

Condom Use and the Prevention of Genital Herpes Acquisition

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CURRENT KNOWLEDGE ON THE EFFICACY OF CONDOMS IN THE PREVENTION OF HERPES SIMPLEX VIRUS TYPE 2 ACQUISITION IS SUMMARIZED IN THIS EXPERT REVIEW BY DRs COREY CASPER AND ANNA WALD

KEY WORDS

■ *HERPES SIMPLEX VIRUS TYPE 2 (HSV-2)* ■ *GENITAL HERPES*
■ *DISEASE PREVENTION* ■ *CONDOM*

SUMMARY

Genital herpes establishes a lifelong infection associated with significant morbidity and mortality. In contrast to other sexually transmitted infections (STIs), herpes simplex virus type 2 (HSV-2) may be transmitted to sexual partners many years after initial infection and at times when the source partner may be asymptomatic. Consequently, HSV-2 has become one of the most common STIs worldwide. Current therapies suppress but do not eradicate infection. While many studies have examined the degree of protection offered through the use of condoms against HSV-2 acquisition, findings have been either difficult to interpret or inconsistent. However, the body of evidence supports the efficacy of condoms in preventing HSV-2 infection among women. More data are required for HSV-2 prevention in men. The infrequent use of condoms during pregnancy, coupled with the high incidence of complications associated with HSV-2 acquisition at this time, warrants efforts to improve condom use among male partners of pregnant women at risk of HSV-2 infection.

Introduction

HERPES SIMPLEX VIRUS TYPE 2 (HSV-2) establishes a chronic infection in humans for which there is no cure. Most people who acquire HSV-2 do so at an early age, often by the time they reach 30,¹ and must live with a wide variety of symptoms throughout their lifetime. Primary infection typically presents with localized pain, pruritis, ulcerations, fevers and malaise, and more severe complications such as neurological involvement, including meningitis, are not uncommon. Recurrences of HSV-2 are frequent, with over 90% of primary infections leading to recurrent episodes in the first year of infection, with a median of four annually.² Between clinical recurrences, most people shed the virus asymptomatically; they are infectious at those times. Additionally, ulcerative sexually transmitted infections (STIs) have been associated with higher rates of HIV acquisition, and HSV-2 infection may hasten the progression of HIV disease.^{3–6} The persistence of HSV-2 and the absence of symptoms during viral shedding afford many opportunities to transmit the infection, both through sexual contact and during delivery of newborns. This has led to HSV-2 being one of the most prevalent STIs worldwide.^{7–17} Additionally, herpes simplex virus type 1 (HSV-1) has been increasingly

recognized as a cause of genital herpes.^{18,19}

Given the morbidity associated with HSV-2 infection and the absence of curative therapy, strategies aimed at prevention of disease acquisition warrant increasing attention from healthcare practitioners and public health leaders.²⁰ The administration of antiviral therapy to persons infected with HSV-2 results in decreased viral shedding,²¹ but has not yet been shown to decrease disease transmission to partners. There is active research aimed at development of candidate vaccine constructs against HSV-2.^{22–33} Early clinical trials have been disappointing,^{34,35} though a recombinant glycoprotein vaccine may offer partial protection against HSV-2 acquisition in seronegative women.³⁶

Campaigns aimed at behavioural change have been a cornerstone of STI prevention. Increased awareness of STIs through education and testing, avoidance of high-risk behaviours and practising 'safer sex' have been effective in reducing the incidence of gonorrhoea, HIV and syphilis. The US Centers for Disease Control and Prevention recently established a prevention agenda for genital herpes, which included all of these activities.^{37,38} It states also: 'The consistent and correct use of latex condoms can help protect against infection. However, condoms do not provide complete protection'. A recent National Institutes of Health workshop concluded: '...the limitations in epidemiological study designs and the lack of primary outcome measurements...prevented the Panel from forming any conclusions about the effectiveness/ineffectiveness of correct and consistent condom use in reducing the risk of genital herpes infection'.³⁹ This article will review the published literature describing the efficacy of condoms in the prevention of HSV-2 acquisition.

