JAMA | Original Investigation

Effect of Pritelivir Compared With Valacyclovir on Genital HSV-2 Shedding in Patients With Frequent Recurrences

A Randomized Clinical Trial

Anna Wald, MD, MPH; Burkhard Timmler, MD; Amalia Magaret, PhD; Terri Warren, ANP; Stephen Tyring, MD, PhD; Christine Johnston, MD, MPH; Kenneth Fife, MD, PhD; Stacy Selke, MA; Meei-Li Huang, PhD; Hans-Peter Stobernack, PhD; Holger Zimmermann, PhD; Lawrence Corey, MD; Alexander Birkmann, PhD; Helga Ruebsamen-Schaeff, PhD

Editorial page 2493

Supplemental content

IMPORTANCE Current therapy of herpes infections relies on nucleoside analogues. Pritelivir is a well-tolerated novel herpes simplex virus (HSV) helicase-primase inhibitor that reduced genital shedding and lesions.

OBJECTIVE To compare the efficacy of pritelivir with valacyclovir for suppression of genital HSV-2 infection.

DESIGN, SETTING, AND PARTICIPANTS A phase 2, randomized, double-blind, crossover clinical trial at clinical research centers in 4 US cities (October 2012-July 2013) compared daily oral doses of 100 mg of pritelivir with 500 mg of valacyclovir. The planned sample size was 98 adults, allowing for detection of a 50% reduction in viral shedding between the study treatments. Healthy adults with 4 to 9 annual genital HSV-2 recurrences were eligible. Ninety-one participants were randomized: 45 to receive pritelivir and 46 to receive valacyclovir first when the US Food and Drug Administration placed the trial on clinical hold based on findings in a concurrent nonclinical toxicity study, and the sponsor terminated the study.

INTERVENTIONS Participants took the first drug for 28 days followed by 28 days of washout before taking the second drug for 28 days. Throughout treatment, the participants collected genital swabs 4 times daily for testing by HSV polymerase chain reaction assays.

MAIN OUTCOMES AND MEASURES The primary end point was within-participant genital HSV shedding while receiving pritelivir compared with valacyclovir. Secondary end points included the quantity of HSV in positive swabs and the frequency of genital lesions and shedding episodes.

RESULTS Of the 91 randomized participants (median age, 48 years; 57 women [63%]), 56 had completed both treatment periods at the time of the study's termination. In intent-to-treat analyses, HSV shedding was detected in 2.4% (173 of 7276) of swabs during pritelivir treatment compared with 5.3% (392 of 7453) during valacyclovir treatment (relative risk [RR], 0.42; 95% CI, 0.21 to 0.82; *P* = .01). In swabs with HSV, the mean quantity of HSV was 3.2 $\log_{10}$ copies/mL during pritelivir treatment vs 3.7 $\log_{10}$ copies/mL during valacyclovir treatment (difference, −0.1; 95% CI, −0.6 to 0.5; *P* = .83). Genital lesions were present on 1.9% of days in the pritelivir group vs 3.9% in the valacyclovir group (RR, 0.40; 95% CI, 0.17-0.96; *P* = .04). The frequency of shedding episodes did not differ by group, with 1.3 per person-month for pritelivir and 1.6 per person-month for valacyclovir (RR, 0.80; 95% CI, 0.52 to 1.22; *P* = .29). Treatment-emergent adverse events occurred in 62.3% of participants in the pritelivir group and 69.2% of participants in the valacyclovir group.

CONCLUSIONS AND RELEVANCE Among adults with frequently recurring genital HSV-2, the use of pritelivir compared with valacyclovir resulted in a lower percentage of swabs with HSV detection over 28 days. Further research is needed to assess longer-term efficacy and safety.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01658826

JAMA. 2016;316(23):2495-2503. doi:10.1001/jama.2016.18189
Corrected on January 26, 2017.

Author Affiliations: University of Washington & Fred Hutchinson Cancer Research Center, Seattle (Wald, Magaret, Johnston, Selke, Huang, Corey); AiCuris Anti-infective Cures GmbH, Wuppertal, Germany (Timmler, Stobernack, Zimmermann, Birkmann, Ruebsamen-Schaeff); Westover Heights Clinic, Portland, Oregon (Warren); University of Texas Health Science Center & Center for Clinical Studies, Houston (Tyring); Indiana University School of Medicine, Indianapolis (Fife).

