

Standard-dose and high-dose daily antiviral therapy for short episodes of genital HSV-2 reactivation: three randomised, open-label, cross-over trials



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Summary

Background Skin and mucosal herpes simplex virus type 2 (HSV-2) shedding predominantly occurs in short subclinical episodes. We assessed whether standard-dose or high-dose antiviral therapy reduces the frequency of such shedding.

Methods HSV-2-seropositive, HIV-seronegative people were enrolled at the University of Washington Virology Research Clinic (WA, USA). We did three separate but complementary open-label cross-over studies comparing no medication with aciclovir 400 mg twice daily (standard-dose aciclovir), valaciclovir 500 mg daily (standard-dose valaciclovir) with aciclovir 800 mg three times daily (high-dose aciclovir), and standard-dose valaciclovir with valaciclovir 1 g three times daily (high-dose valaciclovir). The allocation sequence was generated by a random number generator. Study drugs were supplied in identical, numbered, sealed boxes. Study periods lasted 4–7 weeks, separated by 1 week wash-out. Participants collected genital swabs four times daily for quantitative HSV DNA PCR. Clinical data were masked from laboratory personnel. The primary endpoint was within-person comparison of shedding rate in each study group. Analysis was per protocol. The trials are registered at ClinicalTrials.gov (NCT00362297, NCT00723229, NCT01346475).

Results Of 113 participants randomised, 90 were eligible for analysis of the primary endpoint. Participants collected 23 605 swabs; 1272 (5.4%) were HSV-positive. The frequency of HSV shedding was significantly higher in the no medication group ($n=384$, 18.1% of swabs) than in the standard-dose aciclovir group (25, 1.2%; incidence rate ratio [IRR] 0.05, 95% CI 0.03–0.08). High-dose aciclovir was associated with less shedding than standard-dose valaciclovir (198 [4.2%] vs 209 [4.5%]; IRR 0.79, 95% CI 0.63–1.00). Shedding was less frequent in the high-dose valaciclovir group than in the standard-dose valaciclovir group (164 [3.3%] vs 292 [5.8%]; 0.54, 0.44–0.66). The number of episodes per person-year did not differ significantly for standard-dose valaciclovir (22.6) versus high-dose aciclovir (20.2; $p=0.54$), and standard-dose valaciclovir (14.9) versus high-dose valaciclovir (16.5; $p=0.34$), but did for no medication (28.7) and standard-dose aciclovir (10.0; $p=0.001$). Median episode duration was longer for no medication than for standard-dose aciclovir (13 h vs 7 h; $p=0.01$) and for standard-dose valaciclovir than for high-dose valaciclovir (10 h vs 7 h; $p=0.03$), but did not differ significantly between standard-dose valaciclovir and high-dose aciclovir (8 h vs 8 h; $p=0.23$). Likewise, maximum \log_{10} copies of HSV detected per mL was higher for no medication than for standard-dose aciclovir (3.3 vs 2.9; $p=0.02$), and for standard-dose valaciclovir than for high-dose valaciclovir (2.5 vs 3.0; $p=0.001$), but no significant difference was recorded for standard-dose valaciclovir versus high-dose aciclovir (2.7 vs 2.8; $p=0.66$). 80% of episodes were subclinical in all study groups. Except for a higher frequency of headaches with high-dose valaciclovir ($n=13$, 30%) than with other regimens, all regimens were well tolerated.

Interpretation Short bursts of subclinical genital HSV reactivation are frequent, even during high-dose antiherpes therapy, and probably account for continued transmission of HSV during suppressive antiviral therapy. More potent antiviral therapy is needed to eliminate HSV transmission.

