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Review

HSV-2 transmission

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Abstract

A number of important risk factors for the acquisition of HSV-2 have been established including female gender, black or Hispanic ethnic origin, HIV infection, age, and increased number of sexual partners. Transmission is influenced by a number of biological factors such as sexual behavior, use of condoms, duration of relationships, and knowledge of a partner's serologic status. Vertical transmission (transmission of HSV from mother to neonate) is potentially life-threatening; neonatal HSV infection is associated with significant morbidity and mortality. The valaciclovir transmission study provides evidence that an antiviral agent can interrupt the transmission of a viral sexually transmitted disease between serologically discordant sexual partners. This review explores the importance of the cofactors that affect transmission, and makes recommendations on considerations for the prophylactic use of antiviral agents for the prevention of transmission in other patient populations.

Keywords: HSV-2; Transmission; Neonatal HSV-2; Antiviral; Shedding

1. Introduction

Transmission of HSV is influenced by a number of biological factors. When studying transmission, the biological factors are difficult to separate from behavioral factors, such as sexual behavior, use of condoms, duration of relationships, and knowledge of a partner's serologic status. Clearly, more data are required in several key areas: the role of condoms in preventing HSV-2 transmission, the factors that influence transmission for men who have sex with men (MSM), the impact of viral shedding, duration of infection, duration of relationship and awareness of serologic status. This chapter explores the importance of the cofactors that affect transmission and makes recommendations on considerations for the prophylactic use of antiviral agents for the prevention of transmission in other patient populations (e.g. MSM and partners of pregnant women).

2. Vertical transmission of HSV-2 from mother to newborn

The transmission of HSV from mother to neonate is potentially life threatening. Neonatal HSV infection is associated with significant morbidity and mortality. Babies acquire neonatal HSV infection from their mothers, either in utero or intrapartum, by contact with infected genital secretions (Fig. 1).

The incidence of neonatal HSV infection varies around the world (Table 1).

Awareness of the etiology, pathophysiology and epidemiology of neonatal HSV infections is important to effectively

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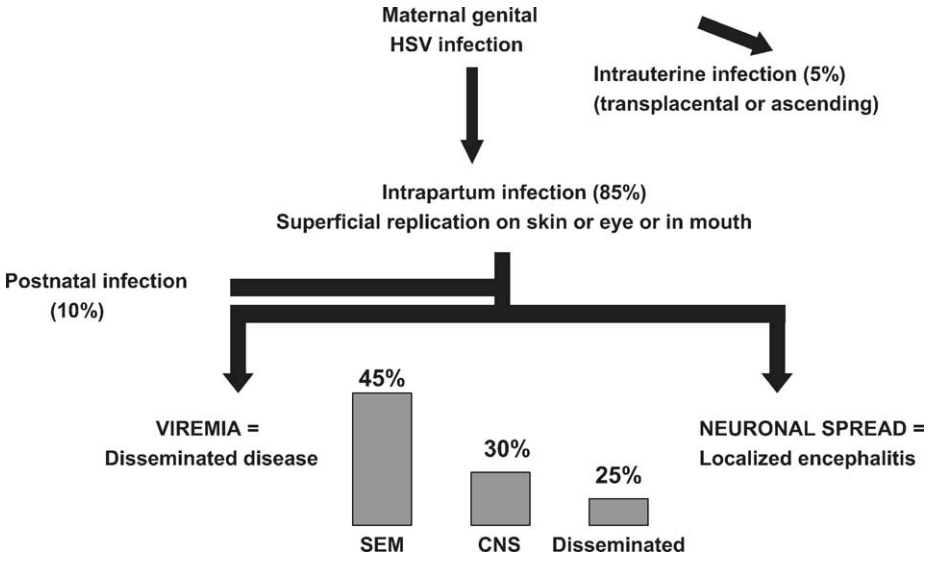

Fig. 1. Pathogenesis of neonatal HSV infection.

Table 1
Incidence of neonatal HSV infection

Country	Population	Rate of neonatal HSV per live births
USA	Seattle, WA	1 in 3200
USA	Birmingham, AL	1 in 2700
UK	National voluntary reporting	1 in 60–70,000
Netherlands	National	1 in 35,000
Norway	National (CNS only)	1 in 25,000
Sweden	Stockholm	1 in 15,000
Japan	National	1 in 14–20,000
USA	Birmingham, AL (1998–2001)	1 in 1000

prevent or manage risk in neonatal disease, and limit the associated psychosocial morbidity for the family. Over 50% of children who develop neonatal herpes will ultimately have CNS disease (Kimberlin, 2001). For babies with encephalitis, 5% die, even when treated with high-dose intravenous aciclovir. Mortality is higher in children with multi-organ disseminated HSV disease, being 25–30%. However, morbidity among children with encephalitis or multi-organ disease is significant (Fig. 2). In contrast, the majority of children with skin, eye, and mouth disease (SEM) go on to develop normally. The survival rate of newborns infected with HSV-2 was higher than those infected with HSV-1 (Kimberlin et al., 2001) although the difference was not significant.

