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Rectal Microbicide Development

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Abstract

The last few years have seen important progress in demonstrating the efficacy of oral pre-exposure prophylaxis, vaginal microbicides, and treatment as prevention as effective strategies for reducing the risk of acquiring or transmitting HIV infection. There has also been significant progress in the development of rectal microbicides. Preclinical non-human primate studies have demonstrated that antiretroviral microbicides can provide significant protection from rectal challenge with SIV or SHIV. Recent Phase 1 rectal microbicide studies have characterized the safety, acceptability, compartmental pharmacokinetics (PK), and pharmaco-dynamics (PD) 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. The PK/PD data generated in these Phase 1 studies may reduce the risk of advancing ineffective candidate rectal microbicides into late stage development. Tenofovir gel is currently poised to move into Phase 2 evaluation and it is possible that a Phase 2B/3 effectiveness study with this product could be initiated in the next 2–3 years.

1 Introduction

The field of vaginal microbicide (VM) 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 (Stein 1990). Nonoxynol-9 (N9) had demonstrated these properties in laboratory experiments (Jennings and Clegg 1993) and was rapidly advanced into effectiveness studies. In addition it was also evaluated as a potential rectal microbicide (RM) (Gross et al. 1999a; Tabet et al. 1999). Unfortunately, N9 was not found to be satisfactory as a VM (Van Damme et al. 2002) and was not further developed as an RM. 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 VM candidates (McGowan 2006). During this period there was no research on specific RM. However, it was clear that men who have sex with men (MSM) were interested in the concept of RM and would be willing to enroll in clinical trials evaluating the safety and effectiveness of these products (Carballo-Dieguez et

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al. 2007b; Gross et al. 1998). It was also apparent that sexual lubricant use, a possible model for RM use, was common among MSM (Carballo-Dieguez et al. 2000). Other important early studies included exploring product formulation preferences in MSM (Carballo-Dieguez et al. 2008a, b) and assessment of the acceptability of different volumes of rectal gels (Carballo-Dieguez et al. 2007a). The HPTN-056 study provided data on the variability of rectal mucosal safety parameters that might be measured in future RM studies (McGowan et al. 2007) and set the stage for the first RM Phase 1 studies evaluating antiretroviral products.

2 The Biology of Rectal HIV-1 Transmission

Ideally, a rectal microbicide should block transmission of HIV-1 regardless if it is the receptive or insertive partner for anal intercourse (AI). The specific processes underlying HIV-1 transmission are still not fully understood, but are dependent on several factors that include the stage of infection (Pilcher et al. 2004), the presence of other sexually transmitted diseases (Cohen et al. 1997; Vernazza et al. 1997), and successful suppression of HIV-1 replication in the infected partner (Baeten et al. 2012; Cohen et al. 2011; Donnell et al. 2010). The risks for HIV-1 acquisition for the receptive partner are about 10-fold higher than for the insertive partner (Boily et al. 2009; Varghese et al. 2002). However, these estimates are quite variable due to the factors discussed above (Baggaley et al. 2010).

The GI tract is a rich source of HIV-1 target cells (Fig. 1). Isolated lymphoid follicles, which serve as inductive sites for immune responses, are located throughout the colon (Koboziev et al. 2010). The number of follicles generally increases toward the anus with the greatest numbers found in the rectum (Langman and Rowland 1986, 1992). Antigen presenting cells (macrophage and dendritic cells) along with effector and regulatory T cells are found within the follicles. These cells are generally activated and express HIV-1 co-receptors, CCR5, and CXCR4, as well as soluble immune mediators (Anton et al. 2000; McGowan et al. 2004; Poles et al. 2001; Zhang et al. 1998) thus creating the perfect environment primed for HIV-1 infection.