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Introduction

Infection with herpes simplex virus type 2 (HSV-2) is a global epidemic,¹ and significantly increases the risk of HIV-1 acquisition.² Despite the increased use of antiviral therapy in the past two decades, the prevalence of, and complications from, HSV-2 infection have changed little.^{3,4} Daily antiviral therapy reduces genital lesions^{5,6} and suppresses detection of HSV on genital mucosal surfaces (shedding).^{7,8} However, treatment with daily valaciclovir results in only a 48% reduction in the

risk of sexual transmission.⁹ Moreover, aciclovir does not effectively reduce the risk of HIV transmission or acquisition in HSV-2-seropositive people.^{10–12} The discrepancy between potent suppression of clinical symptoms and failure of antiviral agents to fully prevent HSV transmission is not well understood.

Intensive genital secretion collection shows that HSV shedding episodes are three-times more frequent than was previously realised.¹³ Nearly 50% of reactivations last less than 12 h; presumably they are cleared by the mucosal

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immune system.^{13,14} Mathematical models suggest that these short bursts of shedding are even more frequent than current sampling methods can detect, constituting 70–85% of all reactivations.¹⁵ Local host immune responses seem to control the severity, duration, and amount of virus detected during an outbreak.¹⁶ Trials using once daily genital sampling suggest that antiviral drugs reduce long episodes of high-copy-number HSV reactivation.⁷ However, whether antiviral drugs suppress short reactivation events is unknown. Failure to do so could account for the lower than expected effectiveness of antiviral drugs in clinical studies of HSV-2 transmission.

We did three complementary clinical studies to assess whether either standard or high doses of aciclovir and valaciclovir affect the frequency of short, subclinical periods of HSV genital reactivation.

Methods

Patients

HSV-2-seropositive, HIV-seronegative healthy adults, aged 18 years or older were recruited at the University of Washington Virology Research Clinic between November, 2006, and July, 2010. In trial 1, patients with both symptomatic and asymptomatic genital herpes were recruited. In trials 2 and 3, participants needed to have had at least four clinical HSV-2 recurrences in the previous year or laboratory-documented primary genital HSV-2 in the previous 6 months. Participants with previous adverse reactions to aciclovir, pregnant women, and those unable to comply with study procedures were excluded. Participants were recruited through newspaper advertisements, fliers, and by word of mouth. The studies were approved by the University of Washington Human Subjects Division and all participants provided written, informed consent.

Randomisation and masking

The random treatment allocation sequence was generated by a study statistician (MS) with a computerised random number generator. The sequence was known only to the statistician and the pharmacist, who prepared sequentially numbered, identical, sealed boxes containing the study drug and the assignment of first group in the crossover. Participants were assigned the next sequential sealed box by a study clinician at enrolment. Randomisation was stratified by sex. Patients were randomly assigned at a ratio of 1:1 for all drug groups. All three trials were open label, but clinical data were masked from laboratory personnel.

Procedures

Participants received the study medication for a prespecified period, had a 1 week wash-out period, and then crossed over to the other study medication for the remaining study period (figure 1). Trial 1 was designed to test whether standard-dose aciclovir (400 mg twice daily) suppressed short subclinical episodes of HSV shedding compared with no medication. Each study period was for 4 weeks. Trials 2 and 3 assessed whether higher doses of antiviral drugs or changes in the dosing schedule could provide more potent suppression of short shedding episodes. Participants in trial 2—standard-dose valaciclovir (500 mg daily) versus high-dose aciclovir (800 mg three times daily)—were followed up for 7 weeks in each group. Participants in trial 3—standard-dose versus high-dose valaciclovir (1 g three times daily) were followed up for 5 weeks in each group. The high doses were selected to provide a two-to-three times (for high-dose aciclovir)^{6,17} and an eight times (for high-dose valaciclovir)¹⁷ increase in the mean daily plasma aciclovir area under the curve (AUC) concentration, relative to

