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Review

# Rectal pre-exposure prophylaxis (PrEP)

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ABSTRACT

Rectal pre-exposure prophylaxis (PrEP) will be a critical component of HIV prevention products due to the prevalence of unprotected receptive anal intercourse among men who have sex with men and heterosexual couples. Given the biological considerations of this compartment and the complexity of HIV infection, design of a successful rectal microbicide product faces a number of challenges. Important information is being compiled to begin to address deficits in knowledge toward design of rectal PrEP products for men and women. Aspects of formulation development and preclinical and clinical evaluation of rectal products studied to date are summarized in this review. This article is based on a presentation at the "Product Development Workshop 2013: HIV and Multipurpose Prevention Technologies," held in Arlington, Virginia on February 21–22, 2013. It forms part of a special supplement to Antiviral Research.


**Contents**



## 1. Introduction

HIV remains a significant global health challenge. Although advances in antiretroviral therapy have extended the life expectancy of HIV infected individuals, much work is still needed in the area of prevention. This review aims to summarize the role of rectal pre-exposure prophylaxis (PrEP) in global HIV prevention. Specifically, it provides justification of need and an overview for the current status of rectal microbicide research. Emphasis has been placed on preclinical evaluation and product development issues specific to rectal microbicides. As this field is in its early stages, the current gaps in knowledge and future directions of the science in the field are also presented.

### 1.1. Are rectal microbicides needed?

The CDC has reported that male to male sexual contact continues to be the highest transmission category for HIV followed by heterosexual contact (CDC, 2012). This statistic accounts for gay and bisexual men representing the population most severely impacted by HIV. Anal intercourse is a common practice among men who have sex with men (MSM). A high prevalence rate of unprotected receptive anal intercourse (RAI) in MSM has been

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shown in a number of studies including the EXPLORE study which evaluated high risk behaviors among MSM in six US cities (Koblin et al., 2003). However a number of studies have shown that heterosexual couples also engage in anal intercourse (Civic, 2000; Erickson et al., 1995; Gross et al., 2000; Mosher et al., 2005) with lifetime anal intercourse estimates in heterosexual couples ranging from 6% to 40% (McBride and Fortenberry, 2010) with up to 10% of sexually active women in the US engaging regularly in RAI. In a CDC report which polled people ages 15–44, 44% of men and 36% of women admitted to having ever had anal sex (Chandra et al., 2011). The risk associated with HIV transmission through unprotected receptive anal intercourse (URAI) is 1.7% per act while the risk associated with unprotected vaginal intercourse is only 0.08% (Boily et al., 2009). This statistic more than likely contributes to URAI being the highest transmission category for HIV acquisition.

A number of anatomical and physiological factors contribute to greater risk of HIV transmission through rectal intercourse (McGowan and Dezzutti, 2013). The rectal epithelia consist of a single layer of cells as opposed to the multilayer squamous epithelium of the vagina and ectocervix. The pH of the rectum is closer to neutral and is an open tube orientation with potential of HIV reaching as far as the splenic flexure. There is a large surface area which requires protection. Finally the gastrointestinal tract is populated with a large number of HIV-1 infectable cells (Ullrich et al., 1998; van Marle et al., 2007). All of these factors make the rectal route a more susceptible route for HIV infection.

### 1.2. Oral vs topical rectal PrEP

Assessments of prevalence studies on anal intercourse as well as men and women's willingness to use microbicide products have indicated a need for the development of a rectal microbicide product. Products designed to protect men or women from HIV transmission through URAI could be either an oral PrEP product or topical PrEP product (also referred to as topical microbicide). With respect to oral PrEP, the U.S. Food and Drug Administration has approved Truvada, an oral tablet combining two antiretroviral drugs (emtricitabine (FTC)/tenofovir disoproxil fumarate(TDF)), for use in uninfected individuals who have a high risk of HIV infection. A key clinical study toward approval of this product was the iPreX study. This study, conducted in 2499 high risk MSM, showed significant reduction of HIV acquisition in men treated with daily oral FTC/TDF (Grant et al., 2010). In addition to oral PrEP, topical rectal PrEP products are being designed. Clinical efficacy studies of vaginal topical microbicides indicate that achieving significant tissue concentration of drug for some APIs may be critical to achieving efficacy (Karim et al., 2011). For oral PrEP studies it is observed that although high tenofovir (TFV) blood level was achieved, drug level at the mucosal site was much lower. However with topical PrEP one can achieve high drug concentration in the local tissue while limiting systemic exposure to the drug. From not only an efficacy standpoint but also considering resistance and toxicity there may be benefit to rectal topical PrEP products.