HIV-1 can reach these activated immune cells in several ways. While micro-tears in the epithelium can occur during coitus, the envelope of HIV-1, gp120, has been shown to increase the permeability of the epithelium allowing HIV-1 to easily traverse to the lamina propria (Nazli et al. 2010). Even with an intact mucosa, epithelial cells can bind and transfer HIV-1 either through active transport, transcytosis (Bomsel 1997), or non-specifically (Dezzutti et al. 2001; Meng et al. 2002; Wu et al. 2003). Finally, dendritic cells extend dendrites through the tight-junctions of the epithelium to sample the luminal environment (Rescigno et al. 2001). HIV-1 can take advantage of this by binding to DC-SIGN and subsequently infect activated lymphocytes (Gurney et al. 2005). Once past the epithelium, HIV-1 preferentially infects local lymphocytes expressing CCR5 (Anton et al. 2000; Meng et al. 2000). Cell-free and cell-associated virus are both present in the ejaculate and so it is still not clear which virus is the primary driver of mucosal infection (Anderson et al. 2010). However, recent sequence analysis of viral RNA and integrated proviral DNA suggests that cell-free virus contributes the most to mucosal transmission (Butler et al. 2010). These early infection events are known to initiate from a single founder virus in heterosexual

transmission (Keele et al. 2008; Sagar et al. 2009), but RAI is associated with a more diverse founder virus population (Li et al. 2010) likely due to direct access to underlying immune cells. This information suggests that an ideal rectal microbicide should protect the epithelium and be active against a swarm of viruses.

2.1 Epidemiology of HIV Infection Associated with Receptive Anal Intercourse

Epidemiological studies have confirmed that receptive anal intercourse (RAI) is a common practice among MSM in the Global North (Hart and Williamson 2005; Wolitski and Fenton 2011). Unfortunately, a significant proportion of RAI among MSM is unprotected (Begley et al. 2008; Chen et al. 2003) and contributes to the growing number of new infections among MSM (Beyrer et al. 2010). More recent data have clearly identified at risk MSM in the Global South (Baral et al. 2012; Beyrer et al. 2012). There are also increasing data demonstrating that women in both the US and Sub-Saharan Africa practice RAI (Gorbach et al. 2009; Kalichman et al. 2009). In the VOICE study (Microbicide Trials Network (MTN-003)) of oral and vaginal tenofovir or Truvada® that was conducted in South Africa, Uganda, and Zimbabwe, approximately 7–20 % of the 5,029 women enrolled in the study reported a history of RAI in the prior 3 months (Marrazzo and VOICE MTN 003 Study Team 2012). This high frequency of RAI in women is important from a public health perspective but it also has the potential to interfere with the ability to conduct effectiveness trials of vaginal microbicides as they may not provide protection against rectal infection (Masse et al. 2009; McGowan and Taylor 2010). These observations emphasize the need to develop new prevention strategies, including RM, in populations at risk of HIV infection through unprotected receptive anal intercourse (URAI) who are unable or unwilling to use a condom.

2.2 The Rectal Microbicide Pipeline

In theory, the RM pipeline could be derived from the VM pipeline. However, the majority of RM 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 (Anton et al. 2011) and the nucleotide inhibitor, tenofovir (Anton et al. 2012). 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 API (Herrera et al. 2009, 2011). The majority of research has been conducted on nucleotide reverse transcriptase inhibitors (tenofovir) or NNRTIs (UC781 and dapivirine (TMC120)). Recent studies have also evaluated L’644, a fusion inhibitor that demonstrated post-exposure activity in both colorectal and cervical explants as well as activity against reverse transcriptase resistant isolates (Harman et al. 2012). Protease inhibitors are also being considered as candidate RM (Herrera and Shattock 2012; Stefanidou et al. 2012). Potential RM candidates are listed in Table 1 together with their current stage of development.

2.3 Formulation Development

Qualitative and clinical studies have suggested that acceptable RM formulations could include gels, suppositories, or douches (Carballo-Dieguez et al. 2008a, b). Gels were considered more acceptable than suppositories (Carballo-Dieguez et al. 2008b) and a

volume escalation trial 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 (Carballo-Dieguez et al. 2007a). The first RM clinical trials evaluated the rectal safety of gels that were being developed as VM. These products had a number of characteristics that were suboptimal for an RM. They were extremely hyperosmolar and had an acid pH. Hyperosmolar products are known to induce mucosal damage (Begay et al. 2011; Fuchs et al. 2007) and may be associated with increased risk of acquiring STIs (Gorbach et al. 2012). Rectal use of the vaginal formulation of tenofovir 1 % gel was associated with gastrointestinal adverse events including diarrhea, bloating, urgency, and abdominal pain (Anton et al. 2012). Consequently, efforts are under way to develop rectal-specific microbicide formulations that are iso-osmolar with a neutral pH (Agashe et al. 2012; Wang et al. 2011). 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 (Dezzutti et al. 2012a). The RG-TFV 1 % also appeared to have improved in vivo safety and acceptability in Phase 1 studies (McGowan et al. 2012a).