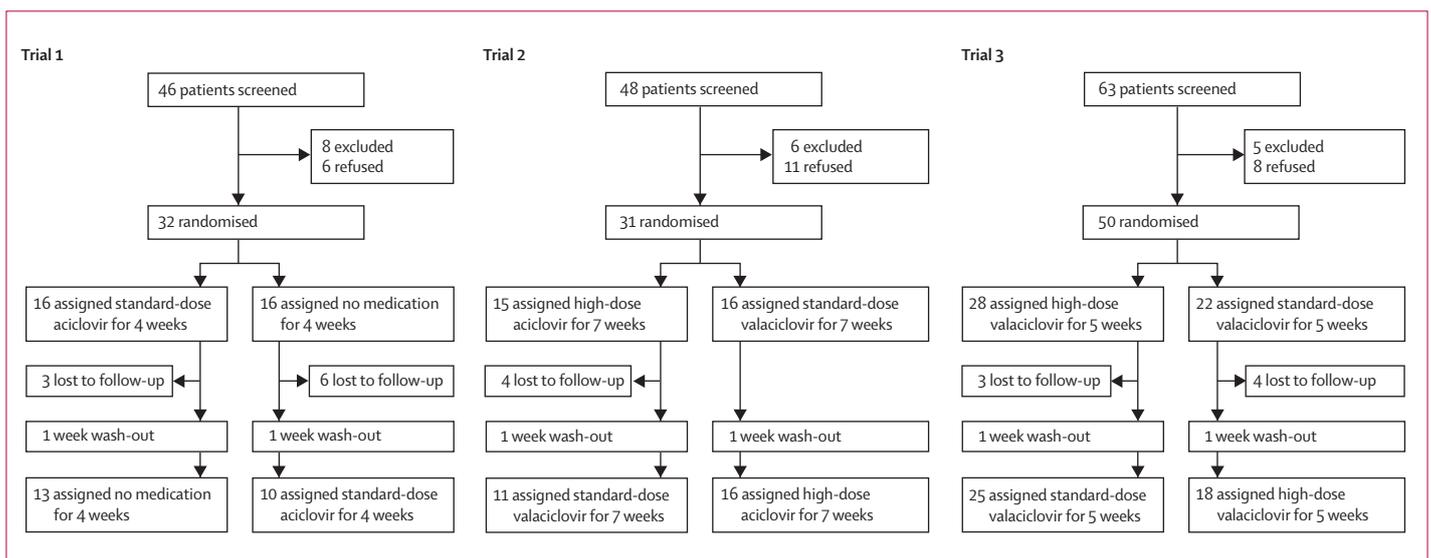


Figure 1: Trial profiles

standard-dose valaciclovir. The high-dose valaciclovir dose, which is also used for treatment of herpes zoster,¹⁷ was selected because clinical data suggest that this dose is safe. The study period was longer in trials 2 and 3 because we expected shedding rates during antiviral therapy to be low and we needed sufficient power to detect small differences in shedding rates between the two groups.¹⁸

Participants self-collected one genital swab four times daily, about every 4–6 h while awake, during each study period.¹³ Women swabbed the vaginal vault, the entire labia majora and labia minora, the perineum, and perianal area. Men swabbed the penile shaft, scrotum, perineum, and perianal area. Participants recorded genital symptoms and lesions daily.¹⁹ Participants met a clinician once every 2 weeks for swab collection, medication administration, assessment of side-effects, and genital examination, if symptomatic.

HSV serostatus was tested by western blot.²⁰ Genital swabs were placed in 1 mL 1X PCR buffer and stored at 4°C. DNA was extracted from genital swabs, and HSV was quantified by real-time PCR, with HSV-specific primers to glycoprotein B.²¹ Samples containing 150 copies of HSV DNA or more per mL of PCR buffer were classed as positive.²²

The primary outcome was HSV shedding rate, measured by the number of swabs with HSV detected divided by the number of swabs collected during each treatment period per participant, for each study. Secondary outcomes by treatment group were number of HSV shedding episodes, duration of HSV shedding episodes, and maximum quantity of HSV DNA detected in a shedding episode. Episodes were defined as any number of swabs with HSV detected, immediately preceded by two negative swabs and followed by two negative swabs. Episode duration was extrapolated by estimation of start and stop times at the midpoint between the last HSV-positive and first HSV-negative swabs. Participants who did not collect at least one swab during each study period were excluded from the analyses.