Corresponding Author: Anna Wald, MD, MPH, University of Washington Virology Research Clinic, PO Box 359928, 325 Ninth Ave, Seattle, WA 98104 (annawald@u.washington.edu).

The treatment for genital herpes simplex virus (HSV) infections relies on the nucleoside analogues acyclovir, valacyclovir, or famciclovir administered either for each recurrence or daily to prevent recurrences.[1] In addition, valacyclovir, when taken daily by a person with genital herpes has been shown to reduce the risk of HSV-2 transmission to susceptible partners.[2] However, the protection is only partial (approximately 50%), likely because these drugs neither completely inhibit genital viral shedding nor reduce the risk of human immunodeficiency virus (HIV) acquisition conferred by HSV-2 infection.[3,4] Nucleoside analogues inhibit viral replication by chain termination of viral DNA after monophosphorylation by the viral thymidine kinase followed by phosphorylation to triphosphate by cellular kinases.[5] Drug resistance is uncommon in immunocompetent persons but may occur in immunocompromised hosts in whom treatment is difficult due to lack of safe alternative medications. Therefore, alternative agents to treat HSV infections are needed.

Pritelivir inhibits HSV replication but at the helicase-primase complex and does not require an activation step.[6] In a placebo-controlled study, oral pritelivir was well tolerated and reduced the risk of genital viral shedding in a dose-dependent manner.[7] In the present study, pritelivir was compared with valacyclovir for reduction of genital HSV shedding and lesions in persons with recurrent genital herpes.

Key Points

Question Is pritelivir more effective than valacyclovir for suppression of genital herpes simplex virus 2 (HSV-2) shedding in patients with frequent recurrences?

Findings In this double-blind, randomized crossover study of 91 adults with recurrent genital herpes, the percentage of genital swabs with HSV detected over 28 days was significantly lower during use of pritelivir than use of valacyclovir (2.4% vs 5.3%).

Meaning Pritelivir may be more effective for suppression of genital HSV-2 infection than valacyclovir, but further research is needed to assess longer-term efficacy and safety.

Methods

The trial protocol and statistical analysis plan are available in Supplements 1 and 2.

Participants and Procedures

Eligible participants included healthy adults who were aged 18 years or older, HSV-2 seropositive, HIV seronegative, hepatitis B and C negative, and had a history of 4 to 9 genital herpes recurrences in the last year or in the year prior to starting suppressive antiviral therapy. Race information was self-reported. Participants had to agree to use effective contraception, refrain from using any anti-HSV therapy for 7 days prior to and during the treatment period, and be willing to complete all trial procedures. Exclusion criteria were pregnancy, nursing, malignancy or immunosuppression, steroid administration, other immunosuppressive medications, or medications that induced drug-metabolizing enzymes or transporters. In addition, participants had to avoid grapefruit and products containing quinine or quinidine during the study. All participants gave written informed consent. The study was approved by the institutional review board at each participating institution.

Study Design and Procedures

In this randomized, double-blind, double-dummy crossover trial, participants received 100 mg of oral pritelivir (after a loading dose of 400 mg on day 1) plus placebo or 500 mg of valacyclovir plus placebo daily for 28 days, followed by a 28-day washout period, and then 28 days of the other drug with matching placebo and 28 days of follow-up. Randomization was conducted centrally with random-number generators using a dynamic scheme to ensure treatment balance overall and within strata, allocating each subsequent participant to the least populated group, or in the case of ties, using a pregenerated random-number list to determine assignment; the strata used were sex and study site. Valacyclovir was encapsulated and placebo tablets or capsules were manufactured to be indistinguishable from active agents to permit blinding of participants and investigators. Participants were required to be free of genital lesions on the first day of each treatment period. Throughout the two 28-day treatment periods, participants obtained swabs from their genital area 4 times during each 24-hour period, approximately 6 to 8 hours apart. The swabs were brought to clinic at the next weekly visit.[8] If a lesion consistent with genital herpes developed, an additional swab was obtained from the lesion at home and participants came to clinic for evaluation. Participants maintained a diary of genital lesions and symptoms, and recorded adherence to the swabbing procedure and the study drugs. Adherence was calculated as the proportion of the expected amount of the drug taken and calculated by pill counts of returned blister pack. Adherence to swabs was defined as the proportion of swabs returned of expected.