2.4 Preclinical Evaluation of Rectal Microbicides

Preclinical testing of API, has been standardized to define the API, but there are subtle variations in the specific assays used based on the preferences of the laboratory doing the testing (Buckheit, and Buckheit 2012; Lackman-Smith et al. 2008; Lard-Whiteford 2004). Initial tests using primary immune cells, such as peripheral blood mononuclear cells, and indicator cell lines are performed to determine mechanisms of action and potency of the API against standard laboratory and primary clinical isolates of HIV-1. Some testing is now being conducted with the newly identified primary isolates known as transmitter/founder viruses from persons who acquired HIV-1 through penile-vaginal or penile-rectal coitus (Dezzutti et al. 2012b; Keele et al. 2008). The incorporation of biological fluids such as semen, cervicovaginal fluid, or their simulants is also used early in the testing to ensure the API remains potent during coitus (Neurath et al. 2006; Patel et al. 2007). More recently, mucosal tissues have been used to evaluate API activity. To screen APIs, non-polarized mucosal tissue (ectocervical, vaginal, and colorectal) has been used (Fletcher et al. 2006; Greenhead et al. 2000; Herrera et al. 2009, 2011; McElrath et al. 2010). Typically, small pieces of tissue are exposed to the drug for a short period and then exposed to HIV-1. After an incubation period, the tissue is washed and placed back in culture to monitor for HIV-1 infection. These assays have characterized many potential rectal microbicide candidates from non-specific entry inhibitors (Fletcher et al. 2006) to more specific non-nucleoside and nucleotide/nucleoside reverse transcriptase inhibitors, fusion inhibitors, and protease inhibitors (Fletcher et al. 2006; Harman et al. 2012; Herrera et al. 2009, 2011). These candidates have been typically evaluated as single entity agents. However, combinations of APIs are now being tested and much like therapy, they show that combinations of up to three APIs (tenofovir or emtricitabine with UC781 and dapivirine) are much more potent against HIV-1 infection in colorectal tissue even against drug resistant HIV-1 (Herrera et al. 2011). These data will help inform microbicide developers as to which candidates/combinations are optimal to pursue for further development.

2.4.1 Formulation Considerations in Preclinical Assessment—Formulation of these APIs for rectal use will likely be in a liquid or semi-solid dosage form to cover areas that are at most risk for HIV-1 exposure (Wang et al. 2011). Preclinical testing of formulated APIs adds additional complexity because pH, osmolality, and viscosity of the product will impact the results. For instance, the polymers used in the formulation may enhance toxicity or efficacy due to smothering of individual cells or non-specifically binding HIV-1. These results may be over interpreted by inexperienced researchers. Therefore, it is critical to include the vehicle control—the same formulation but without the API—in all assays to accommodate the impact the formulation may have on the testing results. As with unformulated APIs, testing algorithms have been developed (Rohan et al. 2010). Typically, the testing done with the formulations is to ensure the APIs activity has not been impaired and the formulation is safe. Mucosal tissues are used for testing the formulations, but are polarized, keeping the apical surface at the liquid/air interface (Abner et al. 2005; Cummins et al. 2007; Rohan et al. 2010). The formulation with or without HIV-1 can be applied to the apical surface recapitulating the use by a person. Using this testing algorithm, it was recently reported that the hyperosmolar 1 % tenofovir vaginal gel formulation demonstrated epithelial facture and sloughing in polarized mucosal tissue (Rohan et al. 2010). The gel was reformulated to reduce the glycerin content and thus reduce the osmolality (Dezzutti et al. 2012a). The reduced glycerin 1 % tenofovir gel showed improved epithelial retention in polarized rectal and ectocervical tissue explants. These data support the clinical trial results (discussed below) that showed that gastrointestinal adverse events where significantly more common when the original 1 % tenofovir gel was used rectally compared to the reduced glycerin gel formulation (Anton et al. 2012; McGowan et al. 2012b). The preclinical testing of formulations is thus important to provide assurance that those products that move into clinical trials are safe as well as likely to be effective.