There are a number of risk factors for maternal–fetal transmission, which include the acquisition of first episode genital infection during pregnancy, particularly in the third trimester; the passage of transplacental antibodies; and damage to fetal skin barriers (i.e. fetal scalp monitors or use of forceps).

Asymptomatic first episode infection in the third trimester is commonly found in women who have infants with neonatal HSV infection; 80% of infected infants are born to mothers with no maternal history of genital HSV infection prior to the pregnancy, and these babies have the highest risk of suffering serious disease (Whitley, 1998).

The acquisition of HSV during pregnancy has been studied recently in a population of over 30,000 women (Brown et al., 2003). Of the women susceptible to infection (i.e., to a new infection with a type of HSV of which the mother

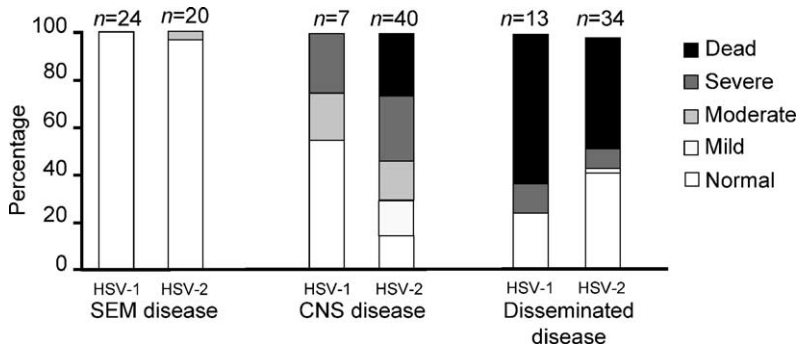

Fig. 2. Morbidity and mortality due to neonatal HSV disease at 1 year. Reprinted with permission from Kimberlin et al., 2001. Copyright © 2001.

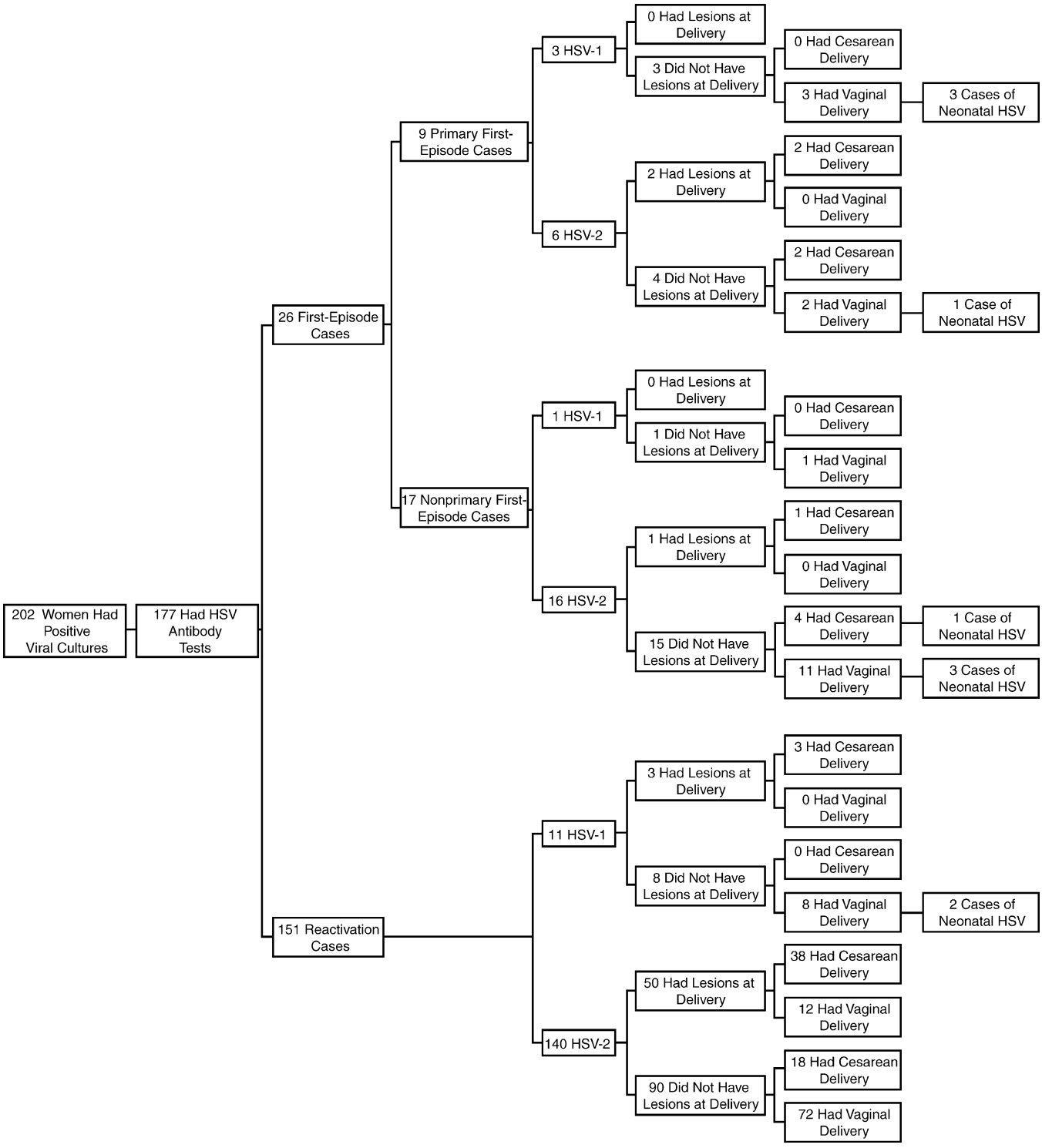

Fig. 3. Risk of transmission of HSV to the neonate during periods of maternal viral shedding at delivery. Reprinted from Brown et al., 2003. Copyright © 2003, American Medical Association.

