Abstract

# Microbicides: Abstracts from global literature

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## Susceptibility to genital herpes as a biomarker predictive of increased HIV risk: Expansion of a murine model of microbicide safety

Wilson SS, Cheshenko N, Fakioglu E, Mesquita PM, Keller MJ, Herold BC. Susceptibility to genital herpes as a biomarker predictive of increased HIV risk: Expansion of a murine model of microbicide safety. Antivir Ther 2009;14:1113-24.

*Background:* A crucial gap in the development of microbicides for HIV prevention is the absence of models predictive of safety. Previous studies have demonstrated an increased susceptibility to genital herpes in mice following repeated applications of nonoxynol-9 (N-9). This study was designed to explore the underlying mechanisms, focusing on the effects that N-9 has on genital tract epithelium and to apply this expanded model to evaluate the safety of microbicides that have been advanced to clinical trials. *Materials and Method:* Mice were treated intravaginally with formulated 3.5% N-9, 1% tenofovir, 0.5% or 2% PRO 2000, hydroxyethylcellulose (HEC) placebo or no treatment and the effect on herpes simplex virus 2 (HSV-2) susceptibility, epithelial cell architecture, junctional proteins and inflammation were assessed. *Results:* Mice treated with seven daily doses of N-9, but not tenofovir, PRO 2000 or HEC, were significantly more susceptible to challenge with low doses of HSV-2; confocal microscopy demonstrated increased numbers of viral particles deep within the genital tract. N-9 disrupted the epithelium with loss of tight and adherens junctional proteins. By contrast, the epithelium was relatively preserved following tenofovir, PRO 2000 and HEC exposure. Additionally, N-9, but not the other microbicides, triggered a significant inflammatory response relative to untreated mice. *Conclusions:* These findings indicate that disruption of the epithelium contributes to increased HSV-2 susceptibility and might provide a biomarker predictive of increased risk for HIV acquisition. The results are consistent with the safety outcomes of the recently completed Phase IIb clinical trial with 0.5% PRO 2000 gel, and predict that tenofovir gel will not adversely affect the genital tract.

## Multivalent benzoboroxole functionalized polymers as gp120 glycan-targeted microbicide entry inhibitors

Jay JI, Lai BE, Myszka DG, Mahalingam A, Langheinrich K, Katz DF, *et al*. Multivalent Benzoboroxole Functionalized Polymers as gp120 Glycan Targeted Microbicide Entry Inhibitors. Mol Pharm 2010;7:116.

Microbicides are women-controlled prophylactics for sexually transmitted infections. The most important class of microbicides target HIV-1 and contain antiviral agents formulated for topical vaginal delivery. Identification of new viral entry inhibitors that target the HIV-1 envelope is important because they can inactivate HIV-1 in the vaginal lumen before virions can come in contact with CD4+ cells in the vaginal mucosa. Carbohydrate-binding agents (CBAs) demonstrate the ability to act as entry inhibitors due to their ability to bind to glycans and prevent gp120 binding to CD4+ cells. However, as proteins they present significant challenges in regards to economical production and formulation for resource-poor environments. We have synthesized water-soluble polymer CBAs that contain multiple benzoboroxole moieties. A benzoboroxole-functionalized monomer was synthesized and incorporated into linear oligomers with 2-hydroxypropylmethacrylamide at different feed ratios using free radical polymerization. The benzoboroxole small molecule analog demonstrated

**How to cite this article:**
Patel P, Patel S, Marfatia YS. Microbicides: Abstracts from global literature. Indian J Sex Transm Dis 2011;32:53-6.

weak affinity for HIV-1BaL gp120 by SPR; however, the 25 mol% functionalized benzoboroxole oligomer demonstrated a ten-fold decrease in the KD for gp120 suggesting an increased avidity for the multivalent polymer construct. High molecular weight polymers functionalized with 25, 50 and 75 mol% benzoboroxole were synthesized and tested for their ability to neutralize HIV-1 entry for two HIV-1 clades and both R5 and X4 coreceptor tropism. All three polymers demonstrated activity against all viral strains tested with EC50's that decrease from 15000 nM (1500 $\mu$g mL$^{-1}$) for the 25 mol% functionalized polymers to 11 nM (1 $\mu$g mL$^{-1}$) for the 75 mol% benzoboroxole-functionalized polymers. These polymers exhibited minimal cytotoxicity after 24 hr exposure to a human vaginal cell line.