2.4.2 Animal Models—In addition to in vitro and ex vivo testing, animal models are used to test the safety and effectiveness of an API/microbicide (see Holt and Nuttall 2013, this volume). Several microbicide products have been evaluated for rectal safety and include BufferGel (Patton et al. 2004), Savvy (Patton et al. 2006b), VivaGel (Patton et al. 2006a), and UC781 (Patton et al. 2007). In general, there has been a good correlation between vaginal and rectal safety findings suggesting no more safety concerns for these vaginal formulations when used rectally.

Animal models also are used to evaluate the efficacy of microbicide candidates against HIV-1, SHIV, and other sexually transmitted diseases and include immunodeficient mouse strains (severe-combined immunodeficient (SCID) and non-obese diabetic (NOD)-SCID) and macaques (rhesus, pig-tailed, and cyno-molgous) (see Herrera and Shattock 2013, this volume). The SCID mouse strains have been reconstituted with human fetal tissue, typically liver, thymus, and bone marrow, which has allowed them to be repopulated with human immune cells throughout their bodies including mucosal tissues (Berges and Rowan 2011; Denton and Garcia 2011). These animals are susceptible to infection with HIV-1 through systemic, vaginal, and rectal routes. Recently, Denton et al. demonstrated that engraftment of intestinal immune cells in the NOD/SCID model was most efficient in mice that had an intact interleukin-2 common γ chain which suggests that these mice would be superior for

rectal microbicide efficacy testing (Denton et al. 2012). All of the published microbicide work to date in the "humanized" mice has focused on vaginal evaluation of microbicide candidates, but work is currently ongoing to adapt this model to evaluate rectal microbicides.

NHP infection models use two different challenge schemes that involve either a multiple low-dose or single high-dose challenge with simian immunodeficiency virus (SIV) or a chimeric SIV/HIV construct (SHIV) (Veazey et al. 2012). Typically the virus used to evaluate microbicides is an SIV modified to express the HIV-1 envelope (SHIV) or the HIV-1 reverse transcriptase (RT-SHIV) (Pal et al. 2012). Using the NHP model, gel formulations of an entry inhibitor, cyanovirin-N (Tsai et al. 2003), and the reverse transcriptase inhibitors, tenofovir, and MIV-150 (Cranage et al. 2008; Singer et al. 2011) prevented rectal challenge of SHIV or RT-SHIV. These data are informative regarding the potential of a low volume of gel to block atraumatic exposure to infectious virus. Of note, there were correlations between plasma drug levels of tenofovir and protection from macaque infection (Cranage et al. 2008). To begin to address where drug distributes after dosing in a more formal way, a multi-compartment pharmacokinetic study in macaques after vaginal or rectal dosing with tenofovir gel was done (Nuttall et al. 2012). Macaques dosed with tenofovir gel vaginally showed rectal drug levels only 1 $\log_{10}$ lower than the vaginal drug levels. And both mucosal compartments were 4–5 $\log_{10}$ higher than plasma drug levels. Similar results were found when the macaques were dosed with tenofovir gel rectally. These data suggest that vaginal or rectal dosing of a soluble microbicide could protect against HIV-1 regardless of the route of exposure.

2.5 Clinical Development of Rectal Microbicides

As with VM, the purpose of Phase 1 RM studies is to generate preliminary data on the safety, acceptability, PK, and PD activity of the candidate microbicide. However, in contrast to VM 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; HIVNET-008 (Nonoxynol-9 (N9) gel) (Tabet et al. 1999), RMP-01 (UC781 0.1 and 0.25 % gel) (Anton et al. 2011; Ventuneac et al. 2010), RMP-02/MTN-006 (oral tenofovir and tenofovir 1 % gel (original formulation)(Anton et al. 2012), and MTN-007 (N9 gel, HEC placebo gel (Schwartz et al. 2007), and tenofovir 1 % gel (reduced glycerin formulation)) (McGowan et al. 2012a). 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 ten 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 to 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 (AEs) 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 to 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 (Gross et al. 1999b).