had no antibodies), 2.1% acquired HSV during pregnancy, the majority of which (~75%) were HSV-2 infections. The infants born to these women are at a much higher risk of acquiring neonatal disease than those born to women with recurrent genital herpes. In a recent study, the risk of transmission of HSV infection to the neonate while the mother was shedding virus asymptomatically was found to be 25–57% in women with primary or non-primary first episode infection with either HSV-1 or -2 (Brown et al., 2003); this translates to an odds ratio of 320. This compares with only 2% among women with recurrent disease (Fig. 3).

Table 2
Maternal antibodies to HSV have a protective effect on the fetus (Prober et al., 1987)

NAb titer (CB or 2 weeks)	Exposed but uninfected ($n = 33$)	Infected ($n = 29$)
<1:5	0 (0)	12 (41) $P < 0.00001$
1:5 to 1:20	7 (21)	15 (52)
>1:20	26 (79)	2 (7) $P < 0.0002$

Maternal transplacental antibodies alter the severity of newborn disease. HSV antibodies have at least an ameliorative effect if not protective, hence the increased risk of vertical transmission associated with primary infection. Furthermore, for women with low titers of neutralizing antibodies, the probability of transmission is significantly higher than in children born to mothers with high antibody levels (Table 2, Prober et al., 1987).

There are several experimental strategies to prevent neonatal disease:

- Prevent maternal first episode infection.
- Prevent transmission to fetus at delivery.
- 'Convince' fetus that mother is experiencing a recurrent infection.

2.1. Prevent maternal first episode infection

Theoretically, primary infection in the mother could be prevented by testing sexual partners of seronegative women and encouraging abstinence, or providing an antiviral agent to those who are discordant; or with an effective vaccine to provide transplacental antibodies. Prevention of transmission to the fetus at delivery could be achieved by preventing contact with infected maternal genital tract secretions by Cesarean delivery, or administering an antiviral drug to the pregnant 'at risk' woman.

2.2. Prevent transmission to fetus at delivery

A recent study found that the rate of neonatal HSV infection was reduced from 7.2% of vaginal deliveries to 1.5% by Cesarean section ($P = 0.005$) (Brown et al., 2003). These data confirm findings from an uncontrolled cohort study involving a small number of women (Nahmias et al., 1971).

Suppressive antiviral therapy during pregnancy has been a controversial area. The Aciclovir in Pregnancy Registry was in operation for about 14 years and evaluated safety of exposure to aciclovir in over 1200 pregnant women who were exposed to aciclovir and no apparent adverse effect was detected (Reiff-Eldridge et al., 2000). In four studies (Scott et al., 1996; Smith et al., 1998; Stray-Pedersen, 1990; Braig et al., 2001), aciclovir therapy reduced the clinical evidence of HSV infection, the number of Cesarean sections and asymptomatic virus shedding. Although these studies were predominantly small or in uncontrolled cohorts, no cases of neonatal herpes were reported. A recent meta-analysis of published data indicates that prophylactic aciclovir beginning at 36 weeks' gestation reduces the risk of clinical HSV recurrence at delivery, Cesarean delivery for recurrent genital herpes, and the risk of HSV viral shedding at delivery (Sheffield et al., 2003). In a recent study of valaciclovir prophylaxis (Andrews et al., 2003), suppressive antiviral therapy reduced recurrent genital herpes in a pregnant woman.

2.3. 'Convince' fetus that mother is experiencing a recurrent infection

Antenatal management could include antiviral prophylaxis in the newborn, or use of high-titer monoclonal antibodies immediately prior to delivery or immediately postpartum. The American Academy of Pediatrics recommends that aciclovir be administered for 10–14 days IV to babies born to women with first episode genital infection, but that those babies born to women with established recurrent infection should simply be observed. More data are required to improve the management of high-risk pregnancies; however, the ethics of placebo-controlled studies in these populations are questionable.

3. HSV-2 Transmission to sexual partners

Transmission of genital herpes to a sexual partner or infant is a great concern to people who have genital herpes, affecting psychosocial and psychosexual aspects of their lives (VanderPlate and Aral, 1987; Catotti et al., 1993). A survey of more than 3000 patients with genital herpes indicated that the psychosocial impact of herpes can be serious and long-lasting; diagnosis is often associated with emotional upheaval, and many patients expressed dissatisfaction with their diagnosing health-care providers. Over one-half of the respondents in the survey reported feelings of depression and fear of rejection in the last year. Sexual enjoyment and activity also were negatively affected by herpes (Catotti et al., 1993).