Adverse events were assessed at each study visit. White blood cell count, and renal and liver function tests were done once every 2 weeks in people enrolled in trial 3. Adverse events were graded with National Cancer Institute common terminology criteria (version 3.0).²³

Statistical analysis

Estimates of shedding frequency were based on natural history studies using four samples per day,^{13,14} and within-person correlation was estimated to be 0.2.⁷ Use of a sample size calculation for repeated-measures binary data²⁴ and assumption of a genital shedding rate of 10% with no medication provides trial 1 with 80% power to detect a 35% reduction in genital shedding rates for standard-dose aciclovir. Assumption of a genital shedding rate of 3% for standard-dose valaciclovir⁷ provides trials 2 and 3 with 80% power to detect a 50% reduction in HSV genital shedding rates for high-dose aciclovir or valaciclovir

compared with standard-dose valaciclovir. A 20% loss to follow-up was assumed for all trials. The first day in each treatment period was excluded from the analysis. HSV genital shedding rates and episode rates were compared by Poisson regression, including a scale parameter for overdispersion and the log number of swabs as the offset. Sequence and period effects were included in the model. Generalised estimating equations were used to compare shedding rates between no medication and drug groups in trials 2 and 3. Linear mixed models were used to compare episode rate, episode duration, maximum HSV log₁₀ copy number during episodes, and HSV log₁₀ copy number in positive swabs by treatment group, and to test for an association between episode duration and maximum HSV log₁₀ copy number. Episode kinetics were calculated by computation of the slope of a linear regression line from the beginning to peak (expansion) or peak to end (clearance) of an episode.²⁵ The Wilcoxon signed rank test for matched pairs was used to compare drug adherence rates by treatment as measured by pill counts. Correlation between adherence and genital shedding rate was measured with the Spearman correlation coefficient. The yearly episode rate was calculated by dividing the number of episodes by the person-years of follow-up per treatment group. Two-sided p values less than 0.05 were judged statistically significant. Data were analysed with Stata version 10.1. The trials are registered at ClinicalTrials.gov (NCT00362297, NCT00723229, NCT01346475).

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of 157 participants screened, 90 were enrolled and took samples for both study periods (figure 1); three participants enrolled in both trial 1 and trial 3, so were excluded from the comparison of shedding rates between the no medication and drug groups. The median age was 43 years (IQR 30–51). 49 (54%) participants were women, and 76 (84%) were white. 50 (56%) participants were HSV-2 seropositive only; 39 (43%) were HSV-1 and HSV-2 seropositive. The median duration of HSV-2 infection was 7.6 years (IQR 1.8–19.5). The demographics of the study population were similar in each of the trials (webappendix).

90 participants took 23605 (86%) of a possible 27319 swabs. Swabs were taken a median of 5.8 h (IQR 4.5–7.2) apart. 23 participants took 2123 swabs while receiving no medication, and HSV was detected in 384 (18%) of these swabs (table, figure 2). Although all doses of aciclovir reduced the frequency of detection of HSV compared with no medication (no medication vs standard-dose valaciclovir, $p=0.003$; no medication vs