RMP-01—Thirty-six HIV-1 seronegative, sexually-abstinent men and women were enrolled in Los Angeles, CA, and randomized into a double-blind, 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 AEs 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-1_{BaL} showed marked suppression of HIV-1 p24 in tissues exposed in vivo to 0.25 % UC781 (Fig. 2).

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 (TFV) 1 % gel or the HEC placebo gel. Safety endpoints included clinical AEs 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 PK analysis and ex vivo challenge with HIV-1. No serious AEs were reported. However, AEs, especially gastrointestinal AEs, were significantly increased with seven-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_{max} 30 min after single rectal exposure was 112 times greater than single oral-exposure with tissue seven-day exposure 5 times greater than single rectal-exposure. Seven-day exposure to rectal TFV was associated with significant suppression of ex vivo infection of colorectal explants collected by biopsy. Increased AEs suggested that the vaginal formulation of tenofovir 1 % gel used rectally was not entirely safe 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 ≥94 %. AEs were generally mild or moderate. There was no significant difference in the prevalence of AEs 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 micro-flora, which were mostly confined to the N9 gel arm. Overall, the study suggested that the RG formulation of 1 % tenofovir was safe and well tolerated and should be advanced to Phase 2 RM development.

A number of additional RM studies are ongoing or will start enrollment in 2012. The National Institutes of Health (NIH) has 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, 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-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 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 PK/PD 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, PK, 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 (Cao et al. 2012; Louissaint et al. 2012). Collectively, these studies will provide unique data on the influence of formulation characteristics, including osmolality, and product safety, PK/PD, and distribution.

The final RM 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 women in the US, 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 (Abdool et al. 2010)). Apart from general safety and acceptability, a subset of approximately 30 participants in the US and Thailand will undergo more intensive mucosal sampling for evaluation of mucosal safety biomarkers and PK/PD. If successful, it is hoped that MTN-017 will set the stage for a Phase 2B/3 RM trial in 2015.

3 Rectal Microbicide Advocacy

Drug development does not occur in a vacuum and from the outset advocacy groups have played a critical role in RM development. The International Rectal Microbicide Advocates group (IRMA; http://www.rectalmicrobicides.org/) has helped focus attention on RM development including conducting community/ internet-based studies on lubricant usage (Javanbakht et al. 2010). IRMA has also lead efforts to define the need for RM for men and women at risk of HIV infection associated with URAI in Africa. IRMA convened a meeting in Addis Ababa, Ethiopia in November 2011 that has helped catalyze community interest in RM within Sub-Saharan Africa (http://www.rectalmicrobicides.org/ProjectARMreport2012.pdf). Unfortunately, MSM activity is stigmatized, illegal, and even punished by death in many countries across the world (Altman et al. 2012) and conducting RM trials or indeed rolling out RM as prevention in these communities would currently be difficult if not impossible (Kyomya et al. 2012; Semugoma et al. 2012). From a human rights perspective, as well as a drug development perspective, there is much to be done.

4 Conclusions

Given the ongoing epidemic of HIV infection associated with URAI it is clear that there is an urgent need to develop safe and effective methods of HIV prevention that the target population will be willing to use. Although the iPrEx study demonstrated the efficacy of PrEP in MSM (Grant et al. 2010), overall adherence in the participants receiving Truvada was estimated to only be about 50 %. This suggests that an RM, possibly used in addition to oral PrEP, might increase overall protection from HIV infection. The design of Phase 1 RM studies has evolved such that key data on safety, acceptability, and PK/PD can be generated at an early stage of product development. This will allow for refinements of rectal-specific formulations and the development of combination antiretroviral products. Collectively, this will increase the likelihood of developing a safe and effective RM. However, RAI is a stigmatized human behavior and research in this area remains an important but difficult endeavor.