A number of important risk factors for the acquisition of HSV-2 have been established including female gender, black or Hispanic ethnic origin, HIV infection, and increased number of sexual partners (Mertz, 1993). Age is a risk factor for HSV-2 seropositivity. This may be due to an increased number of sexual partners; however, those partners themselves are also likely to be older.

Fig. 4 depicts the virological events during a single transmission event.

A study of 528 monogamous discordant couples who received counseling and education about condom use found that condoms offer significant protection for acquisition for HSV-2 in susceptible women. Furthermore, there was a reduction in HSV-2 acquisition over time (Wald et al., 2001).

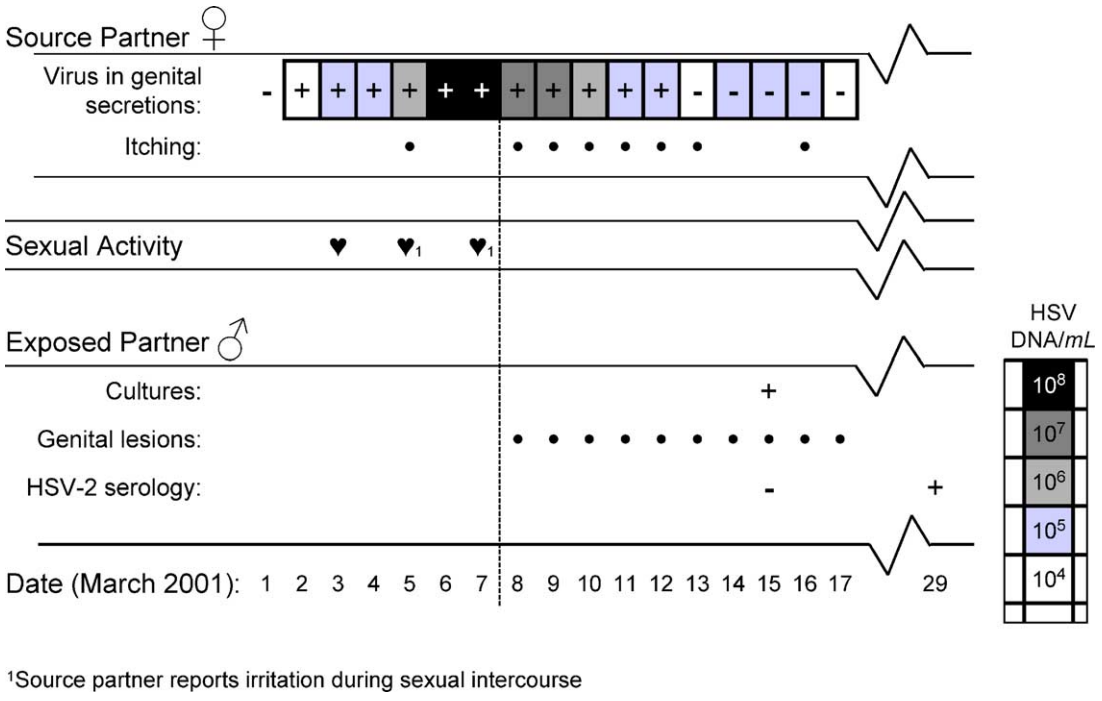

Fig. 4. Transmission of HSV-2 in a discordant couple.

3.1. The valaciclovir transmission study

The body of data correlating antiviral therapy and PCR analyses have consistently shown that antiviral drugs successfully reduce the amount of viral DNA. However, while it is plausible that this may translate into reduced risk of transmission, no data are available. A question remains about the quantitative relationship between exposure and risk of infection. The valaciclovir transmission study (Corey et al., 2004) was performed with the aim of providing definitive data on whether chronic suppressive therapy with an antiviral agent – valaciclovir – reduced the transmission of genital herpes in heterosexual monogamous couples discordant for HSV-2 antibodies. This study provides more evidence that an antiviral agent can indeed interrupt the transmission of a viral sexually transmitted disease, after the discovery that AZT can prevent transmission of HIV from mother to child.

The valaciclovir transmission study was an international, randomized, double-blind, placebo-controlled study at 126 study sites, 96 of which entered couples into the trial. The source partners were randomized to valaciclovir 500 mg once daily or placebo for 8 months, and couples were evaluated monthly for genital herpes. At each monthly visit, couples were counseled on safe sex behavior and offered condoms. The primary endpoint of the study was clinical evidence of genital herpes in the susceptible partner.

The study randomized 1484 couples discordant for the presence of HSV-2 antibodies, all of whom were at least 18 years of age, in good general health, and in a monogamous heterosexual relationship (median duration 2 years). The source partners were seropositive for HSV-2, with a history of <10 genital HSV recurrences per year, and were candidates for suppressive antiviral therapy. The susceptible partners were seronegative for HSV-2, although they could be seropositive for HSV-1, and were required to have no history of symptomatic genital herpes.

