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JAC Advance Access originally published online on March 2, 2005

Journal of Antimicrobial Chemotherapy 2005 55(4):420-423; doi:10.1093/jac/dki056

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Leading article

Topical microbicides for the prevention of genital herpes infection

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Genital herpes is one of the most prevalent sexually transmitted infections worldwide and is the most common cause of genital ulcers. Despite increased public awareness and the initiation of efforts to prevent transmission, the prevalence of herpes simplex virus (HSV) type 2 continues to increase. What makes HSV so difficult to control is that most sexual and perinatal transmission occurs during unrecognized or asymptomatic shedding. The impact of genital herpes as a public health threat is amplified because of its epidemiological synergy with HIV/AIDS. Thus, there is an urgent need for novel prophylactic methods, such as topical microbicides designed for genital application, to prevent both HSV and HIV transmission. Several candidate microbicides are being advanced to clinical trials based on *in vitro* activity and animal studies. These include compounds that inactivate virus directly, those that enhance innate immunity, and drugs that block viral binding and entry. A more vigorous evaluation of the safety of these and other candidate topical microbicides in development should include assessment of the impact of repeated application on innate host defences in the genital tract.

Keywords: HIV , HSV , innate immunity

Forty-five million individuals and one in four women of child-bearing age in the USA are infected with herpes simplex virus type 2 (HSV-2), the serotype responsible for the majority of genital herpes infections.^{1,2} Population-based studies in developing countries show HSV-2 seroprevalence rates ranging from 60 to 80% in young adults.³ Asymptomatic viral shedding episodes are a major factor in viral transmission.³ The impact of genital herpes as a public health threat is augmented because epidemiological studies clearly demonstrate a strong link to the HIV epidemic. More than 30 epidemiological studies have demonstrated that HSV-2 is associated with a two- to four-fold increased risk of HIV-1 acquisition.⁴ At all levels of plasma HIV-1 RNA in the source partner, the probability of HIV-1 transmission per sexual contact was five-fold greater if the susceptible partner was HSV-2 seropositive.⁵ Studies suggest that both mucosal and serum HIV-1 RNA levels may be higher during HSV-2 replication, including subclinical reactivations.⁶ These observations support the notion that prophylactic treatment of HSV-2 could have a substantial public health impact on both HSV and HIV transmission, and have led to intervention trials to determine the effect of aciclovir or valaciclovir prophylaxis on HIV transmission.⁴

Genital herpes may facilitate HIV acquisition by disrupting the epithelial barrier, thereby increasing exposure of virus to target cells. Even in the absence of genital ulcers, HSV may modify the mucosal environment by activating proinflammatory or suppressing protective factors. Proinflammatory cytokines are capable of stimulating HIV replication⁷ and defensins and secretory leucocyte inhibitor (SLPI) have been shown to inhibit HIV infection *in vitro*.⁸⁻¹⁰ We recently found that *in vitro* exposure of cells resident in the female genital tract to HSV-2 leads to an increase in the proinflammatory cytokines and a marked reduction in SLPI. This cellular response is independent of viral replication, as similar results are obtained in the presence of aciclovir. Culture supernatants obtained from HSV-exposed, but not mock-exposed, macrophages induce activation of HIV-1 replication in latently infected U1 cells.¹¹ These preliminary findings support a model that may contribute to the epidemiological observations of enhanced HIV acquisition or replication in the setting of HSV infection.

Consistent and correct use of male condoms reduces transmission of HSV from men to women.¹² Female condoms may also protect against HSV, although this has not been confirmed by clinical studies. However, the lack of acceptance and inconsistent use is a major barrier to condom effectiveness. While there have been great strides in vaccine development, a fully protective vaccine for genital herpes or HIV is unlikely to be available for many years. Thus, there is a vital need for novel prophylactic methods to prevent HIV and HSV transmission. Topical microbicides designed for vaginal application may provide a realistic method of intervention that can be distributed worldwide. Ideally, some will protect against unintended pregnancy; others will allow conception, and women will be empowered by user-controlled products.

Candidate microbicides in development include: (i) surfactants or detergents that directly inactivate HSV; (ii) products that enhance the natural defences of the vaginal mucosa; and (iii) compounds that prevent viral attachment and/or fusion with host cells. Compounds that directly inactivate the virus include nonoxynol-9 (N-9), benzalkonium chloride, SDS and C31G. N-9, in particular, has been widely used as a spermicide and is still being evaluated by some as a candidate microbicide. However, the doses of N-9 required for antiviral activity are associated with significant inflammation and cytotoxicity.^{13,14} These *in vitro* findings are consistent with the results of a multicentre international placebo-controlled Phase III trial, which demonstrated a higher risk of acquisition of HIV following frequent N-9 use relative to placebo.¹⁵ While the preclinical data indicate that SDS and C31G have less cytotoxicity than N-9,¹⁶ their clinical safety and efficacy have yet to be established, and there are concerns that frequent use of any surfactant or detergent will have a deleterious effect on the vaginal environment.