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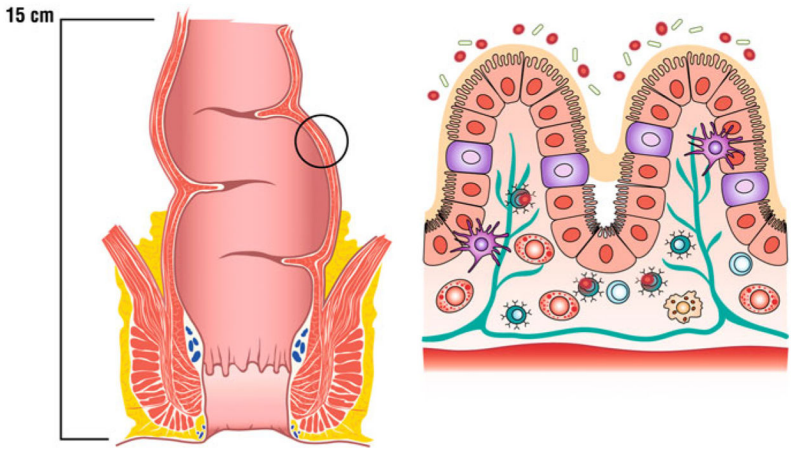

Fig. 1.

A detailed view of the colon. The colon is lined with a single layer of epithelium, covered by mucus that separates the luminal contents from the underlying lamina propria. The lamina propria is a rich source of immune cells that includes dendritic cells (*purple*), T cells (*blue*), plasma cells (*pink*), and tissue macrophage (*tan*). Virus (*red*) can reach the lamina propria through micro tears, transcytosis through the epithelium, or by binding to epithelial cells or dendritic cells. Recent data suggest cell-free virus reaches immune targets to infect the resident immune cells (T cells in *blue/red*)

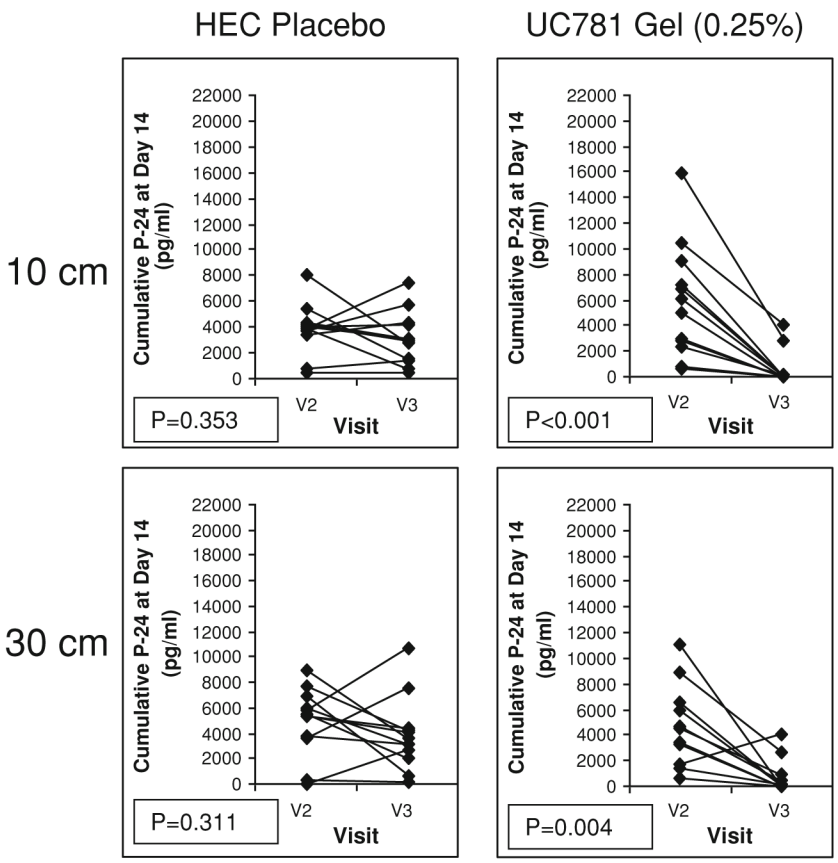

Fig. 2.