The dose of 100 mg of pritelivir daily was chosen based on phase 1 and 2 studies suggesting safety and tolerability of this regimen and also on the high efficacy of 75 mg of pritelivir in suppressing viral shedding in the prior trial.[7]

Safety of the study drugs was evaluated with a weekly history and physical examination; laboratory assays for hematology, metabolic panel, and liver function tests; and an electrocardiogram during each treatment period. All adverse events were graded using the division of acquired immunodeficiency syndrome (DAIDS) table of adverse events.[9]

Laboratory Studies

The University of Washington Western blot was used to assess HSV-2 antibody status.[10] Samples of genital secretions were tested for HSV DNA with a real-time, quantitative polymerase chain reaction TaqMan assay at the University of Washington Virology Laboratory.[11] Swabs were considered positive for HSV when at least 150 (2.2 $\log_{10}$) HSV DNA copies per mL were detected.[12] To monitor potential signals of drug-resistance, HSV detected during administration of pritelivir at more than 5000 copies of DNA per mL were sequenced in the resistance-associated regions within *UL5* and *UL52* of HSV-2.[13,14]

Sample Size

The sample size estimate for the primary efficacy end point was based on the anticipated occurrence of genital shedding, defined as the number of swabs that tested positive for HSV for study participants relative to the total numbers of swabs collected from each participant. We estimated HSV shedding at 5% during valacyclovir administration and 1% to 2% during pritelivir therapy.[3] Using a crossover design with 80% power, 5% type 1 error, and a discontinuation rate of 6%, we planned to screen 120 volunteers and randomize 90. However, after trial initiation, the decision was made to increase enrollment to 98 because of concern for the possibility that a greater number of participants would drop out given the burden of the study procedures.

Outcomes

The primary end point was the intent-to-treat comparison of within-participant HSV shedding, defined as the number of swabs that tested positive for HSV per study participant relative to the total number of swabs collected per participant, during pritelivir vs valacyclovir therapy. Secondary end points included a comparison of copy number of the HSV DNA on the days that HSV was detected, HSV shedding on days with and without lesions, frequency of lesions, and frequency of episodes. An episode was defined as an event in which consecutive swabs tested positive for HSV DNA and were preceded and followed by swabs that tested negative. Additional secondary analyses evaluated the duration of pain, shedding episodes, and recurrences.

Statistical Analyses

The analysis was conducted using a nonlinear mixed-effects model with a log link with a random intercept for each participant to account for extra-Poisson variability.[15] Period and carryover effects were examined at a 10% significance level using, respectively, a term for time period and an interaction term between the treatment group and time period. Analyses of duration used Wilcoxon signed rank test.

The intent-to-treat analyses included all randomized participants who received at least 1 dose of the study drug and obtained at least 1 genital swab; per-protocol analyses excluded persons with major protocol deviations, including early discontinuation of the study or study medication. The first day of treatment was excluded from efficacy analyses.

Safety analyses included all randomized participants who received at least 1 dose of the study drug. Missing data were not imputed. Statistical significance was defined as a 2-sided *P* value of <.05. Analyses were performed using SAS 9.4 statistical software (SAS Institute Inc).

Results

Study Population

The study was conducted at 4 clinical research centers located in Seattle, Washington; Portland, Oregon; Indianapolis, Indiana; and Houston, Texas, between October 2012 and July 2013. Of 150 screened participants, 91 were randomized (45 to receive pritelivir first) and took at least 1 dose of the study drug (**Figure 1**). The most common cause of ineligibility was lack of HSV-2 antibody (n = 11). Seventy-five participants received pritelivir and 76 received valacyclovir. On May 9, 2013, the US Food and Drug Administration (FDA) imposed a clinical hold (an order to the sponsor to suspend ongoing investigation), based on hematologic and dermatologic findings such as dry skin, crusty skin lesions, and alopecia in a chronic toxicity study involving monkeys. Because the duration of the clinical hold was uncertain, the sponsor terminated the study on June 24, 2013. At the time of the study termination, 74 participants completed their first treatment period and 56 completed both treatment periods.

