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## Famciclovir Reduces Viral Mucosal Shedding in HSV-Seropositive Persons

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### Abstract

**Objective:** Many cases of herpes simplex virus (HSV) infection occur through asymptomatic shedding from persons without evidence of clinical disease. This study explores whether famciclovir reduces HSV shedding in HSV-2 seropositive persons with or without a history of symptomatic genital herpes.

**Study Design:** One hundred twenty-seven HSV-2 seropositive participants were randomly assigned to 42 days of famciclovir, followed by 14 days of washout and 42 days of placebo, or vice versa. All subjects swabbed the genital/perianal area; those with HSV-1 infection also swabbed the oral area daily for HSV DNA PCR.

**Results:** Famciclovir reduced genital and oral HSV shedding from 11.4% of days during the placebo period to 4.7% of days during famciclovir therapy. The reduction was greater in participants with a history of genital herpes (74%) than in those without such a history (30%). In multivariate analyses, famciclovir protected against total (clinical and subclinical) genital shedding among persons with a clinical history of genital herpes (RR, 0.23; 95% CI, 0.15-0.35;  $P < 0.001$ ). Among HSV-2 seropositive participants without a history of genital herpes, 60% had HSV detected in the genital area at least once during the study. Famciclovir therapy did not result

in a statistically significant reduction in total HSV shedding in participants without a history of genital herpes.

Conclusion: Famciclovir therapy decreases genital HSV shedding in HSV-seropositive persons, especially those with a history of genital herpes. Overall, antiviral drugs may have varying effects on symptomatic and asymptomatic viral shedding, depending on the clinical history of the disease.

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APPROXIMATELY 17% OF PEOPLE in the United States are infected with herpes simplex virus type 2 (HSV-2).<sup>1</sup> Despite this high seroprevalence, only 14% of HSV-2 infected adults are aware that they have genital herpes, and most HSV-2 seropositive persons remain undiagnosed<sup>1</sup> because of clinically mild disease, difficult-to-visualize lesions, and/or lack of available diagnostics.<sup>2</sup> Asymptomatic HSV-2 infected persons still experience intermittent viral shedding from the genital tract and can transmit HSV-2 infection.<sup>2-7</sup> Control of genital viral shedding is therefore more likely to curtail HSV-2 transmission than the treatment of symptomatic recurrences. Recent studies have also highlighted an increase in genital HSV-1 infection, suggesting potential transmission from oral HSV shedding in some cases.<sup>8-10</sup>

Previous studies have investigated the role of antiviral therapy in decreasing the frequency of genital HSV shedding<sup>11-13</sup> and its potential for reducing the risk of sexual transmission of HSV-2<sup>14</sup>; however, these studies have focused primarily on the symptomatic HSV-2 infected source partners, not on the persons with subclinical or unrecognized infections who are responsible for the greatest number of new infections. We investigated whether antiviral therapy with suppressive famciclovir can reduce the amount of genital and oral viral shedding in persons with and without a history of recognized lesions.

## Materials and Methods

### Study Design

This randomized, double-blind, multicenter, placebo-controlled crossover study was conducted in 7 centers in the United States. The objective was to determine the effect of oral famciclovir 250 mg bid on mucosal HSV shedding in HSV-2 seropositive persons with or without a history of symptomatic genital herpes. The study protocol was approved by the institutional review board at each site, and participants provided written informed consent.

Participants who met the entry criteria were randomly assigned to receive 1 of 2 treatment sequences: 42 days of famciclovir treatment followed by 14 days of washout followed by 42 days of placebo, or 42 days of placebo followed by 14 days of washout followed by 42 days of famciclovir treatment. Participants were asked to perform daily swabs of the anogenital area during the course of the study, including the washout period, as described previously.<sup>11,12</sup> Participants who were both HSV-2 and HSV-1 seropositive were also asked to collect daily oral swabs. Participants returned to the clinic every 2 weeks; at each visit, medication bottles and swab kits were collected and reviewed for adherence.

