

Expert Commentary: Genital Herpes Transmission

Peter Leone, Department of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA.

GENITAL HERPES INFECTION is extremely common. There are an estimated 45 million adults infected with herpes simplex virus type 2 (HSV-2),¹ and 1–1.5 million incident HSV-2 infections annually in the USA.² HSV-2 prevalence and transmission rates are similarly high throughout many developed and developing countries.³

The Importance of HSV-2 Shedding

Two factors have contributed greatly to HSV transmission. First, HSV-2 infection is rarely recognized.⁴ Secondly, nearly 100% of individuals experience reactivation of genital infection either clinically or asymptotically.⁵ Our understanding of the natural history of genital herpes infection has improved since HSV type-specific serological and polymerase chain reaction (PCR) tests became available: for example, PCR has demonstrated that HSV-2 is frequently isolated on the genital mucosal surface in the absence of clinical symptoms. During the first 6 months of infection, HSV shedding occurs on 20–40% of days; with longer-term infection, shedding rates range from 5–20% of days.^{5,6} HSV-2 shedding is responsible for genital herpes transmission whether these episodes lead to recognized outbreaks or are clinically asymptomatic; in fact, up to 70% of transmissions can be attributed to asymptomatic shedding.^{7–9} Strategies to reduce genital herpes transmission are further complicated by HSV shedding from multiple genital sites.

As a result, the challenge of dealing with genital herpes has been how to prevent transmission. Until the recent study by Corey *et al.*,¹⁰ strategies to reduce transmission risk consisted of disclosure of infection status to partners, recognizing outbreaks, abstaining during those times, and the use of condoms with all sexual encounters.¹¹ Offering antiviral therapy was undertaken to reduce the frequency and severity of outbreaks; other benefits were 'softer', serving to reduce the psychological burden of a life-long, chronic, sexually transmitted infection.

The world of therapy was essentially divided into two: episodic therapy to treat outbreaks and suppressive therapy to reduce the frequency of recurrences. All therapeutic options focused on disease management, while data suggested that unrecognized viral shedding was the driving force behind transmission. Daily antiviral therapy was found to reduce viral shedding by 85–95%, but whether this was sufficient to reduce transmission risk was unclear.^{11,12} The study by Corey *et al.*¹⁰ confirmed that daily, suppressive valaciclovir therapy resulted in a significant reduction in frequency and quantity of viral shedding; the correlate of this was eloquently demonstrated by the reported reductions in transmission of infection by 48% and disease occurrence in susceptible partners by 75%. Clearly, reduction in HSV-2 shedding reduces HSV-2 transmission in heterosexual relationships, and has the additional benefit of improving the psychological and sexual wellbeing of both infected and susceptible partners.^{13,14}

Suppressive Antiviral Therapy

Population-based models suggest that suppressive antiviral therapy would not impact significantly on genital herpes prevalence rates but could reduce incidence.^{15,16} However, whether suppressive therapy could result in an incidence shift and what impact such a shift might have on the secondary outcomes of acquisition of HIV and neonatal herpes – the secondary outcomes of genital herpes – are not known. Studies on whether episodic or suppressive therapy for genital herpes infection will lower HIV incidence are currently being conducted. The importance and urgency of these studies cannot be overstated.¹⁷

The Corey *et al.*¹⁰ study offers important information coupled with a few reality checks. It was remarkable that the study demonstrated that suppressive antiviral therapy was associated with a significant reduction in transmission. Partners in this study had been together for a median time of 2 years and reported a history of genital herpes for a median of 7 years. In essence, the study enrolled low transmitters and took all recommended steps to reduce HSV-2 transmission: all couples were well educated to recognize outbreaks and to abstain during such periods, given episodic therapy for genital herpes recurrences, and encouraged to use condoms for all sexual encounters. However transmission still occurred. This only serves to illustrate that all individuals with genital herpes infection should be offered suppressive therapy as a means of further reducing transmission to uninfected partners.

There are limitations to the study worth mentioning, since it was conducted with mutually monogamous, heterosexual, discordant couples. The study period only lasted 8 months, although the Kaplan–Meier survival analysis for both disease and infection remained divergent throughout the study period with continued benefit of valaciclovir over placebo for the course of the study (suppressive therapy studies in immunocompetent hosts have shown continued benefit of therapy for years).^{18,19} Long-term studies of transmission reduction will almost certainly never be done, but viewing subclinical shedding as a surrogate marker for transmission risk suggests that the benefit of suppressive therapy should well exceed the duration of the study period.