The median age of participants was 48 years; 57 (63%) were women; and 66 (72%) were white (**Table 1**). The median time from HSV-2 acquisition was 17 years and the median number of recurrences in the year prior was 5 (range, 4-9 years). The demographic and clinical characteristics were similar in participants initially randomized to pritelivir and those initially randomized to valacyclovir. Overall, 7276 swabs were collected during pritelivir and 7453 swabs were collected during valacyclovir treatment (**Table 2**). In both groups, more that 96% of participants collected at least 80% of the expected genital swabs. Adherence to the study drug was very high, as measured by returned study medication, with 93% of persons reporting having taken at least 95% of prescribed doses.

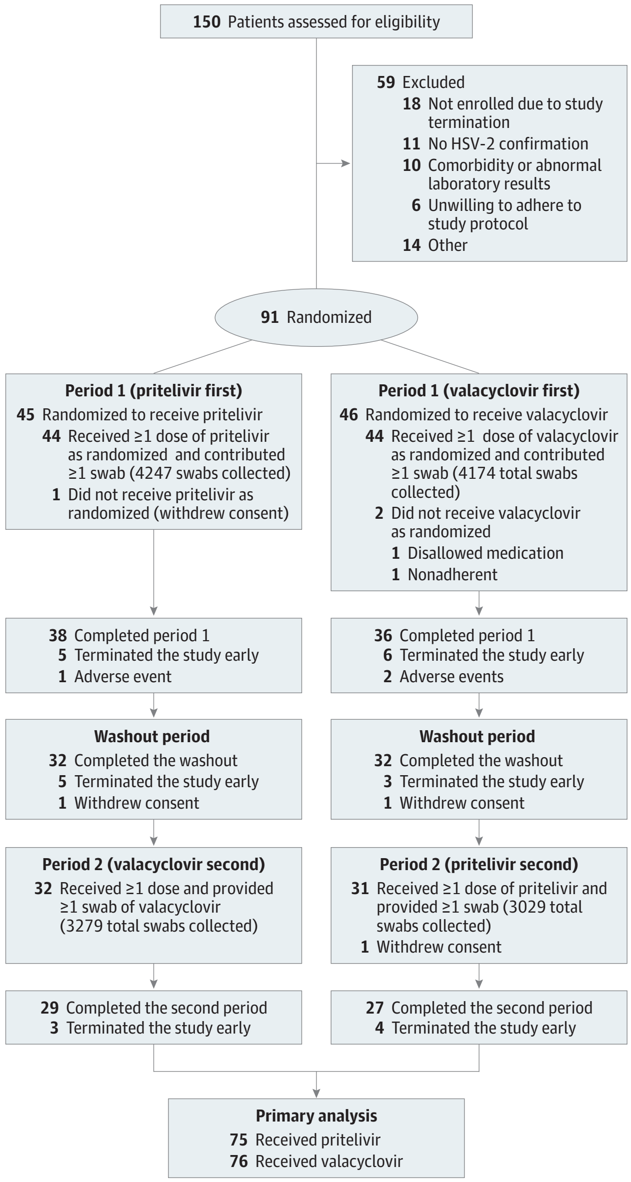
HSV Genital Shedding

Herpes simplex virus was detected in 173 of 7276 swabs (2.4%) obtained during pritelivir treatment and 392 of 7453 swabs (5.3%) obtained during valacyclovir treatment. The frequency of detection of HSV in genital swabs was lower during pritelivir treatment than during valacyclovir treatment (relative risk [RR], 0.42; 95% CI, 0.21-0.82; *P* = .012; Table 2 and **Figure 2**A). The HSV copy number on the days that HSV was detected did not differ by group: for a mean 3.2 $\log_{10}$ copies/mL during pritelivir treatment vs a mean 3.7 $\log_{10}$ copies/mL during valacyclovir treatment (*P* = .83; Figure 2B). The frequency of subclinical shedding was significantly lower during pritelivir treatment than during valacyclovir treatment, 1.8% vs 4.1% (RR, 0.40; 95% CI, 0.20-0.81; *P* = .01; Figure 2C). The rate of shedding when patients reported genital lesions was not significantly different during pritelivir and valacyclovir treatment, 29.9% vs 37.1% (*P* = .76).