### Participant Population

The study included HSV-2 seropositive men and women aged 18 years or older, who were in good health. Participants who were taking antiviral therapy were asked to stop treatment 7 days before randomization if they were taking acyclovir or valacyclovir, or 14 days before randomization if they were taking famciclovir, due to the respective differences in intracellular half-life of these drugs.<sup>15,16</sup>

Participants were excluded from the study if they had a history of renal dysfunction, had a known allergy to nucleoside analogues, or were immunosuppressed due to underlying disease (e.g., HIV infection) or treatment (e.g., cancer chemotherapy). Women of childbearing potential were excluded if they were pregnant, breastfeeding, or unwilling to use acceptable modes of contraception for the duration of the study.

### Laboratory Methods

The University of Washington Western blot was used to determine HSV antibody status,<sup>17</sup> and skin and mucosal samples from each participant were tested for HSV DNA using a real-time quantitative PCR assay<sup>18-20</sup> at the Molecular Diagnostic Laboratory at the University of Washington, Seattle, WA.

### Statistical Analysis

All randomized participants who took at least one dose of study drug comprised the intent-to-treat population. Efficacy variables included total, subclinical, and lesional (shedding at a time of lesions) viral shedding, number of HSV DNA PCR copies during HSV

shedding, percent of days with genital lesions, and time to first recurrence.

Frequency of viral shedding was calculated by dividing the number of HSV PCR-positive days for the outcome variable by the total number of days with valid specimens during the famciclovir period and the placebo period (excluding the washout period, the first day on each treatment, and any swabs taken before the study). Relative risk of total and subclinical HSV genital or oral shedding in the famciclovir versus the placebo period was estimated using generalized estimating equations with the log link. Adjusted relative risk estimates for treatment were based on models using history of genital or oral herpes, gender, and treatment period as covariates. Analyses of quantitative shedding included only days on which shedding was detected. The total number of HSV DNA PCR copies was  $\log_{10}$  transformed before tabulation. Time to onset of genital lesions was defined as the time (in days) from the first dose of study medication to the first day of a genital herpes recurrence. The distribution of the time to first recurrence of genital herpes was estimated using the Kaplan-Meier method. The treatment effect was estimated using a Cox regression model with treatment, gender, and treatment period as explanatory variables, and with recurrences in different treatment periods of the same patient considered as correlated events. The models were constructed separately for persons with and without a history of genital herpes. The robust sandwich estimator for standard error was used for significance tests and 95% CIs.

## Results

### Participant Demographics and Disposition

One hundred twenty-nine participants were randomized, but 2 did not receive the study drug and were not included in the analysis. Of the 127 remaining participants, 61 had a history of symptomatic genital herpes and 66 did not; 52 were men and 75 were women, with a median age of 40 years; and 72% were white. Among participants with a history of genital herpes, 37 (60.7%) had HSV-2 antibodies only, and 24 (39.3%) had both HSV-1 and HSV-2 antibodies. In contrast, among participants without a history of genital herpes, 30 (45.5%) had HSV-2 antibodies only, and 36 (54.5%) had both HSV-1 and HSV-2 antibodies (Table 1).

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### Graphic

TABLE 1. Demographics and Clinical Characteristics of Study Participants

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One hundred and six participants (83.5%) completed the study protocol; the most common causes of discontinuation were loss to follow-up (7.9%) and withdrawal of consent (6.3%). Participants without a history of genital herpes were less likely to complete the study than those with a history of clinical disease (77.3% vs. 90.2%). Eighty-one percent of participants collected at least 30 days of genital swabs during each study period. Overall, the median number of days in the study was 99 (range, 5-119), and the median time on the study drugs was 42 days for both famciclovir (range, 12-48) and placebo (range, 1-52). Participants obtained a median of 95 (range, 0-112) days of genital swabs; among those persons with HSV-1, a median of 95 oral swabs (range, 0-112) was also obtained. Participants who did not provide any swabs were excluded from shedding analyses. Analyses included swabs collected on 9152 patient-days, of which swabs of oral mucosa were collected on 4265 patient-days. Median adherence to the study drug, as determined by pill count and patient diaries, was 100% (range, 80%-100% during days on study).