See Online for webappendix

	Trial 1		Trial 2		Trial 3	
	No medication (N=23)	Standard-dose aciclovir (N=23)	Standard-dose valaciclovir (N=27)	High-dose aciclovir (N=27)	Standard-dose valaciclovir (N=43)	High-dose valaciclovir (N=43)
Genital HSV shedding rates						
Overall						
Swabs with HSV detected	384/2123 (18%)	25/2129 (1%)	209/4663 (4%)	198/4709 (4%)	292/5008 (6%)	164/4973 (3%)
Days with HSV detected	143/599 (24%)	21/604 (3%)	113/1251 (9%)	110/1274 (9%)	120/1378 (9%)	94/1395 (7%)
Per participant*						
Swabs collected	96 (88–107)	96 (85–106)	180 (155–189)	178 (168–193)	121 (110–130)	117 (105–131)
Days in study	27 (26–28)	28 (26–29)	48 (48–49)	49 (48–50)	34 (34–35)	34 (34–35)
Swabs with HSV detected (%)	11 (0–32)	0 (0–1)	2 (1–4)	1 (0–3)	3 (0–9)	1 (0–4)
Days with HSV detected (%)	21 (0–38)	0 (0–4)	4 (2–13)	2 (0–6)	5 (0–15)	3 (0–10)
Characteristics of genital HSV shedding episodes						
Episodes (n)	49	17	81	74	58	65
Episodes per person	1 (0–4)	0 (0–1)	2 (1–5)	1 (0–3)	1 (0–2)	1 (0–2)
Follow-up (person-years)	1.71	1.70	3.59	3.66	3.89	3.93
Subclinical episodes	32 (65)	16 (94)	74 (91)	68 (92)	37 (64)†	48 (74)‡
Annualised episode rate (episodes per person-year)	28.7	10.0	22.6	20.2	14.9	16.5
Episodes of known duration (n)	36	15	69	57	42	41
Episode duration (h)	13 (7–73)	7 (6–13)	8 (6–18)	8 (6–19)	10 (7–42)	7 (6–9)
Maximum log ₁₀ copies per mL	3.3 (2.5–5.7)	2.9 (2.4–3.4)	2.7 (2.4–3.1)	2.8 (2.5–3.2)	3.0 (2.4–4.5)	2.5 (2.3–2.7)

Data are n/N (%), n (%), or median (IQR) unless otherwise stated. HSV=herpes simplex virus. *The number of participants is as noted in figure 1, excluding those who were lost to follow-up. †Data missing for three episodes. ‡Data missing for 11 episodes.

Table: HSV shedding outcomes

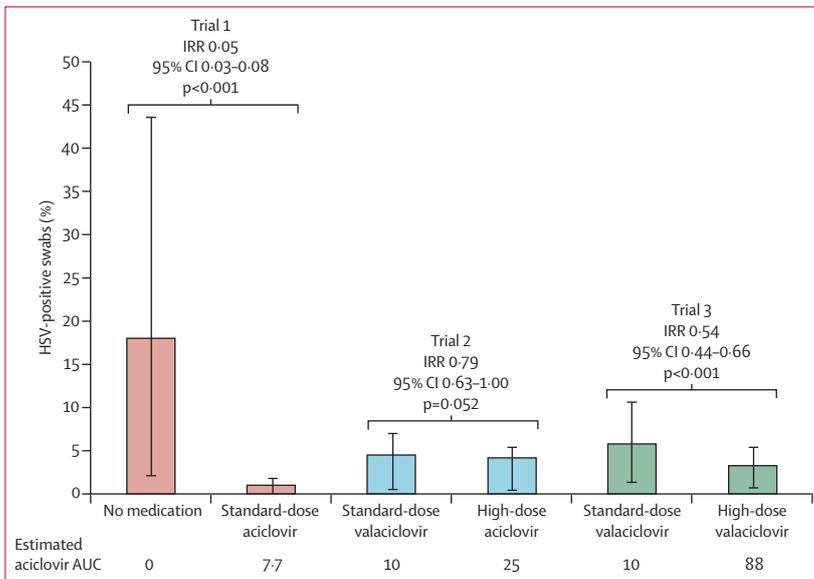


Figure 2: HSV detection in genital swabs
 Error bars are the 95% CIs. AUCs taken from Reitano and colleagues⁶ and Beutner and colleagues.¹⁷ IRR=incidence risk ratio. AUC=area under the curve (μg × h per mL).

