Preventing the Sexual Transmission of HIV-1 with Topical Microbicides: Another Piece of the Equation

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(See the article by Patel et al., on pages 1394–402.)

Since the HIV-1 epidemic was first documented approximately 25 years ago, there has been an increased recognition that impacting the epidemic will require an emphasis on HIV prevention, including development of vaccines, male circumcision, preexposure prophylaxis, and treatment of sexually transmitted infections. With the increased recognition that feminization of the epidemic has occurred and that sexual transmission of HIV-1 drives the epidemic [1], a new focus in the past decade has been on the development of topical microbicide products for the prevention of HIV-1 that can be controlled by the receptive partner.

Several mechanisms of action have been targeted for the clinical development of topical microbicides. The first mechanism is to bolster the innate antimicrobial factors of the vagina. For example, BufferGel and ACIDFORM are products intended to maintain acidic vaginal pH (i.e., <4.5 pH) even after coitus. A low pH naturally inhibits enveloped viruses (e.g., HIV-1 and herpes simplex virus [HSV]) [2, 3]. A second mechanism is to block the binding and/or fusion of HIV-1 to the target cell. This mechanism uses large anionic and/or sulfonated polymers, such as PRO 2000 [4] and cellulose sulfate [5], which compete with the target cells to bind HIV. Another mechanism being pursued is interference with the life cycle of the virus with antiretroviral drugs that target the reverse transcriptase of HIV-1. The nonnucleotide reverse-transcriptase inhibitors (NNRTIs) UC781 [6] and TMC 120 are in clinical trials, as is the nucleoside reverse transcriptase inhibitor (NRTI) 9-[2-(phosphonomethoxy)propyl]adenine (PMPA) [7]. Vaginal acidifiers and fusion inhibitors need to be applied just prior to coitus, whereas the antiretroviral-based microbicides could be applied at the time of coitus, daily, or in a sustained release formulation (independent of coitus). Each approach has advantages and disadvantages, compared with the others. Despite these differences, the ultimate goal is that each will be effective against the sexual transmission of HIV-1.

Typically, a topical microbicide product is evaluated preclinically using various in vitro, ex vivo, and animal models to ensure that those products that move into clinical trials are safe and have high efficacy against a broad range of HIV-1 clades. Efficacy testing is traditionally performed by protecting a susceptible cell, tissue, or animal from a particular pathogen. For example, when products are received by the Microbicide Trials Network (http://www.mtnstopshiv.org), the product is tested to ensure that it will prevent infection with HIV-1 (including several HIV-1 clades) in peripheral blood mononuclear cells [8] and in cervical [9] and colorectal [10] explant cultures. However, this is only a piece of the equation. During coitus, semen and cervicovaginal secretions are present and may impact the activity of some or all of the topical microbicides currently being developed for clinical trials.

In the topical microbicide development field, little effort to date has been made to evaluate the influence of these mucosal secretions on the effectiveness of the topical microbicide products that are intended for use at the time of coitus.

Initial work in the topical microbicide field focused on testing each product for contraceptive activity, because some women may want to use products that are or are not contraceptive. Although this is still done, the paradigm of product evaluation has now shifted from contraception to effectiveness in the presence of mucosal secretions. Limited studies evaluating the impact of mucosal secretions on efficacy have been conducted. For example,
Keller et al. [11] confirmed that PRO 2000, a topical polyanionic microbicide, remained active in women using the product by collecting cervicovaginal lavage (CVL) fluid samples 1 h after the product was applied vaginally. CVL fluid from women using PRO 2000 significantly inhibited HIV-1 and HSV infection in vitro, whereas CVL fluid from women using a placebo did not. Extending this work, the article by Patel et al. [12] in this issue of the Journal methodically evaluates the efficacy of topical polyanionic microbicides (PRO 2000 and cellulose sulfate) on HSV infection in the presence of seminal plasma. The authors report that the anti-HSV activity of PRO 2000 and cellulose sulfate was lost when HSV was added to the receptive cells in the presence of seminal plasma. These data suggest that PRO 2000 may have less activity against HSV when used during coitus than was predicted in earlier studies. Using a murine HSV infection model, these investigators show that the efficacy of PRO 2000 is reduced by 50% when HSV is introduced with seminal plasma, compared to HSV introduced with PBS used as a negative control. The study confirms earlier work by Neurath et al. [13], who reported that the anti–HIV-1 activity of PRO 2000 and cellulose sulfate was reduced in the presence of semen. However, the antiviral activities of topical microbicides that enhance vaginal defenses (e.g., ACIDFORM) [3] or interfere with the viral reverse transcriptase (e.g., UC781) [13] do not appear to be affected by the presence of semen or seminal plasma.