### Effect of Famciclovir on HSV Shedding

Among participants with a clinical history of genital herpes, HSV shedding was detected at least once in 27 of 56 (48.2%) persons during famciclovir treatment versus 40 of 58 (69.0%) persons during placebo treatment. Among participants without a history of symptomatic genital herpes, HSV was detected at least once in 27 of 63 (42.9%) persons on famciclovir treatment and in 29 of 58 (50.0%) persons on placebo treatment (Table 1).

The pattern of total HSV shedding on days before, during, and after famciclovir treatment is shown in Figure 1. Overall, total HSV shedding from genital and oral sites decreased by 58.5%; from 11.4% of days on placebo to 4.7% of days on famciclovir (Table 2). Famciclovir treatment also resulted in a 43.8% reduction in days with subclinical genital and oral HSV shedding versus placebo (7.1% vs. 4%) and a 56.8% reduction in days with lesional genital and oral HSV shedding (64.4% vs. 27.9%). In addition, on days when HSV shedding was detected, fewer  $\log_{10}$  copies of HSV were present during famciclovir therapy compared with placebo therapy in total (4.66 vs. 5.36), subclinical (4.60 vs. 4.97), and lesional shedding (4.95 vs. 5.91), respectively (Table 2).

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**Graphic**

Fig. 1. Shedding frequency during the washout period before and after famciclovir therapy. Dotted lines mark the first and last day of treatment with famciclovir. The curve represents a locally weighted smoothed curve of daily shedding data.

**Graphic**

TABLE 2. Genital and Oral HSV Detection by PCR During the Study: the Entire Participant Population

The effect of famciclovir on genital and oral HSV shedding was further evaluated by history of clinical genital herpes. The number of days of genital and oral HSV shedding in famciclovir-treated participants with a history of genital herpes decreased by 73.7% versus those on placebo (14.7% vs. 3.9%) (Table 3). There was also a 65.5% decrease in subclinical viral shedding (8.6% vs. 3.0%) and a 49.1% decrease in lesional viral shedding (62.6% vs. 31.9%) for famciclovir-treated participants versus those on placebo. Fewer log<sub>10</sub> copies of HSV were present during famciclovir therapy versus placebo for total (4.75 vs. 5.34), subclinical (4.76 vs. 4.88), and lesional shedding (4.72 vs. 5.84), respectively.

**Graphic**

TABLE 3. Genital and Oral HSV Detection by PCR During the Study: Participants With a History of Genital Herpes

In participants without a history of clinical genital herpes, the number of days of HSV shedding decreased by a total of 30.1%: from 8.0% for participants on placebo to 5.6% for those treated with famciclovir (Table 4). There was also a 12.1% decrease in subclinical shedding for famciclovir versus placebo (5.7% vs. 5.0%), and a 66% decrease in lesional shedding (70.5% vs. 23.9%). When HSV shedding was detected, fewer log<sub>10</sub> copies of HSV were present during famciclovir therapy versus placebo for total (4.61 vs. 5.41), subclinical (4.51 vs. 5.10), and lesional shedding (5.24 vs. 6.11), respectively.

**Graphic**

TABLE 4. Genital and Oral HSV Detection by PCR During the Study: Participants Without a History of Genital Herpes

In a univariate analysis of risk factors for HSV genital shedding, famciclovir treatment resulted in a statistically significant reduction in total genital HSV shedding (RR, 0.35; 95% CI, 0.24-0.51;  $P < 0.001$ ) and subclinical genital HSV shedding (RR, 0.50; 95% CI, 0.33-0.75;  $P < 0.001$ ) versus placebo (Table 5). For participants with a history of clinical genital herpes, famciclovir treatment resulted in a statistically significant reduction in total (RR, 0.23; 95% CI, 0.15-0.35;  $P < 0.001$ ) and subclinical (RR, 0.33; 95% CI, 0.20-0.53;  $P < 0.001$ ) genital HSV shedding versus placebo. Famciclovir treatment also resulted in a reduction in risk of total (RR, 0.62; 95% CI, 0.32-1.20;  $P = 0.16$ ) and subclinical (RR, 0.80; 95% CI, 0.41-1.56;  $P = 0.52$ ) genital HSV shedding versus placebo in participants without a history of clinical genital herpes, but the difference was not significant (Table 6). In addition, the risk of total genital HSV shedding was higher for participants with a history of symptomatic genital herpes than for those without a history of clinical genital herpes (RR, 1.62; 95% CI, 1.03-2.56;  $P = 0.037$ ). Although the risk of subclinical genital HSV shedding was higher for participants with a clinical history than for those without, the difference was not significant (RR, 1.31; 95% CI, 0.80-2.14;  $P = 0.28$ ). There were no significant differences between women and men in genital shedding or between treatment periods 1 and 2. An adjusted analysis showed similar results (Tables 5 and 6).