The frequency of shedding episodes was not found to differ by treatment, with 1.3 per person-months while taking pritelivir and 1.6 per person-months while taking valacyclovir (RR, 0.80; 95% CI, 0.52-1.22; *P* = .29). The proportion of episodes lasting less than 24 hours was higher during receipt of pritelivir vs valacyclovir (87% vs 69%, *P* = .005; eFigure 1 in Supplement 3).

Subgroup analyses by sex, age, and duration of genital herpes showed potentially stronger reductions in shedding and lesions for women and for those younger than 50 years. However, this study was not designed to compare efficacy between groups; and group differences were not tested statistically. Per-protocol analyses conducted on 51 persons

Figure 1. Flow of Patients With a History of Genital Herpes Simplex Virus 2 Recurrences Through Crossover Trial Comparing Priteliver With Valacyclovir for Prevention of Genital Herpes Simplex Virus 2 Shedding



The 88 persons included in primary analysis took at least 1 dose and provided at least 1 swab during the first period. "Terminated the study early" indicates hold imposed by US Food and Drug Administration.

who completed study medication without protocol deviations also showed similar results (eTable 1 in Supplement 3), except HSV quantity was significantly lower during treatment with pritelivir (pritelivir, $\log_{10}$ 2.9 vs valacyclovir, $\log_{10}$ 3.7, $P < .001$) and median duration of recurrences was not significantly lower during pritelivir treatment (3.0 days vs 6.0 days, $P = .050$). A sensitivity analysis that excluded the initial week of each group was also consistent (eTable 2 in Supplement 3).

Genital Lesions and Pain

The overall frequency of genital lesions was low, with participants reporting lesions on only 2.9% of days. However, genital lesions were reported on 1.9% of days during pritelivir treatment compared with 3.9% of days during valacyclovir administration (RR, 0.40; 95% CI, 0.17-0.96; $P = .04$; **Figure 3**).

Twenty participants experienced at least 1 recurrence during the study. The median duration of recurrences did not differ by treatment group. The proportion of days with pain was 4.0% while taking pritelivir and 6.7% while taking valacyclovir (RR, 0.53; 95% CI, 0.30-0.93; $P = .03$).

No period or carryover effects were found for genital shedding or lesion occurrence.

Fifty-five swabs collected during pritelivir administration contained HSV DNA of more than 5000 copies/mL. Fifty-four were sequenced for UL5 and 55 were sequenced for UL52. No change from the reference sequence (HSV-2

Table 1. Demographic and Clinical Characteristics of Randomized Study Participants

Characteristic	Randomized First Period: Pritelivir (n = 45)	Randomized First Period: Valacyclovir (n = 46)	Total (n = 91)
Age, median (range), y	46 (21-66)	50 (21-61)	48 (21-66)
Women, No. (%)	28 (62)	29 (63)	57 (63)
White, No. (%)	37 (82)	29 (63)	66 (72)
Antibody status. No. (%)			
HSV-2 only	27 (60)	27 (59)	54 (59)
HSV-1 and 2	18 (40)	19 (41)	37 (41)
Years since HSV-2 acquisition, median (range)	15 (1-41)	20 (1-42)	17 (1-42)
No. of recurrences per year prior to study, median (range)	5 (4-9)	5 (4-9)	5 (4-9)
Suppressive therapy prior to study entry, No. (%)	5 (11)	7 (15)	12 (13)
Contributed to efficacy analyses, No. (%)	44 (98)	44 (96)	88 (97)
Swabs obtained during study, median, No. (range)	213 (2-231)	214 (13-222)	214 (2-231)

Abbreviation: HSV, herpes simplex virus.