There is certainly no biological reason to believe that non-monogamous individuals would not see a similar benefit in transmission reduction with suppressive therapy. The benefits of suppressive therapy appear to be no different for men and women but men who have sex with men may not see a similar reduction in transmission. This is due to higher rates of transmission and possible differences in susceptibility associated with receptive anal intercourse. Furthermore, the study did not address states of increased viral shedding (such as co-infection with HIV or incident HSV infection). Such conditions warrant further analysis, but this may be possible by looking at the impact of antiviral therapy on subclinical shedding.

The only inconsistent finding among secondary end-points in the study was the observation that frequency of asymptomatic HSV-2 seroconversion was not significantly different between the valaciclovir (1.3%) and placebo groups (1.5%). In addition, the times to asymptomatic seroconversion in the valaciclovir and placebo groups were not significantly different. The issue of acquisition of symptomatic disease versus asymptomatic infection has been considered within the context of prophylactic HSV vaccines, where it has been theorized that immunization may protect against clinical disease, but that serum antibodies may not afford protection from initial mucosal infection by HSV-2 and subsequent latency.²⁰ Valaciclovir suppressive therapy may reduce, quantitatively, the shedding of virus to levels below those necessary to establish a symptomatic infection in transmission, but the relationship between the amount of viral inoculum and the host immune response in establishing clinical disease has never been established. Although both viral and host factors are important determinants of whether infection with HSV-2 is ultimately manifested clinically, it is noteworthy that time to overall acquisition was significantly longer in those on valaciclovir compared with the placebo group ($P=0.039$).

Condom Use

Suppressive antiviral therapy did not completely protect against transmission of HSV-2, so infected individuals should be strongly encouraged to employ multiple measures to reduce transmission risk. Condoms are effective in reducing HSV-2 transmission and should still be recommended, but acceptability of their use in long-term relationships remains an issue. Even in studies where patients are counselled regularly about the benefits of condom use, compliance remains poor.²¹ Using suppressive therapy to reduce HSV transmission may result in a decreased use of condoms, which may offset any further benefit of transmission reduction potential. Means of improving adherence to condom use should be explored: in the

valaciclovir study, 37% of couples reported no condom use, despite the availability of free condoms and monthly counselling about their value.²¹

Conclusions

Given the safety of the antiviral agents available for genital herpes, and the lack of resistance to aciclovir with long-term use in immunocompetent hosts, suppressive therapy is now an essential component of options for reducing the HSV transmission risk. Dissemination of the study results, coupled with increased awareness of the role of asymptomatic HSV shedding in transmission, should encourage both clinicians and patients to consider suppressive antiviral therapy.