**Graphic**

TABLE 5. Univariate and Multivariate Analysis of Risk Factors for Total and Subclinical Viral Shedding in the Genital and Oral Area for the Entire Population

## Graphic

TABLE 6. Univariate and Multivariate Analysis of Risk Factors for Total and Subclinical Viral Shedding in the Genital and Oral Area for Participants With or Without a Clinical History of Genital Herpes

In a univariate analysis of risk factors for HSV oral shedding, famciclovir decreased the risk of total and subclinical oral HSV shedding among HSV-1 and HSV-2 infected persons, but the effect was not statistically significant (RR, 0.60; 95% CI, 0.27-1.32;  $P = 0.20$  and RR, 0.63; 95% CI, 0.27-1.46;  $P = 0.29$ , respectively) (Table 5). Adjustment for potential confounders did not appreciably change the estimates. In adjusted analyses among HSV-1 and HSV-2 seropositive participants, those with a history of oral herpes were at higher risk for total HSV oral shedding (RR, 4.27; 95% CI, 1.86-9.77;  $P < 0.001$ ) and subclinical HSV oral shedding (RR, 3.39; 95% CI, 1.53-7.53;  $P = 0.003$ ) than participants without a history of symptomatic oral herpes. Differences in total or subclinical oral shedding frequency between men and women, or treatment periods were not statistically significant. However, for participants with a clinical history of genital herpes, famciclovir significantly decreased the risk of total and subclinical oral shedding (RR, 0.36; 95% CI, 0.14-0.90;  $P = 0.029$  and RR, 0.33; 95% CI, 0.20-0.53;  $P < 0.001$ , respectively) (Table 6). In addition, the risk of total oral HSV shedding was higher for participants with a history of oral herpes than for those without a history (RR, 4.82; 95% CI, 1.62-14.31;  $P = 0.005$ ), but the risk of subclinical oral HSV shedding in this population was not statistically significant (RR, 3.10; 95% CI, 0.96-10.03;  $P = 0.058$ ). There were no significant differences in the risk of total and subclinical oral HSV shedding in participants without a history of genital herpes. An adjusted analysis produced similar results (Table 6).

## Type-Specific Shedding of HSV in the Genital and Oral Areas

The distribution of frequency and quantity of HSV-2 shedding in the genital tract is shown in Figures 2A, B. Most HSV-1 and HSV-2 seropositive participants with a history of clinical genital herpes (Table 7) had HSV-2 detected in the genital area only (34.8% of participants while on famciclovir and 34.8% while on placebo). One participant on famciclovir (4.3%) and 5 on placebo (21.7%) had HSV-2 detected in both the genital and oral areas, and one participant on famciclovir (4.3%) had HSV-2 detected at oral sites only. HSV-1 was detected predominately at oral sites only (13.0% of participants on famciclovir and 30.4% of those on placebo). Only 4 participants (17.4%) had HSV-1 detected either at genital sites only ( $n = 2$ ) or at both genital and oral sites ( $n = 2$ ), all during the placebo period.

## Graphic

Fig. 2. Frequency of HSV-2 DNA detection in the genital tract during famciclovir and placebo administration. A, The frequency of shedding of HSV-2 in the genital tract on the famciclovir arm as compared to the placebo arm. B, The number of copies of HSV-2 per milliliter of genital-swab sample during episodes of shedding on the famciclovir arm as compared with the placebo arm.