At monthly visits, susceptible partners were tested for HSV-2 antibodies, a sexual history diary was collected, and counseling regarding use of condoms provided. Study subjects were required to return to the clinic for examination of any genitourinary symptoms, HSV culture and PCR analysis. Those clinically diagnosed with genital herpes were treated with open label valaciclovir (500 mg twice daily) for 5 days. If genital HSV infection was confirmed by laboratory analysis, they were discontinued from the study; if not, then

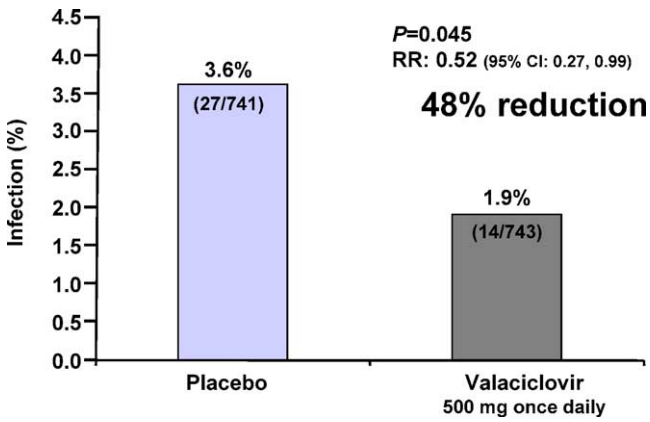

Fig. 5. Proportion of susceptible partners with HSV-2 infection in the valaciclovir transmission study (Corey et al., 2004).

Table 3
Acquisition of HSV infection among susceptible partners in the valaciclovir transmission study (Corey et al., 2004)

	Valaciclovir ($n = 743$)	Placebo ($n = 741$)	Hazard ratio 95% CI	*P*-value
Clinically symptomatic HSV-2 genital herpes—*n* (%)	4 (0.5%)	16 (2.2%)	0.25 (0.08, 0.75)	0.008
HSV-2 infection—*n* (%)	14 (1.9%)	27 (3.6%)	0.52 (0.27, 0.99)	0.039
Asymptomatic HSV-1 infection—*n* (%)	0	4 (0.5%)	NA	NA

they continued. Source partners visited the clinic monthly to submit a diary of recurrences, collect medications, and return pills for counting.

Valaciclovir treatment of the source partner reduced the risk of transmitting symptomatic genital herpes by 75%, and reduced the overall acquisition of HSV-2 by 48% (Fig. 5 and Table 3).

As expected, the rate of acquisition of HSV-2 was higher in women, regardless of which treatment arm they were in, although the study was not designed to investigate gender-specific effects.

A substudy at four US sites also investigated shedding rates in 89 of the source partners in the trial. In those taking suppressive valaciclovir, there was a decrease in the number of symptomatic recurrences, although there were still breakthrough episodes. However, suppressive valaciclovir treatment reduced the number of individuals shedding virus, the number of days on which virus was shed, the number of days on which virus was shed subclinically, and the number of days on which virus was shed during a clinical episode (Table 4).

The PCR data showed that when patients in the valaciclovir arm experienced viral shedding, the quantity of viral genomes detected (copies/mL) was lower than that in the placebo group.

The overall conclusions from this study are that suppressive valaciclovir therapy significantly reduced the rate of transmission of symptomatic genital herpes by 75%; HSV-2 infection by 48%; and total HSV acquisitions by 61%.

Further studies of the impact of suppressive antiviral therapy on the transmission of HSV infection in other populations could be anticipated. For example, studies in discordant couples where the woman is pregnant may provide data on prevention of neonatal HSV infections. Transmission among men who have sex with men (MSM) and individuals who are HIV-positive may also have important implications for public health.

Table 4
Overall rate of virus shedding among source partners in the valaciclovir transmission study (Corey et al., 2004)

Overall shedding rates	Placebo ($n = 50$)	Valaciclovir 500 mg QD ($n = 39$)
Subjects shedding[a]	41 (82%)	19 (49%)
Shedding days[b]	10.9%	2.6%
Subclinical shedding days	7.8%	2.6%
Clinical shedding days	45.8%	2.7%

[a] OR valaciclovir vs. placebo 0.6, $P = 0.002$.
[b] OR valaciclovir vs. placebo 0.20, $P = 0.002$.

4. Known cofactors for HSV-2 transmission

In this trial and others, a number of cofactors were associated with risk of acquisition of HSV-2. Some of these likely relate to exposure to episodes of viral shedding (such as condom use and frequency of sexual contacts), while others are less clear in such relationship (Mertz, 1993; Mertz et al., 1992; Corey et al., 2004):

- Age
- Gender
- Race
- Serologic status
- Condom use
- Frequency of sexual contacts
- Duration of HSV-2 in the source partner
- Duration of relationship

4.1. Gender

Consistent with other studies, the relative risk of acquisition has been shown to be higher for women than for men ($P = 0.009$) (Corey et al., 2004). The risk varies between studies, with some, such as the Chiron study (Wald et al., 2001), reporting that women are up to six times more likely to acquire HSV-2 than men.