Condoms

A wide variety of barrier contraceptives are currently available, with the latex condom most frequently advocated for use in prevention of STIs. Condoms are now available as both female and male versions, and may be coated with lubricant, spermicide or anti-infective agent.

The latex condom provides a mechanical barrier to infectious agents. The efficacy of the barrier in preventing STIs depends on the permeability of the latex. In their function as a contraceptive, condoms would have to be impermeable to spermatozoa, which are approximately 3000 nm in size. HSV-2 is considerably smaller than spermatozoa, at about 160 nm,⁴⁰ and HIV is smaller still at 125 nm (Figure 1). Electron microscopy of male condoms shows an

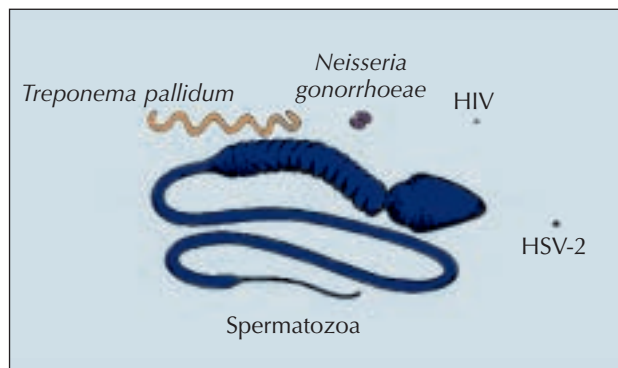


Figure 1:
Relative sizes of human spermatozoa and selected sexually transmitted infectious agents. HSV-2, herpes simplex virus type 2. (Adapted from McNeill et al.⁴² Courtesy of Paul Feldblum/Family Health International.)

absence of full-thickness pores, but occasional pits secondary to imperfections in manufacturing.⁴¹ Permeability depends not just on the size of any pores in the latex barrier, but also variables such as the shape of the infectious agent, surface tension, temperature, pressure and pH of the environment.⁴²

Sophisticated *in vitro* models have been developed to determine the permeability of latex condoms to infectious agents.^{43–46} These models typically instil an infectious agent into the condom, which is suspended in culture medium, agitate the condom, and then process the culture medium to identify infectious agents that have crossed the latex barrier. Two studies have demonstrated that no HSV-2 is recoverable by viral culture in media protected from the virus by a latex condom barrier.^{44,46} Three studies have demonstrated that HSV-2 was uniformly killed by chemical barriers to contraception and infection, including copper cream, nonoxynol-9 and *p*-diisobutylphenoxypolyethoxyethanol, that often coat condoms.^{44,47,48} Studies have found that the integrity of condoms distributed in the USA and Europe is sound, a result of strict quality control and infrequently found manufacturing defects.⁴²

While laboratory studies of the latex condom may indicate that it is efficacious in preventing HSV-2 transmission, several variables are introduced when the condom is used in the 'real world'. Men shed HSV-2 from penile epithelial cells, which are nearly completely covered by the proper application of a latex condom, and therefore may protect sexual partners from disease acquisition. Women, on the other hand, shed HSV from a greater mucosal area in the genital region, which may afford more opportunities to transmit the virus to partners, despite the correct use of condoms. 'Condom failure' may result from the incorrect use of condoms (inconsistent use, failure to completely unroll condom, unrolling condom completely prior to application, opening packaging with sharp objects, using non-compatible lubricants), excessive stress on the condom (traumatic sexual behaviour, large penile size, storage in excessive heat) or slippage of the condom from the penis during sexual activity.⁴² Studies investigating the *in vivo* efficacy of condoms in preventing HSV-2 acquisition have proved challenging.