REFERENCES

1. Fleming DT, McQuillan GM, Johnson RE, Nahmias AJ, Aral SO, Lee FK *et al*. Herpes simplex virus type 2 in the United States, 1976 to 1994. *N Engl J Med* 1997;**337**: 1105–1111.
2. Armstrong GL, Schillinger J, Markowitz L, Nahmias AJ, Johnson RE, McQuillan GM *et al*. Incidence of herpes simplex virus type 2 infection in the United States. *Am J Epidemiol* 2001;**153**:912–920.
3. Griffiths PD. When is sexually transmitted viral disease not an STD? *Rev Med Virol* 2000;**10**:71–73.
4. Cusini M, Ghislanzoni M. The importance of diagnosing genital herpes. *J Antimicrob Chemother* 2001;**47** (Suppl T1):9–16.
5. Wald A, Zeh J, Selke S, Ashley RL, Corey L. Virologic characteristics of subclinical and symptomatic genital herpes infection. *N Engl J Med* 1995;**333**:770–775.
6. Corey L, Wald A. Genital Herpes. In: *Sexually Transmitted Diseases*, 3rd edn (Holmes KK Mardh PA, Sparling PF, eds). New York, NY: McGraw Hill, 1999; pp285–312.
7. Rooney JF, Felsner JM, Ostrove JM, Straus SE. Acquisition of genital herpes from an asymptomatic sexual partner. *N Engl J Med* 1986;**314**: 1561–1564.
8. Mertz CJ, Coombs RW, Ashley R, Jourdan J, Remington M, Winter C *et al*. Transmission of genital herpes in couples with one symptomatic and one asymptomatic partner: a prospective study. *J Infect Dis* 1988;**157**:1169–1177.
9. Mertz GJ, Schmidt O, Jourdan JL, Guinan ME, Remington ML, Fahnlander A *et al*. Frequency of acquisition of first-episode genital infection with herpes simplex virus from symptomatic and asymptomatic source contacts. *Sex Transm Dis* 1985;**12**:33–39.
10. Corey L, Wald A, Patel R, Sacks SL, Tyring SK, Warren T *et al*. Once-daily valaciclovir to reduce the risk of transmission of genital herpes. *N Engl J Med* 2004; **350**:11–20.
11. Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines. *Morb Mortl Wkly Rep* 2002;**51**:RR-6.
12. Wald A, Zeh J, Barnum G, Davis LG, Corey L. Suppression of subclinical shedding of herpes simplex virus type 2 with acyclovir. *Ann Intern Med* 1996;**124**:8–15.
13. Goldberg L, Kaufman R, Terrance O, Kurtz DO, Batenhorst R, Bonne G and the Acyclovir Study Group. Long term suppression of recurrent genital herpes with acyclovir. *Arch Dermatol* 1993;**129**:582–587.
14. Carney O, Ross E, Ikkos G, Mindel A. The effect of suppressive oral acyclovir on the psychological morbidity associated with recurrent genital herpes. *Genitourin Med* 1993;**69**:457–459.
15. White PJ, Garnett GP. Use of antiviral treatment and prophylaxis is unlikely to have a major impact on the prevalence of herpes simplex virus type 2. *Sex Transm Infect* 1999;**75**:49–54.
16. Garnett G, Williams J, Jordan J, Davis EA. The epidemiological impact of suppressive therapy to reduce transmission of genital herpes (abstract C03D). 2004 National STD Prevention Conference, Philadelphia, PA, 2004. Available at: <http://www.stdconference.org>. Last accessed 19 July 2004.
17. Wald A, Corey L. How does herpes simplex virus type 2 influence human immunodeficiency virus infection and pathogenesis? *J Infect Dis* 2003;**187**:1509–1512.
18. Baker DA, Safran S, Deeter RG, Walker A, Barton G and the Acyclovir Study Group. Nine year effectiveness of continuous suppressive therapy with acyclovir (ACV) in patients with recurrent genital herpes (RGH). *J Eur Acad Dermatol Venerol* 1995;**5**(Suppl 1):S169.
19. Mattison HR, Reichman RC, Benedetti J, Bolgiano D, Davis LG, Bailey-Farchione A *et al*. Double-blind, placebo-controlled trial comparing long-term suppressive with short-term oral acyclovir therapy for management of recurrent genital herpes. *Am J Med* 1988;**85**(Suppl 2A): 20–25.
20. Stanberry LR, Cunningham AL, Mindel A, Scott LL, Spruance SL, Aoki FY *et al*. Prospects for control of herpes simplex virus disease through immunization. *Clin Infect Dis* 2000; **30**:549–566.
21. Wald A, Langenberg AG, Link K, Izu AE, Ashley R, Warren T *et al*. Effect of condoms on reducing the transmission of herpes simplex virus type 2 from men to women. *JAMA* 2001;**285**:3100–3106.

Expert Commentary: Genital Herpes Transmission • **HERPES** 11:2 2004

Key Paper

Famciclovir suppression of asymptomatic and symptomatic recurrent anogenital herpes simplex virus shedding in women: a randomized, double-blind, double-dummy, placebo-controlled, parallel-group, single-centre trial. Sacks SL. *J Infect Dis* 2004;**189**:1341–1347. E-pub 2004 Apr 05.

HSV

Genital herpes is most often transmitted while the patient is asymptomatic, presumably during episodes of viral shedding. To determine whether famciclovir is effective in reducing asymptomatic shedding, women with frequent, recurrent genital outbreaks were enrolled in a randomized, double-blind, double-dummy, placebo-controlled, parallel-group, 112-day trial of suppressive treatment with famciclovir for anogenital viral shedding. Sixty women received 125 mg of famciclovir three times daily, 59 received 250 mg of famciclovir three times daily, and 58 received placebo. Patients recorded symptoms and self-obtained cultures daily. Famciclovir reduced asymptomatic shedding,

compared with placebo ($P < 0.0001$). The onset of asymptomatic shedding was also delayed ($P < 0.0001$). Famciclovir reduced symptomatic shedding in a dose-dependent manner (0.72% for 125 mg three times daily versus 0.19% for 250 mg three times daily [$P < 0.0001$] versus 5.53% for placebo [$P < 0.0001$]). In conclusion, suppressive treatment with famciclovir reduced both asymptomatic and symptomatic viral shedding and delayed the onset of asymptomatic shedding in women with frequently recurring genital herpes. Studies to examine the effects of suppression by famciclovir on the transmission of genital herpes are warranted.