To date rectal microbicide clinical trials have only evaluated UC781 or TFV. Preclinical studies have been conducted for a number of additional microbicide drug candidates which were intended for vaginal administration. However they also have potential for administration by the rectal route. These include cellulose acetate, PRO2000, SPL7013, vena gel (Abner et al., 2005), dextrin sulfate (Fletcher et al., 2006), C34, T20, T1249, L'644 (Harman et al., 2012), TMC120 (dapivirine) (Herrera et al., 2011), saquinavir, MIV-150, carrageenan, zinc acetate (Kenney et al., 2013, 2012), BufferGel, C31G, octylglycerol (Patton et al., 2009), maraviroc, griffithsin (Wang et al., 2012). Vaginal administration of several of these drug candidates was tested in the clinic. Notably PRO2000 (McCormack et al., 2010) carrageenan (Skoler-Karpoff et al., 2008) were found to be safe but not efficacious against vaginal transmission of HIV. Early efforts in the area of rectal microbicides looked at the safety or efficacy of products designed for vaginal use in the rectal compartment. More recently rectal specific dosage forms are being designed for application as rectal PrEP products. Additionally dual compartment (vaginal and rectal) products are also being formulated.

## 2. Preclinical evaluations for rectal PrEP

Pharmaceutical product development requires a considerable amount of preclinical assessment prior to its entry into the clinic. Once a lead drug candidate has been identified preformulation evaluations, formulation development and assessment, and preclinical studies are required. For rectal microbicide products preclinical safety, stability, and efficacy have been evaluated in *in vitro*, *ex vivo*, and animal studies. An algorithm for preclinical evaluation for vaginal and rectal microbicide products was presented by Buckheit and Buckheit (2012). This algorithm incorporates assessment in the presence of biological relevant fluids and tissues. One of the key preclinical evaluations which has been explored is the utilization of the colorectal explant system for safety and efficacy testing of rectal microbicide drug candidates and products. This model developed by Dezzutti et al. Abner et al. (2005) has been utilized to screen a large number of microbicide candidates and commonly used lubricants for their impact on the excised target tissue of interest. The model also allows for product and drug candidate evaluation in the presence of biologically relevant fluids.

### 2.1. Animal testing for rectal PrEP

Both small and large animal models have been implemented in rectal PrEP product development. Specifically animal models have been used to provide preclinical safety data as well as efficacy or proof-of-concept for PrEP strategies administered both vaginally and rectally. Rodents, rabbits, non-human primates (NHP), and sheep have been applied for such evaluation of vaginal or rectal products. One of the earliest studies which evaluated rectal product application safety was conducted by Phillips and Zacharopoulos in the mouse model (Phillips and Zacharopoulos, 1998). In this study, the rapid exfoliation induced by rectal application of N-9 was demonstrated. This effect was also shown in the NHP model in a study conducted by Patton et al. (2002). Several early vaginal HIV prevention products were evaluated for safety in the rectal compartment in the macaque. Buffergel (Patton et al., 2004), Savvy (Patton et al., 2006b) and VivaGel (Patton et al., 2006a) are among those early products with nonspecific action against HIV which were tested rectally that demonstrated safety in the macaque model. Efficacy has also been evaluated in animal models in the field. The 1% TFV gel product was the first to demonstrate efficacy in blocking HIV transmission effectively by rectal application in a mouse model (Chateau et al., 2013). Additionally, NHP models have also been utilized to evaluate the efficacy of rectal PrEP products. The first study to demonstrate efficacy in this macaque model was conducted by Tsai et al. (2003). This study showed complete protection from rectal HIV challenge after rectal administration of 1% or 2% cyanoviran gel. Additional examples of specific applications of these animal models in preclinical development are provided in the following section of this review.

#### 2.1.1. Small animal models

Rodent models are generally used in drug development to screen active compounds for efficacy and safety. Although rodents