high-dose aciclovir, $p=0.002$; no medication vs high-dose valaciclovir, $p<0.0001$), breakthrough reactivation occurred at all drug doses (figure 2). Fewer swabs had detectable HSV during standard-dose aciclovir compared with no medication (IRR 0.05, 95% CI 0.03–0.08). HSV

detection was lower for high-dose aciclovir compared with standard-dose valaciclovir (table; IRR 0.79, 95% CI 0.63–1.00). A dose effect on HSV shedding was noted during high-dose valaciclovir compared with standard-dose valaciclovir (table; IRR 0.54, 95% CI 0.44–0.66). No sequence effects were detected for any trial (data not shown). Period effects were present in all three trials and the models were adjusted accordingly.

In total, 344 genital HSV shedding episodes occurred (webappendix). The table shows characteristics of HSV shedding episodes by treatment group. Most shedding episodes were subclinical during all active treatment periods. Episodes were significantly less frequent in patients receiving standard-dose aciclovir than in those receiving no medication ($p=0.001$). Episode frequency did not differ between standard-dose valaciclovir and high-dose aciclovir ($p=0.54$), or between standard-dose and high-dose valaciclovir ($p=0.34$).

The median maximum number of HSV copies detected per episode was significantly higher during no medication than with standard-dose aciclovir (table; $p=0.02$). The quantity of HSV detected did not differ during episodes for standard-dose valaciclovir and high-dose aciclovir ($p=0.66$), but it was significantly lower for high-dose valaciclovir than for standard-dose valaciclovir ($p=0.001$). The distribution of quantity of HSV detected on each antiviral dose is shown in the webappendix.

Of the 344 HSV shedding episodes, 84 were of unknown duration; in 44 (13%) cases the episode was detected at the

beginning or end of the treatment period, and in 40 (12%) swabs were missing. Of the 260 HSV shedding episodes of known duration, median episode duration was longer with no medication than for standard-dose aciclovir (table; $p=0.01$). The median episode duration was the same for standard-dose valaciclovir and high-dose aciclovir ($p=0.23$), but it was significantly shorter for high-dose than for standard-dose valaciclovir ($p=0.03$). The median viral expansion in 6 h was much the same for standard-dose valaciclovir (4.6 log, IQR 1.5–5.7), high-dose aciclovir (4.8 log, 1.5–5.5) and high-dose valaciclovir (4.7 log, 4.4–5.2). However, viral clearance in 6 h was greater for high-dose valaciclovir (4.7 log, 4.4–5.2) than for standard-dose valaciclovir (4.4 log, 0.8–4.7, $p=0.016$). Most shedding episodes on antiviral therapy were short irrespective of dose: 75 (60%) of 126 episodes with standard-dose antiviral therapy, 33 (58%) of 57 with high-dose aciclovir, and 32 (78%) of 41 with high-dose valaciclovir lasted less than 12 h (webappendix). Episode duration was correlated with maximum \log_{10} copy number during the episode (0.15 log for each 6 h increase, $p<0.0001$).

Demographic characteristics and shedding rates of participants who were lost to follow-up and those who completed the study did not differ (data not shown). 78–96% of participants in each study reported more than 85% adherence to the study medication, with a median adherence of 98–100% for each study group. No correlation between drug adherence and shedding was detected (data not shown). 3748 swabs were missing for participants included in the final analysis, which corresponds to 1630 intervals when at least one swab was not taken. Of these intervals, 1129 (69%) had a swab missing at one point, 410 (25%) were missing a swab at two to five consecutive points, and 91 (6%) were missing swabs from more than five consecutive timepoints. Each study group and trial had a similar proportion of missing swabs (11.4%, 14.3%, and 14.8% for trial 1, 2, and 3, respectively).