4.2. Serologic status

The data on the role of past HSV-1 infection as measured by HSV-1 serologic status on reducing HSV-2 acquisition are less clear. Some studies have shown that being HSV seronegative appears to be of little importance for acquisition (Brown et al., 1997; Corey et al., 1999; Corey et al., 2004). For example, in the covariate analysis reported in the transmission study, there was a non-significant increase in risk associated with being HSV seronegative (Corey et al., 2004). However, another study of a subunit glycoprotein vaccine (Stanberry et al., 2002) indicated that being HSV seronegative placed the person at a higher risk for acquiring HSV-2. In that study, persons who were HSV-1 seronegative and who had been vaccinated acquired HSV-2 at the same rate as HSV-1 seropositive individuals.

4.3. Condom use

As condom use increases, the risk of transmission appears to decline. However, condom use appears to be only partially

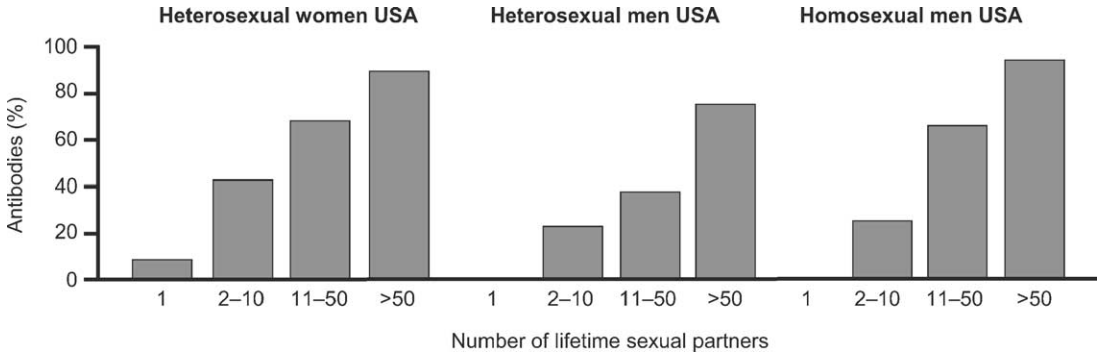

Fig. 6. HSV-2 seropositivity increases with the number of lifetime sexual partners. Reprinted from Nahmias et al., 1990.

protective, with a 50% reduction in the risk of acquiring HSV-2 in persons who use condoms (Wald et al., 2001).

4.4. Sexual contact

Sexual behavior is, not surprisingly, an important factor in the transmission of HSV-2. The risk of acquiring HSV-2 is higher in those who have more frequent sexual contact and whose relationships are of shorter duration (Corey et al., 2004). In most studies, a higher number of lifetime sexual partners correlates with a greater risk of being seropositive for HSV-2. The prevalence of HSV-2 antibodies in 18 countries was correlated with number of sexual partners in a seroepidemiological study of herpes simplex virus types 1 and 2 using an enzyme immunoassay on over 40,000 sera from 18 countries from 1964 to 1983. The proportions of people infected with the virus ranged from zero in nuns and 0.3% in American children, to 50% in pregnant Black women from Haiti (Nahmias et al., 1990). The prevalence of HSV-2 antibodies was greater than 75% of all individuals who had had more than 50 lifetime sexual partners (Fig. 6).

The observation that short relationships represent a higher risk of transmission is problematic since these new relationships are especially difficult to study prospectively.

The duration of HSV-2 infection in the source partner is also significant: duration of less than 2 years is linked with an increased risk of transmission, although this may reflect the duration of the relationship (Corey et al., 2004). This was reflected in the Chiron Couples Study (Wald et al., 2001) that showed a decline in the rate of acquisition over time (Fig. 7).

The declining rate of HSV-2 transmission was observed when data were analyzed both by 100 person-years and by 10,000 sexual acts. In a univariate analysis, the time interval was significantly associated with a declining risk of HSV-2 acquisition; relative risk 0.57 ($P = 0.002$) (Wald et al., 2001). However, in a multivariate analysis adjusted for sexual activity in the follow-up period and age and gender, the time interval became less important; relative risk 0.69 ($P = 0.049$) (Wald et al., 2001). This may be partly explained by greater sexual activity in newer relationships.

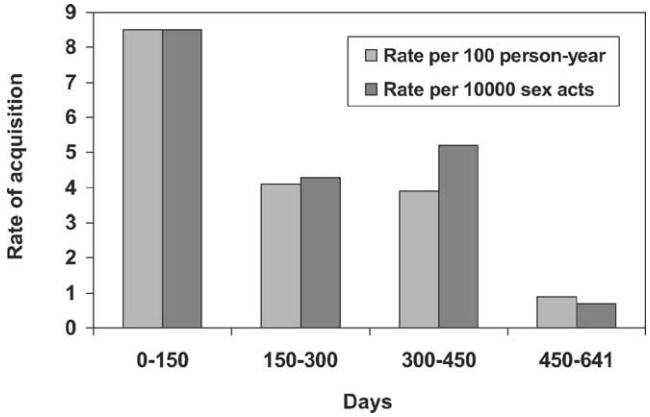

Fig. 7. Change in HSV-2 acquisition over time in the Chiron Couples study. Reprinted from Wald et al., 2001. Copyright © 2001, American Medical Association.