## Graphic

TABLE 7. HSV Detection by Viral Type and Site in HSV-1 and HSV-2 Seropositive Participants

Among HSV-1 and HSV-2 seropositive participants without a history of clinical genital herpes (Table 7), 22.9% of those receiving famciclovir and 34.4% of those receiving placebo had HSV-2 detected in the genital tract only. HSV-2 was detected in both the genital and oral areas in 6 participants. HSV-1 was predominately detected at oral sites only (22.9% of participants on famciclovir and 31.3% of those on placebo) and 2 (6.3%) had HSV-1 detected at both genital and oral sites.

The frequency of genital and oral HSV-1 and HSV-2 detection in participants with or without a history of clinical genital herpes who were both HSV-1 and HSV-2 seropositive was also evaluated (Table 8). Overall, most genital shedding was caused by HSV-2 (250 days of genital HSV-2 detection vs. 22 days of genital HSV-1 detection). Genital HSV-2 shedding in participants with a history of clinical genital herpes decreased from 10.1% of days for those on placebo to 3.1% of days for those on famciclovir, and genital HSV-1 shedding also decreased, from 2.0% of days for participants on placebo to no days for those on famciclovir. In participants without a

history of genital herpes, genital HSV-2 shedding decreased from 7.8% for those on placebo to 2.7% for those on famciclovir, and genital HSV-1 shedding decreased from 0.3% of days for those on placebo to no days for those on famciclovir.

**Graphic**

TABLE 8. Frequency of HSV Detection by Viral Type and Site in HSV-1 and HSV-2 Seropositive Participants

Most oral shedding was caused by HSV-1. Of 169 days on which oral HSV was detected, 143 were HSV-1 and 26 were HSV-2. Oral shedding caused by HSV-1 in participants with a clinical history of genital herpes decreased from 4.5% for those on placebo to 1.1% for those on famciclovir, whereas oral shedding decreased slightly in participants without a history, from 3.9% for those on placebo to 3.5% for those on famciclovir. Oral HSV-2 shedding also decreased slightly with famciclovir versus placebo in participants with (1.2% vs. 0.8%) and without (0.5% vs. 0.2%) a history of clinical genital herpes (Table 8).

### Effect of Famciclovir on Frequency of Genital and Oral Lesions in Participants With or Without a History of Genital Herpes

Genital lesions were noted in 17.2% of participants with a history of symptomatic genital herpes during the famciclovir treatment period versus 39.0% during the placebo treatment period, and in 17.5% of participants without a clinical history of genital herpes during famciclovir treatment versus 17.2% of participants during placebo treatment (Table 1). Time to first recurrence of genital herpes was shorter among placebo recipients than famciclovir recipients (hazard ratio, 0.56; 95% CI, 0.35-0.91;  $P = 0.019$ ); in addition, oral lesions were identified in 13.0% of HSV-1 and HSV-2 seropositive participants with a history of symptomatic genital herpes during famciclovir treatment, and in 26.1% of participants during the placebo period.

Overall, the percent of days with lesions decreased from 6.2% during placebo administration to 2.3% during famciclovir administration (Table 2). Among participants with a history of genital herpes, the percent of days with lesions also decreased, from 9.1% during placebo administration to 2.7% during famciclovir administration (Table 3). A small decrease in the percent of days with lesions was noted among those without a history of genital herpes, from 3.2% during placebo administration to 2.0% during famciclovir administration (Table 4).

### Safety of Famciclovir

The overall proportion of participants with adverse events (AEs) was similar for the famciclovir and placebo treatment periods. The most commonly reported AEs ( $\geq 4\%$  for the famciclovir group) were headache (6.6% vs. 4.2%, respectively), nausea (5.8% vs. 2.5%), sinusitis (5.0% vs. 3.4%), diarrhea (4.1% vs. 2.5%), and fatigue (4.1% vs. 0.8%). Serious AEs were detected in 5% of participants taking famciclovir and in 4.2% of those taking placebo; no serious AEs were considered related to the study drug.