During high-dose valaciclovir therapy, 13 (30%) of 43 participants complained of headache on at least 1 day (compared with none for standard-dose valaciclovir). Nausea ($n=3$; 7%), and myalgias ($n=2$; 5%) were also reported during high-dose valaciclovir. Two (5%) participants developed grade 2 neutropenia with high-dose and standard-dose valaciclovir. No additional abnormalities in complete blood count, liver function, or renal function, or adverse events related to study medication were noted. We sequenced the HSV thymidine kinase gene from a representative swab sample²⁶ of one participant with high rates of shedding in both study periods in trial 2 (webappendix), and did not detect any mutation known to confer aciclovir resistance (Genbank accession number HM446467).²⁷

Discussion

Although daily antiviral therapy nearly eliminated symptomatic recurrences and reduced the frequency of episodes of shedding with high copy number, short

Panel: Research in context

Systematic review

A meta-analysis²⁸ of 14 randomised clinical trials of antiviral therapy for herpes simplex virus type 2 (HSV-2) showed a 47% (95% CI 45–49) overall relative risk reduction of recurrence in patients receiving suppressive therapy compared with placebo.²⁸ Aciclovir and valaciclovir also suppress genital herpes shedding by 70–80% compared with placebo.⁷ Suppression of genital herpes with aciclovir and valaciclovir has been studied for public health benefit; to prevent both HSV-2 transmission,⁹ and HIV transmission¹² and acquisition.^{10,11} Despite a 70% reduction in genital HSV-2 shedding, HSV-2 transmission was suppressed by only 48%.⁹ Furthermore, HSV-2 suppression was not effective in preventing HIV transmission¹² or acquisition.^{10,11} These results have led to questions about the discrepancy between shedding rates and clinical outcomes, and whether increased doses of antiviral agents would be effective.

Interpretation

Our results show that short episodes of subclinical shedding persist with both standard-dose and high-dose aciclovir and valaciclovir. Although HSV shedding was reduced by 50% with the highest doses of valaciclovir (1 g, three times daily), the rate of breakthrough shedding episodes did not change—about 16–20 episodes per year. These data suggest that novel therapies are needed to completely prevent HSV reactivation.

episodes of genital HSV shedding occur frequently with antiviral therapy, even for high-dose regimens that increase the aciclovir AUC eight times compared with standard suppressive doses of aciclovir or valaciclovir. These breakthrough episodes are typically subclinical, last several hours, and occur at much the same rate irrespective of antiviral dose, providing a likely explanation for the inability of daily suppressive therapy to completely abrogate HSV-2 transmission.

Studies measuring the clinical effectiveness of aciclovir and valaciclovir in immunocompetent people have shown similar efficacy, except in people with very frequent recurrences (panel).⁶ Initial clinical trials of aciclovir and valaciclovir showed high efficacy for the prevention of genital herpes symptomatic recurrences.^{5,6} Trials that assessed suppression of subclinical shedding also showed a substantial effect, although efficacy was greater when measured by viral culture (roughly 95%)⁸ than by PCR (70–80%).⁷ Because of the high success in reduction of clinical and subclinical shedding, valaciclovir 500 mg daily was selected as the dose to test for reduction in sexual transmission of HSV. Interestingly, this dose reduced the sexual transmission of HSV by only 48% in discordant couples, despite a 73% reduction in subclinical shedding in the same population.⁹ In our study, most participants had one or two shedding episodes per month with both standard-dose and high-dose antiviral therapy. Despite the

short duration of these episodes, a substantial proportion—20% for standard-dose antiviral therapy—had more than 10^4 HSV copies per mL; these episodes were not eliminated with high-dose valaciclovir. Our data suggest that anti-HSV therapy, although clinically effective, does not substantially alter the underlying pathobiology of frequent, subclinical HSV-2 reactivation. That we could not eliminate or even alter the frequency of shedding episodes with high-dose valaciclovir suggests that the maximum benefit of shedding reduction has probably been reached for currently available antiviral drugs.