Table 2. Bivariable Analysis of Virologic and Clinical Efficacy End Points by Treatment

Characteristic	Pritelivir (n = 75)	Valacyclovir (n = 76)	Relative Risk or Difference in Copy No., Pritelivir vs Valacyclovir (95% CI)	*P* Value
Virologic End Points				
Genital HSV shedding, No./total (%)				
Overall[a]	173/7276 (2.4)	392/7453 (5.3)	0.42 (0.21 to 0.82)	.01
Subclinical	127/6989 (1.8)	284/6984 (4.1)	0.40 (0.20 to 0.81)	.01
Lesional	40/134 (29.9)	106/294 (37.1)	0.86 (0.22 to 3.30)	.76
Episode/person-mo	78/60	97/61	0.80 (0.52 to 1.22)	.29
Incidence rate per person-mo	1.3	1.6		
HSV DNA $\log_{10}$ copies/mL, mean (SD)				
Overall	3.2 (1.2)	3.7 (1.3)	−0.1 (−0.6 to 0.5)	.83
On days with no lesions	2.8 (0.6)	3.3 (1.0)	−0.3 (−0.5 to −0.1)	<.001
On days with lesions	4.4 (1.3)	4.8 (1.4)	0.7 (0.3 to 1.0)	<.001[b]
Duration of shedding episodes, median (IQR), h	6.0 (6.0 to 12.0)	6.0 (6.0 to 36.0)		.06[c]
Clinical End Points, No./Total (%)				
Days with lesions[d]	35/1855 (1.9)	75/1900 (3.9)	0.40 (0.17 to 0.96)	.04
Recurrences/person-mo[d]	11/61	18/63	0.65 (0.35 to 1.22)	.18
Incidence rate per person-mo	0.2	0.3		
Days with pain	72/1778 (4.0)	123/1878 (6.7)	0.53 (0.30 to 0.93)	.03
Duration, median (IQR), d				
Pain	4.0 (2.0 to 4.0)	4.0 (2.0 to 4.0)		.83[c]
Recurrences	3.0 (1.0 to 4.0)	5.0 (3.0 to 6.0)		.10[c]

Abbreviations: HSV, herpes simplex virus; IQR, interquartile range.

[a] Shedding is defined as the number of HSV-positive swabs per study participant relative to the total number of swabs collected per participant. Subclinical shedding includes only swabs on days without genital lesions and lesional shedding includes only swabs on days when genital lesions were present. Three randomized participants are not included in the intent-to-treat efficacy analyses because they either contributed no swabs or received no study medication.

[b] This result is due to 1 person who started in the pritelivir group during a lesion, a protocol violation. When the person with the lesion at the start was removed, the effect was reversed −0.4 (−0.6 to −0.2; *P* < .001). Model-predicted differences (ratios) do not always match raw differences (ratios) due to weighting in correlated regression.

[c] From Wilcoxon rank-sum test, predicted to be shorter on pritelivir, if significant.