The Ideal Condom Efficacy Trial

The ideal trial to determine the efficacy of condoms in preventing infection with HSV-2 would have several characteristics. Accurately identifying a group of HSV-2-negative but susceptible persons is of paramount importance. The close follow-up of these participants to mark the time of acquisition of the infection and the description of condom use at the time of infection is equally essential. Also, the control of other factors that might distort a relationship between condom use and HSV-2 acquisition, such as frequency of sexual activity,

presence of active lesions on the partner, use of antiviral therapy, etc. would be necessary. Unfortunately, such a study is difficult to design and execute. Although a randomized, controlled trial of condom use would be the most definitive study design, ethical concerns would make such a trial unfeasible, leaving a cohort study the best alternative.

As yet, almost all published studies on condoms and HSV-2 infection have been retrospective or cross-sectional, as such studies are completed with greater expediency and lower cost. They do not, however, allow definitive establishment of the temporal relationship between HSV-2 acquisition and the use of condoms. For example, if people infected with HSV-2 used more condoms after infection to protect a partner from acquiring the disease, a retrospective survey might conclude that increased condom use was associated with HSV-2 infection.

Bias also plays a role in distorting what may be the true relationship between condom use and HSV-2 acquisition. Participants enrolled in a study of HSV acquisition may incorrectly report their use of condoms, either because they may not remember correctly or because they were trying to please the investigators (a phenomenon known as 'social desirability bias').^{49–51} As evidence of this phenomenon, biological end-points of STI detection do not always correlate with reported history of condom use. In one study at a Baltimore STI clinic, participants who reported 'never using condoms' had the same incident rate of gonorrhoea, chlamydia, syphilis or trichomoniasis as those who reported 'always using condoms'.⁵² Despite these limitations, several studies of condom use and HSV-2 acquisition have been completed over the past decade. (A systematic review of the literature was performed by searching the MEDLINE database for the medical subject headings 'herpes simplex' and 'contraceptive devices' and the keywords 'incidence' or 'prevalence'. References from retrieved articles, books and meeting reports were reviewed for additional information. No data on the efficacy of the female condom in the prevention of genital herpes acquisition was found in the literature, resulting in a focus on the male condom for this review.)

Studies of Prevalent HSV-2 Infection

To date, no published study has been designed specifically to determine the degree of protection offered by condoms in the acquisition or transmission of HSV-2. Several trials have been published comparing behaviours reported by HSV-2-positive versus HSV-2-negative participants, including the use of condoms.

STI CLINICS

The highest prevalence of HSV-2 infection has been found among persons attending STI clinics, making this an opportune population in which to study risk factors for HSV-2 acquisition. In one study, women attending an STI clinic in Alabama, USA, were asked about their use of barrier contraception with vaginal sex within the month prior to interview.⁵³ Women categorized as 'consistent' versus 'inconsistent' users had similar rates of HSV-2 seroprevalence of 64% and 66%, respectively. Over 60% of the study participants in both groups had a history of genital warts, gonorrhoea, syphilis, chlamydia or trichomoniasis. Clearly, retrospective accounts of condom use in the month prior to study entry are not a sufficient marker of risk for a chronic viral infection. A more recent study from a Swedish STI clinic found that condom use among HSV-2-positive individuals did not lead to a lower seroprevalence of HSV-2 among their partners, although no numbers were given.⁵⁴ Similarly, one study of HSV-2 cites unpublished data in which prostitutes who report 'always using condoms' have a similar seroprevalence of HSV-2 to those reporting 'never using condoms'.¹²

PRIMARY CARE CLINICS

Women attending a primary care clinic in Seattle, USA, were more likely to be HSV-2 seropositive if they used condoms less frequently (odds ratio [OR] 4.6, 95% confidence interval [95% CI] 1.0–10.7 for condom use with 0–10% of partners versus 91–100%).⁵⁵ This finding was associated only with condom use by percentage of partners, not by percentage of sexual encounters. However, women with multiple partners were less likely to report condom use, suggesting that the observed effect of condoms is related to the degree of sexual activity and exposure to HSV-2, rather than condom use *per se*. Among men, no association between reported condom use and HSV-2 seroprevalence was noted.

