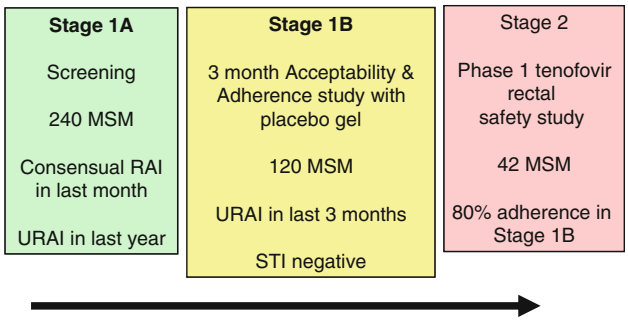

Fig. 1 Microbicide acceptability and safety in young men [McGowan and Carballo-Dieguez (R01: HD059533-01A1)]: study stages and eligibility criteria

be conducted in Sub-Saharan Africa, where it is possible to identify populations of at risk women with annual HIV seroconversion rates in excess of 3%. One advantage for the RM development field is that it should be possible to identify high risk MSM populations in North America, Europe, and Asia [5, 43]. This will simplify the operational complexities associated with these large trials and hopefully encourage sponsors to advance RM candidates into Phase 2B/3 evaluation.

Other HIV Prevention Tools in Development

Rectal microbicide development is not occurring in a vacuum. Several other HIV prevention tools are being developed simultaneously, and these may impact the design of future RM Phase 2B/3 studies. The most relevant study in this regard is the iPrEx study of oral Truvada® pre-exposure prophylaxis (PrEP) currently being conducted in MSM at sites in Peru, Ecuador, Brazil, Thailand, South Africa, and the U.S. (http://globaliprex.com). Data from iPrEx is anticipated to be available late in 2010. Depending on the level of effectiveness seen in the iPrEx study, Truvada PrEP may need to be added to the prevention standard of care package; it would be difficult to contemplate conducting placebo-controlled Phase 2B/3 prevention studies unless participants were also receiving open label Truvada.

Another possible development that could affect the design of future RM studies would be the identification of a partially effective HIV vaccine. Data from the Thai Phase 3 HIV vaccine clinical trial, also known as RV144, tested the "prime-boost" combination of two vaccines: ALVAC® HIV vaccine (the prime) and AIDSVAX® B/E vaccine (the boost) and demonstrated efficacy of 31.2% (95% CI, 1.1–52.1; $P = 0.04$) [44]. This was encouraging but probably insufficient to warrant roll out of this specific vaccine. Nonetheless, it is safe to say that the HIV prevention research environment is extremely dynamic and that results from ongoing studies have profound implications on the design and feasibility of future RM studies.

Implementation of Rectal Microbicides for HIV Prevention

Assuming that we can develop a safe and effective RM, the next major step would be to determine who would use these products and under what circumstances. The current generation of RMs under development are all antiretroviral gels. They could only be used by HIV negative individuals and would have to be distributed through a health care system. Unintended exposure to an antiretroviral RM by an individual with untreated HIV infection would likely result in the development of HIV resistance. This might generate subsequent challenges in providing an effective antiretroviral regimen for treatment of HIV infection and also present broader public health issues in terms of dissemination of resistant virus throughout at-risk populations. Consequently, provision of antiretroviral RMs will require extensive voluntary counseling and testing for HIV infection as well as ongoing surveillance of individuals using these products. These issues may limit the social desirability of these products unless there is a carefully orchestrated public health campaign

Table 1 Completed or planned RM studies

Study	Stage and population characteristics	Product	Sponsor	Status
RMP-002/MTN-006	Phase 1 (sexually abstinent)	Vaginal tenofovir gel	NIH/DAIDS/IPCP Program	Completed
MTN-007	Phase 1 (sexually abstinent)	Reduced glycerin formulation of vaginal tenofovir	NIH/DAIDS/MTN	Q4 2010
Project Gel	Phase 1 (sexually active)	Reduced glycerin formulation of vaginal tenofovir	NIH/NICHD	Q2 2011
CHARM Program	Pre-Phase 1 (single dose, sexually abstinent)	Rectal specific tenofovir gel	NIH/DAIDS/IPCP Program	Q2 2011
MTN-017	Phase 1 (sexually abstinent)	Reduced glycerin formulation of vaginal tenofovir	NIH/DAIDS/MTN	Q4 2011

that targets RMs to those individuals who could gain the most to benefit from their use. Characterizing this population will be challenging but necessary to focus limited prevention resources to individuals who really need RMs. Parameters may include a history of frequent unprotected RAI and perhaps anorectal STIs. Such individuals may also benefit from using both oral and topical PrEP. Ongoing Phase 1 RM studies will hopefully provide data on the pharmacological consequences of using both oral and topical PrEP as well as preliminary data on the relative efficacy of single or dual therapy using ex vivo explant challenge studies [45]. Successful roll out of RM will also probably require focused marketing and the development of more user friendly delivery devices.

Advocacy for Rectal Microbicides

The increasing momentum of RM development is encouraging and has been driven to a large extent by community advocacy as well as by the reality of the U.S. HIV epidemic that is now clearly concentrated in young ethnic minority MSM [46, 47]. The efforts of groups such as the International Rectal Microbicide Advocates (IRMA) have played a key role in educating the community about advances in RM development. IRMA is composed of a diverse group of community advocates, clinicians, sponsors, and scientists working on RM. Through their website (http://www.rectalmicrobicides.org), frequent interactive teleconferences, and satellite conferences, IRMA plays a critical role in maintaining momentum in RM research.

Conclusion

Rectal microbicide candidates are likely to move into effectiveness studies in the next 5 years. Operational roll out of antiretroviral RMs will be both complex and challenging and will of necessity target the highest risk populations first. Hopefully, RMs will ultimately provide another component of the HIV prevention package that collectively can impact the spread of HIV infection in at risk populations.

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