### Discussion

Famciclovir 250 mg bid effectively reduced the frequency of total and subclinical HSV shedding and percent of days with genital lesions for study participants with or without a history of genital herpes; however, the effect was more pronounced among persons with a history of symptomatic genital herpes, and for lesional shedding. Less effect was observed among participants without a history of genital herpes and with subclinical shedding. In addition, famciclovir significantly reduced the risk of total and subclinical genital HSV shedding among persons with a history of clinical genital herpes. The reduction in shedding occurred within 5 days of initiation of famciclovir therapy, and was maintained throughout the use of famciclovir treatment.

Because transmission of genital herpes often occurs during asymptomatic viral shedding,<sup>2,4</sup> it is important to determine the effect of antiviral therapy on such shedding. Although viral shedding among participants in this study was low compared with some previous study populations,<sup>11</sup> it was similar to that of participants enrolled in the valacyclovir transmission study.<sup>14</sup> Our results, which show that daily famciclovir treatment reduces subclinical viral shedding, support data from previous studies.<sup>13,21</sup>

To our knowledge, this is the first study to evaluate the frequency of genital HSV shedding by PCR in HSV-2 seropositive positive persons without a history of genital herpes. As seen in studies utilizing viral culture for HSV detection,<sup>6,22</sup> genital HSV reactivation in these persons is lower than HSV reactivation among persons with diagnosed genital herpes; however, even among persons without a history of genital herpes, 60% had at least one occurrence of viral shedding. These observations support prior studies showing that serologically diagnosed HSV-2 infection is both clinically and virologically active.<sup>4,6,22</sup> Although the reduction in risk in genital HSV shedding with famciclovir treatment was not statistically significant in persons without a clinical history of genital herpes, the benefit

of daily therapy in decreasing viral shedding might still extend to this subgroup of HSV-infected individuals.

Although previous studies have demonstrated cases of genital HSV-1 shedding and oral HSV-2 shedding, the frequency is not as great as that of genital HSV-2 and oral HSV-1 shedding—our findings are consistent with those previous studies.<sup>8,9,23,24</sup> Overall, famciclovir appeared to be effective in reducing both genital HSV-2 and oral HSV-1 shedding. Famciclovir treatment also appeared to decrease genital HSV-1 and oral HSV-2 shedding. Further studies are necessary to validate these findings.

In conclusion, famciclovir is effective in decreasing HSV shedding in HSV-2 seropositive individuals with and without a history of genital herpes, and reduces the risk of genital HSV shedding in individuals with a history of genital herpes. Future studies of HSV shedding should examine both HSV-1 and HSV-2 in order to provide a more accurate assessment of mucosal HSV infections, and to determine the most appropriate therapy. The potential differential effect of antiviral drugs on viral shedding in HSV-2 seropositive persons with and without a history of genital herpes warrants further study.

## References

1. Xu F, Sternberg MR, Kottiri BJ, et al. Trends in herpes simplex virus type 1 and type 2 seroprevalence in the United States. *JAMA* 2006; 296:964-973. [\[Context Link\]](#)
2. Wald A. Herpes simplex virus type 2 transmission: risk factors and virus shedding. *Herpes* 2004;11 (Suppl 3):130A-137A. [\[Context Link\]](#)
3. Koelle DM, Benedetti J, Langenberg A, et al. Asymptomatic reactivation of herpes simplex virus in women after the first episode of genital herpes. *Ann Intern Med* 1992; 116:433-437. [\[Context Link\]](#)
4. Mertz GJ, Schmidt O, Jourden JL, et al. Frequency of acquisition of first-episode genital infection with herpes simplex virus from symptomatic and asymptomatic source contacts. *Sex Transm Dis* 1985; b12:33-39. [\[Context Link\]](#)
5. Wald A, Zeh J, Selke S, et al. Virologic characteristics of subclinical and symptomatic genital herpes infections. *N Engl J Med* 1995; 333:770-775. [\[Context Link\]](#)
6. Wald A, Zeh J, Selke S, et al. Reactivation of genital herpes simplex virus type 2 infection in asymptomatic seropositive persons. *N Engl J Med* 2000; 342:844-850. [\[Context Link\]](#)
7. Wald A, Krantz E, Selke S, et al. Knowledge of partners' genital herpes protects against herpes simplex virus type 2 acquisition. *J Infect Dis* 2006; 194:42-52. [\[Context Link\]](#)
8. Chernes TL, Meyn LA, Hillier SL. Cunnilingus and vaginal intercourse are risk factors for herpes simplex virus type 1 acquisition in women. *Sex Transm Dis* 2005; 32:84-89. [\[Context Link\]](#)
9. Lafferty WE, Downey L, Celum C, et al. Herpes simplex virus type 1 as a cause of genital herpes: impact on surveillance and prevention. *J Infect Dis* 2000; 181:1454-1457. [\[Context Link\]](#)
10. Roberts CM, Pfister JR, Spear SJ. Increasing proportion of herpes simplex virus type 1 as a cause of genital herpes infection in college students. *Sex Transm Dis* 2003; 30:797-800. [\[Context Link\]](#)
11. Gupta R, Wald A, Krantz E, et al. Valacyclovir and acyclovir for suppression of shedding of herpes simplex virus in the genital tract. *J Infect Dis* 2004; 190:1374-1381. [\[Context Link\]](#)
12. Wald A, Zeh J, Barnum G, et al. Suppression of subclinical shedding of herpes simplex virus type 2 with acyclovir. *Ann Intern Med* 1996; 124:8-15. [\[Context Link\]](#)
13. Wald A, Selke S, Warren T, et al. Comparative efficacy of famciclovir and valacyclovir for suppression of recurrent genital herpes and viral shedding. *Sex Transm Dis* 2006; 33:529-533. [\[Context Link\]](#)
14. Corey L, Wald A, Patel R, et al. Once-daily valacyclovir to reduce the risk of transmission of genital herpes. *N Engl J Med* 2004;