SPECIAL POPULATIONS

The risk factors associated with prevalent HSV-2 infection have been investigated in a number of other special populations. Young adolescents in developed countries have been receiving increasing attention, in recognition of the decrease in the age of sexual debut and frequent high-risk sexual behaviour. Adolescents detained in a juvenile detention facility in California, USA, were found to have no significant differences in HSV-2 prevalence whether they reported using condoms with '≥50% of sexual encounters' or '≤50% of sexual encounters'.⁵⁶ Among adolescents in Seattle, WA, USA, males and females aged 14–19 years who were HSV-2 seropositive were more likely to report not using a condom with their last sexual encounter than those who were HSV-2 seronegative (OR 1.5, 95% CI 0.7–3.3), although this finding was not statistically significant.⁵⁷ Female prisoners in Australia were found to have an HSV-2 seroprevalence of 58%, and those who reported using condoms 'occasionally or never' were found to be less likely to be HSV-2 seropositive in univariate analysis (OR 0.3, 95% CI 0.1–0.9).⁹

Additionally, female prisoners were more likely to use condoms if they did not report a 'stable partner', leading the authors to speculate that 'the use of condoms may have been a marker of selecting higher risk sexual partners'. The association between condom use and HSV-2 infection was not seen in male prisoners.

DEVELOPING WORLD

Risk factors for prevalent HSV-2 infection have also been studied in developing nations, with two studies evaluating the use of condoms among study participants. Among women in Brazil, those who were HSV-2 seropositive were less likely to report 'ever using condoms' (OR 0.2, 95% CI 0.03–0.8).⁵⁸ The opposite was found to be true in Filipino women, where participants who were HSV-2 seropositive were more likely to report ever using condoms (OR 2.7, 95% CI 0.8–9.4), although the finding was not statistically significant. Of interest was the low HSV-2 seroprevalence among Filipino as compared with Brazilian women (9% versus 42%), and the absence of 'high risk' sexual behaviour in the Philippines – 90% of Filipino women reported having only one lifetime sexual partner. Similarly, monogamous women in Costa Rica were less likely to report condom use if they were HSV-2 seropositive (seroprevalence of 44.3% among women who reported never using condoms versus 33.5% for women using condoms with a partner for 1–23 months, versus 28.9% for women using condoms for ≥24 months).⁵⁹

Young male conscripts entering the army in Thailand were found to have an HSV-2 seroprevalence of 14.9%.⁶⁰ The seroprevalence of HSV-2 was higher among men who reported having had sex with a female sex worker, at 18.2%. In this high-risk subgroup of conscripts, higher HSV-2 seroprevalence was found in those who used condoms versus men who never used condoms. This finding was also true of HIV seroprevalence, suggesting that perhaps these men modified their sexual behaviour according to the degree of perceived risk of STI acquisition.

In summary, differences in methodology and limitations in study design render the data on condom use from studies of prevalent HSV-2 infection difficult to interpret.

Studies of Incident HSV-2 Infection

There are substantially fewer investigations focusing on condom use in persons who newly acquire HSV-2. A serological survey among factory workers in Zimbabwe revealed that the incidence of HSV-2 was the same among workers who did or did not receive intensive HIV-prevention education advocating the use of condoms.¹¹ Unfortunately, no data on the actual use of condoms or the efficacy of the programme in preventing HIV were available.

Sexual partners who are serodiscordant for HSV-2 provide a convenient opportunity to investigate the incidence of infection. Three discordant couple studies have been published that have assessed the effect of condom use on HSV-2 acquisition.

Among heterosexual couples in Seattle and New Mexico, USA, where one partner was infected with HSV-2 and not taking suppressive antiviral therapy, the annual rate of infection in couples reporting the use of barrier methods of contraception was nearly one-third of that of couples who did not use such methods (5.7% versus 13.6%), although this finding was not statistically significant.⁶¹ Further analyses on types and frequency of use of barrier methods of contraception were not provided.