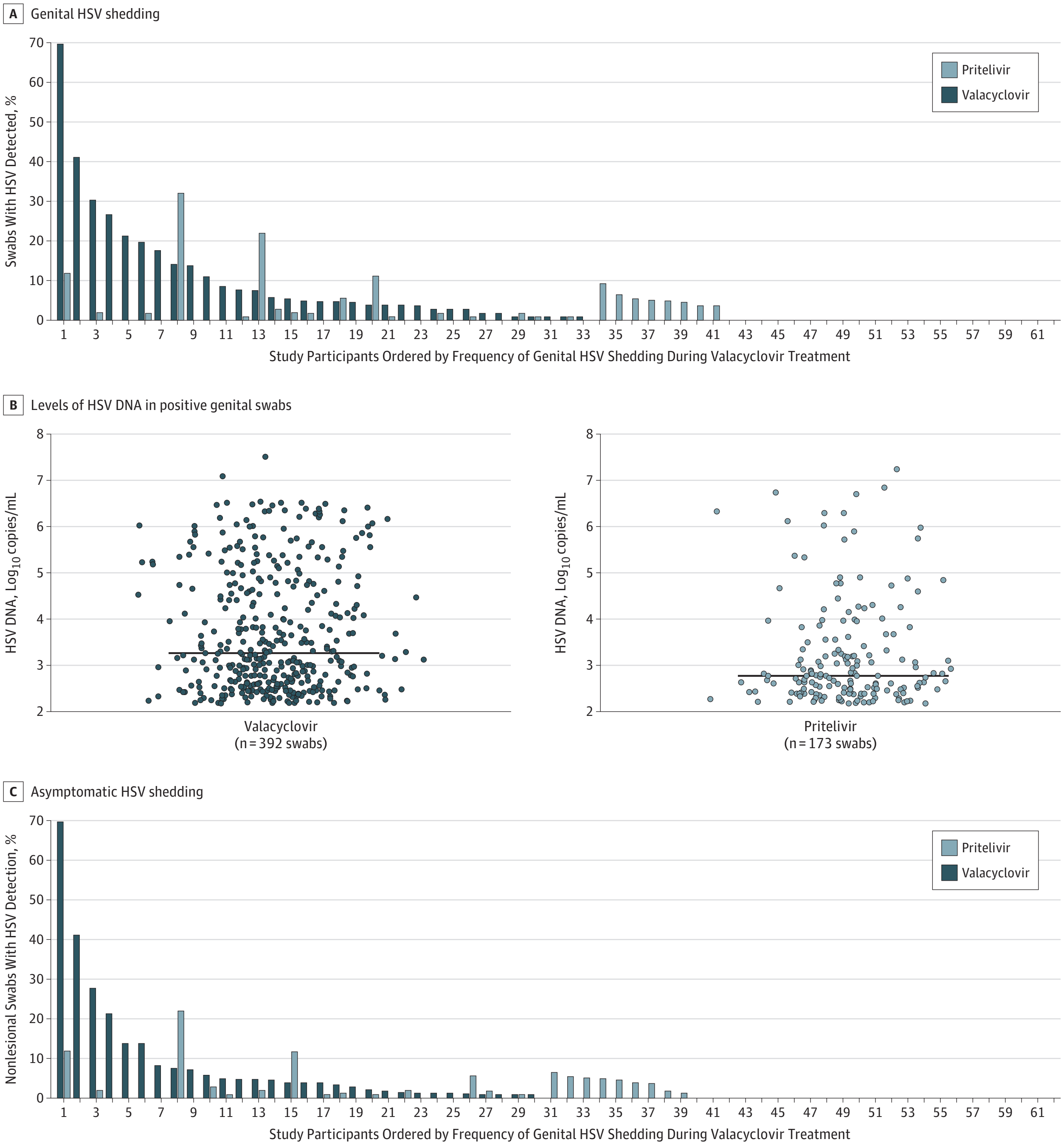
[d] These regressions were not adjusted for site and sex because the outcome was too uncommon, and the model did not converge.

strain HG52, accession No. NC_001798.1) was detected in any of the samples.

Adverse Events

Safety was assessed in all 91 randomized persons; the mean number of days of exposure was 26 for both pritelivir and valacyclovir. Overall, 48 participants (62.3%) had a treatment-emergent adverse event while taking pritelivir and 54 (69.2%) while taking valacyclovir (**Table 3**; eTables 2 and 3 in Supplement 3). No participant had a DAIDS grade 4 treatment-emergent adverse event; 3 participants had a DAIDS grade 3 treatment-emergent adverse event

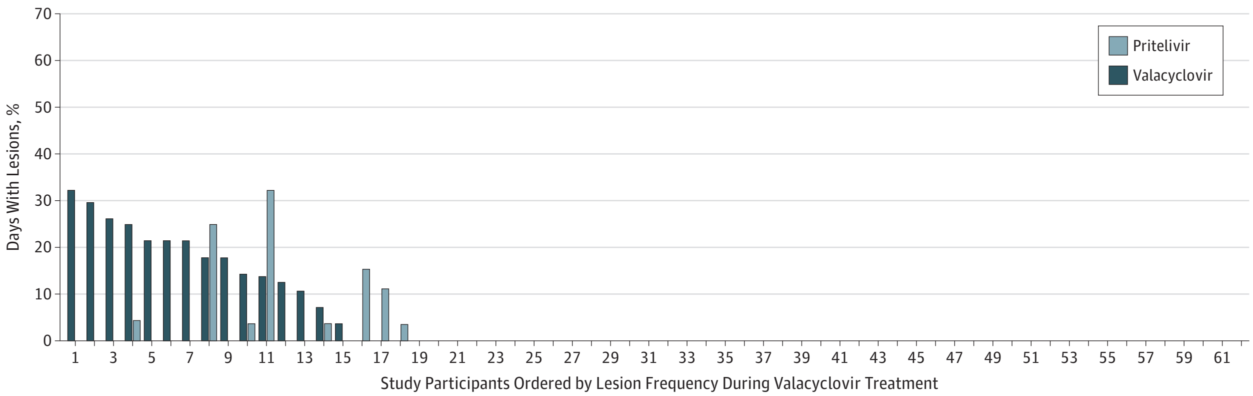
Figure 2. Herpes Simplex Virus Detection and Viral Load by Study Group