Because preclinical testing has not been validated with data on clinical outcomes, uncertainty remains as to whether these tests will predict effectiveness in clinical trials evaluating topical polyanionic microbicides. Factors that may contribute to this uncertainty include the size of the viral inoculum and the presence of concomitant genital tract infections. During primary HIV-1 infection, the viral RNA level is very high [14]. Pilcher et al. [14] showed that recently infected people are more likely to transmit HIV to their sexual partner. In fact, persons with peripheral blood viral loads of >10,000 RNA copies/mL, which are significantly correlated with mucosal HIV-1 RNA levels, were more likely to transmit their infection to their sexual partner [15]. A topical polyanionic microbicide used during coitus involving a person with a high HIV-1 viral load may not be able to inactivate the infectious virus as efficiently in the presence of semen. Moreover, because HIV-1 infected cells may be just as important for the sexual transmission of HIV-1 as cell-free virus, the effect that semen may have on polyanionic microbicides with respect to the transmission of cell-associated HIV-1 is unknown. Concomitant sexually transmitted infections also increase the local (i.e., vaginal or urethral) HIV-1 RNA levels. Infection with bacterial [16–18], viral [19, 20], and protozoan [21] sexually transmitted pathogens have been shown to increase the amount of HIV-1 shed in mucosal secretions. How effective this class of topical microbicides will be in this milieu is unknown. The ongoing Phase 2b/3 clinical trials to evaluate the topical polyanionic microbicides will need to carefully determine their effectiveness in the face of these issues. This is especially important in light of the recently halted cellulose sulfate phase 3 clinical trial [22].

There are still additional pieces of the equation that remain unknown in preclinical evaluation of topical microbicides. Clearly, mucosal secretions will need to be included in preclinical evaluations to fully evaluate new and existing topical microbicide products. However, identification and/or validation of biomarkers for product safety and evaluation of product formulations need to be considered. Biomarkers for topical microbicide safety are currently being investigated by testing for inflammatory mediators [23] or alterations in natural host defense [24]. How mucosal secretions may affect preclinical evaluation of biomarkers or natural host defense has not been evaluated. For example, do mucosal secretions interfere with the detection or activity of these molecules? A comprehensive evaluation of the impact of mucosal secretions on topical microbicide formulations needs to be considered as well. When products encounter mucosal secretions, dissolution, distribution, and retention may be affected [25–27]. Further, these secretions may interact with the formulated drug as well as excipients, potentially altering the efficacy and availability of the drug. Mucosal secretions have the potential to change the ionization state of the drug and/or the excipients, which will impact critical characteristics of the products, such as the solubility or reactivity of the drug and its in vitro release profile. Additionally, it has been shown that some over-the-counter vaginal lubricant preparations have detrimental effects on colonic tissue and may actually increase the likelihood of HIV-1 transmission [28, 29]. Formulation of topical microbicides will need to take into account how mucosal secretions may affect both the toxicity and activity of the drugs and excipients [30], and work in this regard has recently begun [31, 32]. In addition to these parameters, new “bioreponsive” drug delivery systems are being designed, which can coat the tissues and release the active drug component only when exposed to semen [32].

The important finding that topical polyanionic microbicides are not as effective in the presence of semen or seminal plasma raises the issue of how products will be considered for inclusion in the development of combination products, that is, products from one class of microbicides combined with products from another. This is often done in HIV-1 therapy, in which NNRTIs and/or NRTIs are combined with protease inhibitors to provide the patients with highly active antiretroviral therapy. Topical polyanionic microbicides that, in general, are effective against several sexually transmitted infections could be combined with topical NNRTI microbicides that are effective only against HIV-1. This combined product may be more effective than either
References