Modelling studies suggest that reported shedding patterns can be replicated by simulated frequent release of small amounts of HSV from neurons.¹⁵ The short episodes noted in our trial might be the earliest HSV replication events during or after neuronal HSV reactivation. Possible explanations for this finding include inadequate aciclovir concentrations in neurons because of the blood–brain barrier²⁹ or less efficient conversion to aciclovir triphosphate in neurons than in epithelial cells.³⁰ Our finding that high-dose valaciclovir increases the kinetics of viral clearance, but not expansion, supports the hypothesis that these antiviral drugs do not suppress the release of virions into the genital tract.

Our study had several strengths, including a rigorous cross-over design, which allowed for intraperson comparisons, and motivated participants who complied with intensive swabbing schedules. The high medication adherence rate, the inclusion of a three times daily drug regimen, and the similarity in episode frequency and duration across trials suggest that our findings are not affected by the absorption kinetics of these antiviral drugs, but by their underlying mechanism of action. Additionally, we used a validated, highly sensitive and specific PCR assay,²² minimising the likelihood of false-positive detection of HSV. Although the threshold copy number necessary or sufficient for transmission has not been established, HSV transmission from culture-negative, PCR-positive secretions has been documented.³¹ Additionally, the linear relation between log copy numbers and probability of viral replication in tissue media suggests that a threshold for infectivity is unlikely to be defined.³²

Ideally, these trials would have had several dose cross-overs for each participant.⁷ However, the intensity of taking swabs very frequently made this impracticable—such a design would have necessitated intensive swabbing for nearly 150 days for each participant. Our study was not powered to compare shedding rates for different antiviral doses between trials, because the cross-over design relied on comparison of the shedding rates within each person. The similarity in shedding rates for all doses shows the reproducibility of the results. However, in view of the differences in study design and population, we caution against direct comparisons between the antiviral doses of the three trials. We recruited people with clinically recognised disease who would be expected to have higher shedding rates in the trials of high-dose aciclovir and

valaciclovir, to better detect a difference in shedding rates between the study periods. Despite the attempt to show such a difference, even very high doses of valaciclovir were associated with breakthrough genital HSV shedding. The trials were done at a single site, and enrolled mostly white, healthy, sexually active adults.³³ The generalisability of these data to other geographic regions or racial or ethnic groups is unknown. Furthermore, we cannot extrapolate these findings to immunosuppressed patients. Although the studies were open label, we do not expect that this introduced bias because the endpoint (HSV shedding) is not subjective and laboratory personnel were masked to study group.

Although currently available anti-HSV therapy benefits patients by preventing clinical HSV recurrences, suppressive therapies with greater potency, including antiviral drugs or immunotherapy in the form of therapeutic vaccines, are needed to provide substantial public health benefits, such as prevention of HSV-2 transmission and HIV-1 acquisition and transmission.

Contributors

CJ, AW, and LC designed the trials. SK and SS collected the data, supervised by CJ. MLH and DMK did the laboratory assays. MS, AM, JTS, and CJ analysed the data. CJ drafted the manuscript. All authors interpreted the data and edited the manuscript. All authors approved the final version of the manuscript.

Conflicts of interest

CJ is a research investigator for AiCuris, GmbH, which is developing treatments for HSV. AW and LC are consultants for AiCuris GmbH. LC is the head of the scientific advisory board for, and holds stock (<1% of company) in Immune Design Corp. LC and DMK are listed as co-inventors in several patents describing antigens and epitopes to which T-cell responses to HSV-2 are directed. AM and DMK are consultants for Immune Design Corp. DMK is a consultant to Sanofi-Pasteur and Agenus, for HSV-2 vaccines, and is contracted by Coridon, Vical, and PATH for preclinical assessment of a candidate HSV-2 vaccine. MS, SK, SS, MLH, JTS declare that they have no conflicts of interest.

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