350:11-20. [\[Context Link\]](#)

15. Earnshaw DL, Bacon TH, Darlison SJ, et al. Mode of antiviral action of penciclovir in MRC-5 cells infected with herpes simplex virus type 1 (HSV-1), HSV-2, and varicella-zoster virus. *Antimicrob Agents Chemother* 1992; 36:2747-2757. [\[Context Link\]](#)

16. Vere Hodge RA, Sutton D, Boyd MR, et al. Selection of an oral prodrug (BRL 42810; famciclovir) for the antiherpesvirus agent BRL 39123 [9-(4-hydroxy-3-hydroxymethylbut-1-yl)guanine; penciclovir]. *Antimicrob Agents Chemother* 1989; 33:1765-1773. [\[Context Link\]](#)

17. Ashley RL, Militoni J, Lee F, et al. Comparison of Western blot (immunoblot) and glycoprotein G-specific immunodot enzyme assay for detecting antibodies to herpes simplex virus types 1 and 2 in human sera. *J Clin Microbiol* 1988; 26:662-667. [\[Context Link\]](#)

18. Ashley RL, Corey L. Effect of acyclovir treatment of primary genital herpes on the antibody response to herpes simplex virus. *J Clin Invest* 1984; 73:681-688. [\[Context Link\]](#)

19. Corey L, Huang ML, Selke S, et al. Differentiation of herpes simplex virus types 1 and 2 in clinical samples by a real-time taqman PCR assay. *J Med Virol* 2005; 76:350-355. [\[Context Link\]](#)

20. Jerome KR, Huang ML, Wald A, et al. Quantitative stability of DNA after extended storage of clinical specimens as determined by real-time PCR. *J Clin Microbiol* 2002; 40:2609-2611. [\[Context Link\]](#)

21. Sacks SL. 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-center trial. *J Infect Dis* 2004; 189:1341-1347. [\[Context Link\]](#)

22. Sizemore JM Jr, Lakeman F, Whitley R, et al. The spectrum of genital herpes simplex virus infection in men attending a sexually transmitted disease clinic. *J Infect Dis* 2006; 193:905-911. [\[Context Link\]](#)

23. Kim HN, Meier A, Huang ML, et al. Oral herpes simplex virus type 2 reactivation in HIV-positive and -negative men. *J Infect Dis* 2006; 194:420-427. [\[Context Link\]](#)

24. Wald A, Ericsson M, Krantz E, et al. Oral shedding of herpes simplex virus type 2. *Sex Transm Infect* 2004; 80:272-276. [\[Context Link\]](#)

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