Products that may enhance the natural vaginal defences include acid-buffering agents and synthetic defensins or related antimicrobial peptides. The human vagina has a pH range of 3.5–4.5, which is presumed to inactivate sexually transmitted infection (STI) pathogens. This acidity is neutralized by alkaline semen for up to 6 h following intercourse. The notion that acidic pH may be protective has led to the development of acid-buffering products, such as BufferGel (ReProtect; buffers to a pH ≈5.35) or Acidform (Instead; buffers to a pH ≈4.5) as candidate vaginal microbicides. Surprisingly, the extent of antiviral activity and the mechanism by which acid prevents HIV or HSV infection have not been systematically evaluated. We found that following exposure of clinical or laboratory isolates of HSV-2 to a pH of 4.5, the HSV-2 titre is reduced by ≈90%. Mechanistic studies indicate that acidic pH modifies the viral envelope and prevents viral entry. To determine whether this degree of anti-HSV activity is sufficient to prevent HSV transmission, the ability of Acidform to prevent HSV infection in a murine model of genital herpes was evaluated. Mice were pretreated with Acidform or a vehicle gel (control group), and 15 min later intravaginally challenged with a clinical isolate of HSV-2. Acidform protected 80% of mice from genital herpes compared with none of the control animals. The protective activity exceeded that predicted by its *in vitro* anti-HSV activity. These results suggest that Acidform may offer substantial protection against HSV infection itself, and may be an optimal vehicle for formulation of acid-stable topical microbicides to prevent acquisition and transmission of HSV and other STI (Tuyama, A. G., Carlucci, M. J., Li, J. H., Cheshenko, N., Goldberg, C., Keller, M. J. and Herold, B. C., unpublished results).

Defensins are small (< 4 kDa) cationic molecules that protect the host against microbial invasion at the mucosal barrier.¹⁷ The human neutrophil peptides 1–3 inhibit both laboratory and clinical isolates of HIV and HSV *in vitro*.^{17,18} In addition to these neutrophil defensins, epithelial cells secrete two additional α -defensins, HD-5 and HD-6. We found that synthetic HD-5 and HD-6 (gifts from W. Lu, Institute of Human Virology, Baltimore,

MD, USA) substantially inhibit HSV-2 infection. The female reproductive tract is also a significant site of human β -defensin (hBD) production.¹⁹ While hBD2 and hBD3 have been shown to inhibit HIV-1 replication,⁸ no anti-HSV activity has been reported. We hypothesize that defensins, which are present in cervical secretions, contribute to the innate defences against HSV-2. Their broad-spectrum antimicrobial properties make human defensins possible candidate topical microbicides; however, technical limitations related to their size and complex structures have impeded such development.

Given the ability of HSV to establish latency and reactivate frequently, the ideal microbicide to prevent HSV transmission should prevent the establishment of infection. Thus, compounds that prevent entry into target cells may be most advantageous. PRO 2000, Carraguard, polystyrene sulphonate and cellulose sulphate are sulphated or sulphonated polymers that interact directly with viral envelope glycoproteins (including glycoprotein B of HSV-2 and gp120 of HIV) and competitively inhibit viral attachment and prevent entry.²⁰ These products exhibit little or no cytotoxicity even at high doses, do not disrupt normal vaginal flora and do not induce a significant inflammatory response. However, the concentration of SLPI, which may be important in protecting the host from HIV and HSV, is substantially reduced following acute or chronic exposure of human epithelial cells to sulphonated/sulphated polymers *in vitro*.²⁰ It remains to be determined whether the reduction of SLPI observed *in vitro* would increase susceptibility to HSV, HIV or other STI. A potential limitation of this class of compounds is that they do not actually kill the pathogen, and thus optimally might be used in combination with other candidate agents. Several of these compounds are in Phase II or III clinical trials.

Additional compounds in development that are structurally distinct, but also block HSV (and HIV) binding and entry, include sulphuric acid modified mandelic acid (SAMMA) and SpM8CHAS, a persulphated amphiphilic polymer. SAMMA is a polymer of phenylacetic acid synthesized by condensation of mandelic acid. SAMMA exhibits an excellent safety profile and is active against HSV, HIV, bovine papilloma virus and *Neisseria gonorrhoeae*.²¹ Unlike many of the other compounds being developed, it does not contain sulphations and is not a surfactant. Importantly, SAMMA has no deleterious effect on lactobacillus and, following exposure of human cervical epithelial cells *in vitro* to SAMMA, no induction of proinflammatory cytokines was observed, nor was there a reduction in SLPI levels.²⁰ SAMMA also retains its antiviral activity in the presence of cervical secretions and in an acidic environment.

