Valacyclovir reduced genital herpes transmission in couples discordant for herpes simplex virus type 2 infection


Clinical impact ratings GP/FP/Primary care ★★★★★★★ Infectious diseases ★★★★★★★

In heterosexual couples who are serologically discordant for herpes simplex virus type 2 (HSV-2) infection, does once daily valacyclovir reduce the sexual transmission of genital herpes?

METHODS

Design: randomised placebo controlled trial.
Allocation: concealed.
Blinding: blinded (participants, healthcare providers, data collectors, data analysts, and outcome assessors).
Follow up period: 8 months.
Setting: 96 sites in the US, Canada, Europe, Latin America, and Australia.
Participants: 1,498 couples ≥ 18 years who were immunocompetent, heterosexual, monogamous, in good health, and using effective contraception. One (source) partner had clinically symptomatic genital HSV-2 infection, presence of recurrent genital herpes with < 10 episodes/year, and non-use of any daily antiviral therapy. The other (susceptible) partner had HSV-2 seronegativity on Western blot analysis.
Intervention: oral valacyclovir, 500 mg once daily (n = 743), or matching placebo (n = 741) for source partners. Both partners received counselling on safer sex practices and were offered condoms at monthly visits.
Outcomes: laboratory confirmed clinically symptomatic first episode of genital HSV-2 infection (susceptible partner) and recurrence of genital HSV-2 infection (source partner).
Participant follow up: 99% (1,484 couples, median age 34.5 y, 67% women source partners; intention to treat analysis).

MAIN RESULTS

The table shows the results.

CONCLUSION

In heterosexual couples discordant for herpes simplex virus type 2 infection, valacyclovir reduced transmission of infection.

Commentary

Previous studies have shown that antiviral drugs can reduce the frequency of recurrence and subclinical shedding of viral particles. This important, large, well designed trial by Corey et al is the first to show an effect on the transmission of HSV-2 infection to an uninfected partner.

In this study, the reduction in transmission was limited; 62 partners had to take the drug daily for 8 months to prevent 1 infection, and 57 partners had to take the drug daily to prevent overall acquisition of HSV-2 infection. 2 independent predictors were found in addition to the drugs: women as the susceptible partners (hazard ratio [HR] 3.3) and duration of HSV-2 infection < 2 years (HR 2.9). Frequency of condom use was not an independent predictor. One may also ask what the effect would be if both partners used the drug, whether this would give an additional reduction of transmission of HSV-2.

Although the study recruited a high proportion of eligible participants, some methodological questions exist. 325 (22%) couples withdrew from the study. The reasons for withdrawal were similar in the 2 groups, except that 28 in the valacyclovir group and 54 in the placebo group withdrew voluntarily. This raises questions about allocation concealment or blinding in the study. Another concern is the study’s external validity. Monthly follow up may have created a “trial bias” because the compliance with drug and condom use was possibly higher than in real life.

How would I counsel couples with discordant HSV-2 infection? I would discuss the natural history of herpes infections, including the chance of symptomatic infection, long term prognosis, and chance of transmission without antiviral treatment. I would also discuss this study’s results, the concept of number needed to treat, and duration of treatment. Shared decision making would form the basis for the discussion. Further studies are needed to explore how long term treatment affects sexuality and relationships. In countries with a high prevalence of HIV, future research should test whether daily use of an antiviral, including acyclovir, helps reduce the risk of transmission of HIV-1 to negative partners.

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Valacyclovir v placebo for symptomatic genital herpes simplex virus type 2 (HSV-2) infection*

<table>
<thead>
<tr>
<th>Outcomes at 8 months</th>
<th>Valacyclovir</th>
<th>Placebo</th>
<th>Hazard ratio (95% CI)</th>
<th>NNT (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic HSV-2 infection in HSV-2 seronegative partners</td>
<td>0.5%</td>
<td>2.2%</td>
<td>0.25 (0.08 to 0.75)</td>
<td>62 (34 to 202)</td>
</tr>
<tr>
<td>Overall HSV-2 infection in seronegative partners</td>
<td>1.9%</td>
<td>3.6%</td>
<td>0.52 (0.27 to 0.99)</td>
<td>57 (29 to 1051)</td>
</tr>
<tr>
<td>H SV-1 or HSV-2 infection in seronegative partners</td>
<td>1.9%</td>
<td>4.2%</td>
<td>0.45 (0.24 to 0.84)</td>
<td>44 (24 to 174)</td>
</tr>
</tbody>
</table>

RRR (CI)

Genital recurrence in seronegative partners | 39% | 77% | 50% (45 to 55) | 3 (2 to 3) |

*Abbreviations defined in glossary; RRR, NNT, and CI calculated from data in article.