Colorectal biopsies were collected before (V2) and 30 min after (V3) a single rectal dose of UC781 gel. The biopsies were challenged ex vivo with 10^4 $TCID_{50}$ of HIV-1_{BaL} (Fletcher et al. 2006) and explant supernatant was collected for HIV-1 p24 quantification every 3–4 days following infection (Anton et al. 2011). The pharmacodynamic response was calculated as the difference between V2 and V3 Day 14 cumulative HIV-1 p24 levels

Table 1

Products that have been evaluated as candidate rectal microbicides[a]

Product	Development stage	Study	Status	ClinTrials.gov	Reference
Cellulose acetate	Preclinical	Explant model	Completed		Abner et al. (2005)
PRO2000					
SPL7013					
Vena Gel					
UC781					
PRO2000	Preclinical	Explant model	Completed		Fletcher et al. (2006)
Dextrin sulfate					
Tenofovir	Preclinical	Explant model	Completed		Dezzutti et al. (2012)
C34	Preclinical	Explant model	Completed		Harman et al. (2012)
T20					
T1249					
L’644					
Tenofovir	Preclinical	Explant model	Completed		Herrera et al. (2011)
Emtricitabine					
UC781					
Dapivirine (TMC120)					
Saquinavir	Preclinical	Explant model	Completed		Stefanidou et al. (2012)
Maraviroc	Preclinical	Explant model	Ongoing		
Griffithsin					
MIV-150					
Carageenan					
Zinc acetate					
BufferGel®	Preclinical	NHP/safety	Completed		Summarized in Patton et al. (2009)
Nonoxynol-9					
C31G					
Octylglycerol					
Polystyrene sulfate					
Cellulose sulfate					

Product	Development stage	Study	Status	ClinTrials.gov	Reference
SPL7013					
Carraguard					
UC781					
Cyanovirin gel	Preclinical	NHP/Efficacy	Completed		Tsai et al. (2003)
Tenofovir gel	Preclinical	NHP/Efficacy	Completed		Cranage et al. (2008)
MIV-150 gel	Preclinical	NHP/Efficacy	Completed		Singer et al. (2011)
Nonoxynol-9	Phase 1	HIVNET-008	Completed	NCT00000929	Tabet et al. (1999)
UC781 gel	Phase 1	RMP-01	Completed	NCT00408538	Anton et al. (2011); Ventuneac et al. (2010)
Tenofovir 1 % gel (VF)	Phase 1	RMP-02/ MTN-006	Completed	NCT00984971	Anton et al. (2012)
Tenofovir 1 % gel (RGF)	Phase 1	MTN-007	Completed	NCT01232803	McGowan et al. (2012)
Tenofovir 1 % gel (RGF)	Phase 1	Project Gel	Ongoing	NCT01283360	N/A
Tenofovir 1 % gel (VF, RGF, RF)	Phase 1	CHARM-01	Q3 2012	NCT01575405	N/A
Tenofovir 1 % gel (VF, RGF, RF)	Phase 1	CHARM-02	Q3 2012	NCT01575418	N/A
Tenofovir 1 % gel (RGF)	Phase 2	MTN-017	Q3 2012	NCT01232803	N/A

[a]Products that have been studied in colorectal explant systems, animal models, or humans

VF vaginal formulation, *RGF* reduced glycerin formulation, *RF* rectal-specific formulation, *NHP* non-human primate

Table 2

Composition and characteristics of the currently available formulations of tenofovir 1 % gel

Formulation study	Original VF, % w/w (CAPRISA 004)	RGF, % w/w (MTN-007)	RF, % w/w (CHARM-01)
Glycerin	20.00	5.00	2.50
Hydroxyethyl cellulose	2.50	2.75	0
Carbopol 974	0	0	0.50
Sodium carboxymethylcellulose	0	0	1.00
Methylparaben	0.18	0.22	0.18
Propylparaben	0.02	0.024	0.02
Purified water	75.23	89.936	94.78
Disodium edetate (EDTA)	0.05	0.05	0.01
Citric acid	1.00	1.00	0
PMPA	1.00	1.00	1.00
Sodium hydroxide	As needed	As needed	As needed
Diluted hydrochloric Acid	As needed	As needed	As needed
pH	4.5	4.6	7
Osmolality (mOsmol/kg)	3111	836	479

VF vaginal formulation, *RGF* reduced glycerin formulation, *RF* rectal-specific formulation