A series of persulphated molecular umbrella compounds containing different numbers of amphiphilic units composed of cholic acid, spermidine and spermine were evaluated for potential development as topical microbicides. Among those initially evaluated, SpM8CHAS exhibited the most substantial anti-HIV and anti-HSV activity.²² Mechanistically, SpM8CHAS may differ from sulphonated/sulphated polymers because it crosses phospholipids bilayers, possibly contributing to its ability to inhibit HSV penetration at the same concentrations as its blocks binding. SpM8CHAS targets both the virus and the cell. In contrast, the sulphated/sulphonated polymers primarily target the viral envelope and primarily inhibit viral binding. SpM8CHAS and related compounds are being explored as a novel class of topical microbicides.

In addition to its spectrum of microbicidal activity, the ideal topical formulation must not interfere with innate genital tract host defences. A valuable lesson learned from the N-9 trials is that the use of topical microbicides may alter the mucosal environment and, paradoxically, increase susceptibility to HIV or HSV. Recent work from our laboratory demonstrates that cervicovaginal secretions protect against HSV and that α -defensins and SLPI play important roles in this innate defence (John, M., Keller, M. J., Fam, E. H., Cheshenko, N., Hogarty,

K., Kasowitz, A., Wallenstein, S., Carlucci, M. J., Tuyama, A., Lu, W., Klotman, M. E., Lehrer, R. I. and Herold, B. C., unpublished results). Thus, preclinical assessment of the safety profile of microbicides should also include evaluation of the impact of repeated application on these critical innate defences. We are currently conducting a pilot clinical study to assess the impact of repeated daily intravaginal application for 14 days of 0.5% PRO 2000 Gel compared with placebo on mediators of mucosal immunity present in cervicovaginal secretions post-application.

The murine model of genital herpes offers a unique opportunity to evaluate microbicides for efficacy,^{23,24} safety and impact on the vaginal mucosal milieu. The murine model provides clinical (symptoms of disease), virological (isolation of virus from the genital tract) and immunological (recruitment of inflammatory cells, activation of proinflammatory cytokines or changes in mediators of mucosal immunity such as defensins and SLPI) endpoints for evaluating candidates. Advantages of this model include low cost, convenience and the wide array of reagents. Furthermore, murine homologues for relevant mucosal factors (defensins, SLPI) have been identified. However, there are limitations to this model. First, the murine herpes model does not replicate human disease, as illustrated by the requirement for progesterone treatment for consistent infection and the high rates of hind-limb paralysis and death following vaginal challenge. Secondly, the need for hormonal manipulation may be an important variable, as hormones have been repeatedly shown to influence innate and adaptive immune responses.^{25,26} In an effort to optimize this model we have modified the protocol from earlier published studies.^{24,27} First, we use only a single dose of medroxyprogesterone, whereas some studies used multiple or higher doses. Secondly, the inoculum (10^5 pfu/mouse) and viral strains used in our studies (including clinical isolates) are highly virulent, and the primary endpoints are genital lesions and death rather than the presence of infectious virus in vaginal washes.²⁷ This may provide a more stringent model to test the efficacy of candidate microbicides. Thirdly, we use a larger volume of both the microbicide gel and viral inoculum (40 μ L of gel and 20 μ L of virus), which may promote better spreading within the vaginal compartment. In addition, the interval between microbicide placement and viral challenge is longer (15–60 min), whereas some of the earlier studies used an interval as short as 20 s.^{24,27} Using this protocol, we have evaluated and compared several different candidate microbicides. In addition, studies are in progress to assess the impact of repeated applications of microbicides on the mouse cervicovaginal environment. We recognize that the ability of any model to predict the safety and efficacy of a candidate microbicide will only be determined when clinical trials are completed.

In summary, genital herpes is a critical global health priority because of its devastating impact on young adults and infants and its association with the HIV/AIDS epidemic. Topical microbicides that block transmission at the mucosal surface may provide a realistic method of intervention for worldwide distribution. Currently, there are several candidate drugs being advanced to clinical trials that block both HSV and HIV infection by inhibiting binding and entry *in vitro*. Whether blockade of entry will be sufficient to prevent sexual transmission or whether a combination strategy targeting multiple steps in the viral life cycle will be required is not yet known. Importantly, before embarking on large-scale clinical trials, more extensive evaluation of candidate microbicides, including assessment of the impact on innate defences, is warranted. Assessment of the safety and mucosal response to microbicides should be accrued from several different models including cell and organ cultures, animal models and, most importantly, pilot clinical studies.



Acknowledgements

This work was supported by Public Health Service Grants AI37940, HD41763, HD43733 and MO1-RR-0071.

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