5. Extending the transmission study

The valaciclovir transmission study (Corey et al., 2004), as any clinical trial, utilized inclusion and exclusion criteria:

- Heterosexual couples only were enrolled to reduce the heterogeneity of the patient population.
- Couples were both HIV seronegative.
- Couples were required to be monogamous to maintain the link between intervention and outcome.
- Both partners had to be aware of the source partner's infection.
- Participants had to be immunocompetent to ensure that they had known infectivity and susceptibility.
- Source partners had to have clinically symptomatic infection.

Consequently, many susceptible HSV-2 seropositive persons who are at risk for HSV-2 transmission were excluded from this study. Extending the transmission study results to a wider group of people potentially at risk for transmitting HSV-2 infection presents different issues in different patient groups. For instance, including people with HSV-2 and HIV is likely to change the infectiousness of the source partner, and pregnancy may be associated with altered susceptibility

to HSV-2. Type of intercourse can also alter the likelihood of infection.

In contrast the following situations are unlikely to affect antiviral efficacy:

- Asymptomatic HSV-2 infection.
- Source partner having multiple partners.
- Short duration of relationship.
- Short time since source partner has acquired HSV-2.

5.1. Persons who are not monogamous

Non-monogamous persons are unlikely to have any intrinsic biological differences from the patients enrolled in the transmission study. However, there is a probability of a high rate of events in this group and therefore the number-needed-to-treat could be lower than in the valaciclovir transmission study. Compliance to therapy is unknown in this group. For these reasons a community study may be the most successful approach to investigating the prophylactic impact of antiviral therapy in such persons.

5.2. Asymptomatic HSV-2 seropositive persons

The biology of viral shedding is similar in this group and it is expected that their response to antiviral treatment will be comparable to those in the transmission study. However, the rate of transmission from asymptomatic HSV-2 seropositive persons is not known.

5.3. Discordant pregnant couples

For ethical reasons, a placebo-controlled trial in these patients would be difficult. However, the biology of transmission is likely to differ and the rate of transmission may be higher than in the transmission study, as the susceptibility to HSV-2 may be higher during pregnancy.

5.4. Men who have sex with men

This group would be very interesting to study. The biology of the infection may differ because of the different sites of infection (e.g. anal mucosa). HIV has an immunocompromising effect, which may also affect the pathogenesis of HSV infection.

6. Conclusions

- Risk factors for vertical transmission include acquisition of the first episode genital infection during pregnancy, fetal manipulation and instrumented deliveries.
- Eighty percent of infected neonates are born to mothers with no history of genital HSV infection prior to the pregnancy.
- Maternal transplacental HSV antibodies ameliorate neonatal disease. The risk of neonatal HSV disease is lower in mothers with established recurrent herpes during pregnancy.
- Risk factors for transmission between sexual partners include age, female gender, ethnic origin, concomitant HIV infection, number of partners, use of condoms, duration of relationship and duration of HSV infection.
- Antiviral therapy with valaciclovir has recently been shown to reduce transmission of HSV-2 in discordant monogamous heterosexual couples.
- While viral shedding is a risk factor for transmission, this study of genital HSV-2 infection among serodiscordant monogamous couples showed that biological and behavioral aspects of sexual activity and HSV infection also influence person-to-person transmission of these infections.
- The threshold for transmission may be determined by intrinsic and immune factors affecting susceptibility of the recipient as well as viral load and duration in the donor.

References

Andrews, W., Kimberlin, D., Whitley, R., Cliver, S., Deeter, R., 2003. Valaciclovir suppressive therapy in pregnant women reduces recurrent genital herpes (HSV): results of a randomized trial. In: Society for Maternal–Fetal Medicine 23rd Annual Meeting. San Francisco, CA, 3–8 February.

Braig, S., Luton, D., Sibony, O., Edlinger, C., Boissinot, C., Blot, P., Oury, J.F., 2001. Acyclovir prophylaxis in late pregnancy prevents recurrent genital herpes and viral shedding. Eur. J. Obstet. Gynecol. Reprod. Biol. 96 (1), 55–58.

Brown, Z.A., Selke, S., Zeh, J., Kopelman, J., Maslow, A., Ashley, R.L., Watts, D.H., Berry, S., Herd, M., Corey, L., 1997. The acquisition of herpes simplex virus during pregnancy. N. Engl. J. Med. 337 (8), 509–515.

Brown, Z.A., Wald, A., Morrow, R.A., Selke, S., Zeh, J., Corey, L., 2003. Effect of serologic status and cesarean delivery on transmission rates of herpes simplex virus from mother to infant. JAMA 289 (2), 203–209.

Catotti, D.N., Clarke, P., Catoe, K.E., 1993. Herpes revisited. Still a cause of concern. Sex Transm. Dis. 20 (2), 77–80.