A small study from Los Angeles, USA, followed 29 HSV-2 serodiscordant couples for a mean of 16 months and documented four seroconversions.⁶² All seroconverters were women; none used condoms during times that the source partner was asymptomatic.

Recently, a large study of over 500 serodiscordant couples enrolled in a candidate HSV-2 vaccine trial was published.⁶³ Participants were followed for 18 months with regular questionnaires assessing the frequency of sexual acts, condom use, use of aciclovir and sexual activity in the presence of active genital lesions, and with HSV-2 serologies. Participants were categorized as using condoms in more or less than 25% of sexual activity. In multivariate analysis, adjusted for sex, age, condom use and number of sex acts per week, participants using condoms were less likely to acquire HSV-2 (hazard ratio [HR] 0.25, 95% CI 0.07–0.88). The efficacy of condoms was especially marked among women (HR 0.085, 95% CI 0.01–0.67).

Neonatal Herpes

One of the most severe sequelae of HSV-2 infection is neonatal herpes, which is associated with significant infant morbidity and mortality.⁶⁴ The incidence and complications of neonatal herpes are greatest among women who acquire HSV-2 at the end of pregnancy.^{65–67} Therefore, prevention of HSV-2 acquisition in pregnant women is of paramount importance, and the use of condoms might confer safe and effective protection. Unfortunately, condom use among stable, monogamous, heterosexual relationships is infrequent. Only four of 107 HSV-2 discordant couples seen in our clinic used condoms consistently for prevention of HSV-2 transmission, despite regular counselling. Condom use was more likely among couples who used it also as a means for birth control. Similarly, data from high-risk women show that the frequency of condom use during pregnancy declines as potential pregnancy ceases to be a concern.^{68,69} This observation is supported by studies that demonstrate a significantly lower frequency of condom use in women who take oral contraceptives compared with those who rely on barrier methods for pregnancy prevention.^{70–75}

Conclusions

Preventing the acquisition of genital herpes remains the best strategy for reducing the morbidity and mortality associated with this chronic infection. While antiviral medications and vaccines may eventually prove effective in preventing HSV transmission, no current therapy has been shown to be reliably protective. Altering sexual behaviours represents a cost-effective and safe measure that may significantly reduce new infections. Consistent and correct use of latex condoms appears to protect women from HSV-2 infection, and should be emphasized in pregnant women at risk of HSV-2 to prevent neonatal herpes. Future research will

need to focus on additional interventions and on interventions which will protect men from acquiring genital herpes.

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Received for publication: 2 October 2001

Accepted for publication: 9 November 2001

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American Herpes Foundation (AHF) Research Award Winners 2001

The AHF is proud to announce the 2001 winners of two Research Awards for distinguished accomplishment or achievement by new researchers in the herpes area.

WINNER OF THE AHF RESEARCH AWARD 2001

Deepak Shukla, PhD, Assistant Professor, Molecular Microbiology and Immunology, University of Missouri-Columbia, USA, for his research into herpes simplex virus pathogenesis.

WINNER OF THE AHF GERTRUDE B ELION RESEARCH AWARD 2001

Linda F van Dyk, PhD, Assistant Professor, Departments of Microbiology and Immunology, University of Colorado Health

Sciences Center, USA, for her research on gammaherpesvirus pathogenesis. The Gertrude B Elion Award, named after the Nobel prize winner, is presented each year to honour a female resident or fellow.

Each award provides a US\$10 000 cash prize, half to the winning candidate and half to the sponsoring department. On an international basis, department chairs of research facilities are encouraged to nominate promising candidates.

Further details are available from: The American Herpes Foundation, 433 Hackensack Avenue, 9th Floor, Hackensack, NJ 07601, USA. Tel: +1 201 342 4441; Fax: +1 201 342 7555 or from the website: www.herpes-foundation.org