## The paradoxical effects of using antiretroviral-based microbicides to control HIV epidemics

Wilson DP, Coplan PM, Wainberg MA, Blower SM. The paradoxical effects of using antiretroviral-based microbicides to control HIV epidemics. Proc Natl Acad Sci USA 2008;105:9835-40.

Vaginal microbicides, designed to prevent HIV infection in women, are one of the most promising biomedical interventions. Clinical trials of second-generation microbicides have begun; if shown to be effective, they could be licensed within 5-10 years. Because these microbicides contain antiretrovirals (ARVs), they could be highly effective. However, there is concern that, if used by HIV-positive women, ARV resistance may evolve. By analyzing a mathematical model, we find that adherence could have both beneficial and detrimental effects on trial outcomes. Most importantly, we show that planned trial designs could mask resistance risks and therefore enable high-risk microbicides to pass clinical testing. We then parameterize a transmission model using epidemiological, clinical and behavioral data to predict the consequences of wide-scale usage of high-risk microbicides in a heterosexual population. Surprisingly, we show that reducing a participant's risk of resistance during a trial could lead to unexpectedly high rates of resistance afterward when microbicides are used in public health interventions. We also find that, paradoxically, although microbicides will be used by women to protect themselves against infection, they could provide greater benefit to men. More infections in men than in women will be prevented if there is a high probability that ARVs are systemically absorbed, microbicides are less than ~50% effective, and/or adherence is less than ~60%. Men will always benefit more than women in terms of infections prevented per resistant case; but this advantage decreases as the relative fitness of drug-resistant strains increases. Interventions that use ARV-based microbicides could have surprising consequences.

## Effect of acculturation on the acceptability of potential microbicides and sexual risk-taking

Thurman AR, Holden AE, Shain RN, Perdue S, Piper JM. Effect of acculturation on the acceptability of potential microbicides and sexual risk-taking.

*Background:* The objective was to determine the acceptability and use patterns of potential microbicides among African American (AA), Acculturated Hispanic (AH) and Less-acculturated Hispanic (LAH) women. We measured baseline sexual risk taking and the likelihood of behavioral change, given effective microbicides. *Materials and Methods:* Interview of 506 Mexican American and AA women, all of whom have a sexually transmitted infection (STI) enrolled in Project Sexual Awareness for Everyone. *Results:* The three groups reported similarly high acceptance of potential microbicides (76-83%, $P$=0.24). LAHs were most likely to report they would use microbicides covertly ($P$=0.03). Given the possibility of effective microbicides, AHs were consistently more likely to report risk disinhibition. AHs, as compared to LAHs and AAs, respectively, were most likely to report that they would not use condoms, (53% vs. 33% vs. 30%, $P<$ 0.001), would have a one-night stand (18% vs. 8% vs. 6%, $P$=0.02), or would have sex with a man before they got to know him (18% vs. 8% vs. 6%, $P$=0.01). AHs were also most likely to say they would or probably would change from baseline safe sexual practices to unsafe sexual behaviors if potential microbicides were available. Age was controlled in the analysis as AHs were younger than AAs and LAHs. *Conclusion:* Future microbicides were acceptable among this at risk cohort. Acculturation was a predictor of risk disinhibition and should be considered when tailoring STI prevention messages, given the advent of effective microbicides.

## Comparative evaluation of virus transmission inhibition by dual-acting pyrimidinedione microbicides using the microbicide transmission and sterilization assay

Watson KM, Buckheit CE, Buckheit RW. Comparative Evaluation of Virus Transmission Inhibition by Dual-Acting Pyrimidinedione Microbicides Using the Microbicide Transmission and Sterilization Assay. Antimicrob Agents Chemother 2008;52:2787-96.

In the absence of a fully effective human

immunodeficiency virus (HIV) vaccine, topical microbicides represent an important strategy for preventing the transmission of HIV through sexual intercourse, the predominant mode of HIV transmission worldwide. Although a comprehensive understanding of HIV transmission has not yet emerged in the microbicide field, it is likely the result of rapid infection of monocyte-derived cells in the vaginal mucosa by CCR5-tropic viruses. Inhibition of HIV transmission requires agents that prevent entry, fusion, reverse transcription or other preintegrative replication events or agents which directly inactivate HIV or modulate the target cells to render them uninfectable. *In vitro* assays typically used to evaluate the ability of a microbicide to prevent virus transmission use epithelial or human osteosarcoma-derived cells or immune cells more relevant to the development of anti-HIV therapeutic agents and quantify virus production at short-time intervals following infection. We have developed a microbicide transmission and sterilization assay (MTSA) to more sensitively and quantitatively evaluate virus transmission in cell culture in the presence of microbicidal compounds. Results obtained with the MTSA demonstrate that the inhibitory capacity of microbicides is often overestimated in short-term transmission inhibition assays, while some compounds yield equivalent inhibitory results, indicating a biological relevance for the MTSA-based evaluations to identify superior potent microbicides. The MTSA defines the concentration of the microbicide required to totally suppress the transmission of virus in cell culture and may thus help define the effective concentration of the microbicide required in a formulated microbicide product.