Corey, L., Langenberg, A.G., Ashley, R., Sekulovich, R.E., Izu, A.E., Douglas Jr., J.M., Handsfield, H.H., Warren, T., Marr, L., Tyring, S., DiCarlo, R., Adimora, A.A., Leone, P., Dekker, C.L., Burke, R.L., Leong, W.P., Straus, S.E., 1999. Recombinant glycoprotein vaccine for the prevention of genital HSV-2 infection: two randomized controlled trials. Chiron HSV Vaccine Study Group. JAMA 282 (4), 331–340.

Corey, L., Wald, A., Patel, R., Sacks, S.L., Tyring, S.K., Warren, T., Douglas Jr., J.M., Paavonen, J., Morrow, R.A., Beutner, K.R., Stratchounsky, L.S., Mertz, G., Keene, O.N., Watson, H.A., Tait, D., Vargas-Cortes, M., 2004. Valacyclovir HSV Transmission Study Group. Once-daily valacyclovir to reduce the risk of transmission of genital herpes. N. Engl. J. Med. 350 (1), 11–20.

Kimberlin, D.W., Lin, C.Y., Jacobs, R.F., Powell, D.A., Corey, L., Gruber, W.C., Rathore, M., Bradley, J.S., Diaz, P.S., Kumar, M., Arvin, A.M., Gutierrez, K., Shelton, M., Weiner, L.B., Sleasman, J.W., de Sierra, T.M., Weller, S., Soong, S.J., Kiell, J., Lakeman, F.D., Whitley, R.J., 2001. National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. Safety and efficacy of high-dose intravenous acyclovir in the management of neonatal herpes simplex virus infections. Pediatrics 108 (2), 230–238.

Kimberlin, D.W., 2001. Advances in the treatment of neonatal herpes simplex infections. Rev. Med. Virol. 11 (3), 157–163.

Mertz, G.J., Benedetti, J., Ashley, R., Selke, S.A., Corey, L., 1992. Risk factors for the sexual transmission of genital herpes. Ann. Intern. Med. 116 (3), 197–202.

Mertz, G.J., 1993. Epidemiology of genital herpes infections. Infect. Dis. Clin. North Am. 7 (4), 825–839.

Nahmias, A.J., Josey, W.E., Naib, Z.M., Freeman, M.G., Fernandez, R.J., Wheeler, J.H., 1971. Perinatal risk associated with maternal genital herpes simplex virus infection. Am. J. Obstet. Gynecol. 110 (6), 825–837.

Nahmias, A.J., Lee, F.K., Beckman-Nahmias, S., 1990. Sero-epidemiological and -sociological patterns of herpes simplex virus infection in the world. Scand. J. Infect. Dis. Suppl. 69, 19–36.

Prober, C.G., Sullender, W.M., Yasukawa, L.L., Au, D.S., Yeager, A.S., Arvin, A.M., 1987. Low risk of herpes simplex virus infections in neonates exposed to the virus at the time of vaginal delivery to mothers with recurrent genital herpes simplex virus infections. N. Engl. J. Med. 316 (5), 240–244.

Reiff-Eldridge, R., Heffner, C.R., Ephross, S.A., Tennis, P.S., White, A.D., Andrews, E.B., 2000. Monitoring pregnancy outcomes after prenatal drug exposure through prospective pregnancy registries: a pharmaceutical company commitment. Am. J. Obstet. Gynecol. 182 (1 Pt. 1), 159–163.

Scott, L.L., Sanchez, P.J., Jackson, G.L., Zeray, F., Wendel Jr., G.D., 1996. Acyclovir suppression to prevent cesarean delivery after first-episode genital herpes. Obstet. Gynecol. 87 (1), 69–73.

Sheffield, J.S., Hollier, L.M., Hill, J.B., Stuart, G.S., Wendel Jr, G.D., 2003. Acyclovir prophylaxis to prevent herpes simplex virus recurrence at delivery: a systematic review. Obstet. Gynecol. 102, 1396–1403.

Smith, J.R., Cowan, F.M., Munday, P., 1998. The management of herpes simplex virus infection in pregnancy. Br. J. Obstet. Gynaecol. 105 (3), 255–260.

Stanberry, L.R., Spruance, S.L., Cunningham, A.L., Bernstein, D.I., Mindel, A., Sacks, S., Tyring, S., Aoki, F.Y., Slaoui, M., Denis, M., Vandepapeliere, P., Dubin, G., 2002. GlaxoSmithKline Herpes Vaccine Efficacy Study Group. Glycoprotein-D-adjuvant vaccine to prevent genital herpes. N. Engl. J. Med. 347 (21), 1652–1661.

Stray-Pedersen, B., 1990. Acyclovir in late pregnancy to prevent neonatal herpes simplex. Lancet 336 (8717), 756.

VanderPlate, C., Aral, S.O., 1987. Psychosocial aspects of genital herpes virus infection. Health Psychol. 6 (1), 57–72.

Wald, A., Langenberg, A.G., Link, K., Izu, A.E., Ashley, R., Warren, T., Tyring, S., Douglas Jr., J.M., Corey, L., 2001. Effect of condoms on reducing the transmission of herpes simplex virus type 2 from men to women. JAMA 285 (24), 3100–3106.

Whitley, R.J., 1998. Neonatal herpes simplex virus infections. Clin. Perinatol. 15 (4), 903–916.