## Chemokine analogs show suitable stability for development as microbicides

Cerini F, Landay A, Gichinga C, Lederman MM, Flyckt R, Starks D, *et al*. Chemokine Analogues Show Suitable Stability for Development as Microbicides. J Acquir Immune Defic Syndr 2008;49:472-6.

PSC-RANTES, a human chemokine analog, has shown promise as a candidate microbicide, but because it contains non-natural structures that necessitate chemical synthesis steps, it is not suitable for production at a feasible cost and scale for general distribution in developing countries. We have recently developed 2 new fully recombinant chemokine analogs, 5P12-RANTES and 6P4-RANTES, which show equivalent anti-HIV activity to PSC-RANTES. In this study, we tested the stability of these molecules under conditions related to use as microbicides. Our results suggest that stability issues will not present a major obstacle to the further development of these promising molecules as microbicides

## Using objective markers to assess participant behavior in HIV prevention trials of vaginal microbicides

Mauck CK, Straten A. Using Objective Markers to Assess Participant Behavior in HIV Prevention Trials of Vaginal Microbicides. J Acquir Immune Defic Syndr 2008;49:64-9.

The need to verify participant behavior exists in any study in which behavior may affect outcomes. In vaginal microbicide trials, the act of having sex and the use of study products and condoms all affect the risk of acquiring HIV/sexually transmitted infections (STIs). Until now, these behaviors have been assessed using self-reports. But self-reports are limited by participant cooperation in answering questions, imperfect recall and social desirability biases. Biomarkers are increasingly being used in medicine to reduce the time and resources needed to bring a drug to market. The use of biomarkers in vaginal microbicide trials has been proposed as a means of assessing factors that affect the risk of sexual acquisition of HIV/STIs, namely, the presence of pre-existing infection, cervicovaginal inflammation and the presence of HIV/STIs. Biomarkers for some of these already exist. What are needed are validated markers of behaviors that might affect risk, namely, markers for sexual behavior and for the use of study products and condoms. Validating and working out the logistics of collecting such markers in large trials will be a challenge. But finding objective markers for behavior may help improve adherence measurement during a trial and is a rate-limiting step in the field of vaginal microbicides. Resources and funding should be mobilized to develop and validate markers of sexual behavior and product use as a high priority in vaginal microbicide research.

## Safety and pharmacokinetics of dapivirine delivery from matrix and reservoir intravaginal rings to HIV-negative women

Nel A, Smythe S, Young K, Malcolm K, McCoy C, Rosenberg Z, *et al*. Safety and Pharmacokinetics of Dapivirine Delivery From Matrix and Reservoir Intravaginal Rings to HIV-Negative Women. J Acquir Immune Defic Syndr 2009;51:416-23.

Vaginal microbicides for the prevention of HIV transmission may be an important option for protecting women from infection. Incorporation

of dapivirine, a lead candidate non-nucleoside reverse transcriptase inhibitor, into intravaginal rings (IVRs) for sustained mucosal delivery may increase microbicide product adherence and efficacy compared with conventional vaginal formulations. Twenty-four healthy HIV-negative women of 18-35 years of age were randomly assigned (1:1:1) to dapivirine matrix IVR, dapivirine reservoir IVR or placebo IVR. Dapivirine concentrations were measured in plasma and vaginal fluid samples collected at sequential time points over the 33-day study period (28 days of IVR use, 5 days of follow-up). Safety was assessed by pelvic/colposcopical examinations, clinical laboratory tests and adverse events. Both IVR types were safe and well tolerated with similar adverse events observed in the placebo and dapivirine groups. Dapivirine from both IVR types was successfully distributed throughout the lower genital tract at concentrations over 4 logs greater than the EC50 against wild-type HIV-1 (LAI) in MT4 cells. Maximum concentration (Cmax) and area under the concentration-time curve values were significantly higher with the matrix than reservoir IVR. Mean plasma concentrations of dapivirine were <2 ng/mL. These findings suggest that IVR delivery of microbicides is a viable option meriting further study.

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