A, Genital samples with 150 $\log_{10}$ copies/mL of herpes simplex virus (HSV) DNA or more were considered positive for the virus. Of the 63 persons contributing swabs while taking both treatments, 62 contributed at least 15 swabs for both periods and were included in the figure. The median number of swabs contributed was 108 (interquartile range [IQR], 105-109) while taking valacyclovir and was 108 (IQR, 105-109) while taking pritelivir. B, There were 392 positive samples taken during valacyclovir treatment, and 173 positive samples taken during pritelivir treatment. The horizontal bars indicate the median $\log_{10}$ copies/mL of HSV DNA. C, Of 63 persons contributing swabs while taking both treatments, 62 contributed at least 15 asymptomatic swabs during both periods and were included in the figure. The median number of swabs contributed was 105 (range, 93-109) while taking valacyclovir and was 108 (range, 101-109) while taking pritelivir.

during pritelivir administration (elevated lipase, elevated alanine aminotransferase, and migraine); and 3 participants had a DAIDS grade 3 treatment-emergent adverse event during valacyclovir administration (dyspareunia, tooth infection and back pain, and headache and malaise). No deaths or serious adverse events were observed. Potential changes in hemoglobin, white blood cell count, and liver function tests were evaluated statistically. In a paired analysis,

Figure 3. Percentage of Days With Genital Lesions



Of 63 persons recording symptoms while taking both treatments, 62 recorded at least 6 diary days during both periods and were included in the figure. The median number of diary days contributed was 28 (interquartile range [IQR], 27-28 days) while taking valacyclovir and was 28 (IQR, 27-28) while taking pritelivir.

Table 3. Participants With Treatment Emergent Adverse Events by Treatment Group

Variable	No. (%) Pritelivir 100 mg Daily (n = 77)	Valacyclovir 500 mg Daily (n = 78)	Total (n = 91)
Treatment emergent adverse events			
Any	48 (62.3)	54 (69.2)	71 (78)
Serious	0	0	0
Leading to discontinuation	1 (1.3)	1 (1.3)	2 (2.2)
DAIDS 2 TEAEs[a]	11 (14.3)	12 (15.4)	21 (23.1)
DAIDS 3 TEAEs	3 (3.9)	3 (3.8)	5 (5.5)
Common TEAEs			
Headache, total	10 (13.0)	13 (16.7)	21 (23.1)
DAIDS 2	3 (3.9)	3 (3.8)	6 (6.6)
DAIDS 3	0	1 (1.3)	1 (1.1)
Nervous system disorders, total	14 (18.2)	14 (17.9)	25 (27.5)
DAIDS 2	3 (3.9)	4 (5.1)	7 (7.7)
DAIDS 3	1 (1.3)	1 (1.3)	2 (2.2)
Skin and subcutaneous tissue disorders, total	8 (10.4)	7 (9.0)	12 (13.2)
DAIDS 2	1 (1.3)	0	1 (1.1)
DAIDS 3	0	0	0
Respiratory, thoracic and mediastinal disorders, total	2 (2.6)	2 (2.6)	4 (4.4)
DAIDS 2	0	0	0
DAIDS 3	0	0	0

Abbreviations: DAIDS, Division of Acquired Immunodeficiency Syndrome; TEAEs, treatment emergent adverse events.

[a] NIH/NIAID DAIDS table for grading the severity of adult and pediatric adverse events, version 2.0.

although white blood cell counts were was unchanged at every visit, there were statistically significant but not clinically relevant changes in the mean lymphocyte count (110-230 100 × ^{3}/μL lower) and creatinine levels (0.03 and 0.05 mg/dL higher [to convert to μmol/L, multiply by 76.25]) during pritelivir administration (eFigure 2 in Supplement 3). At the week-4 visit following cessation of therapy, only the creatinine levels remained 0.02 mg/dL higher in pritelivir than in the valacyclovir group.

One participant was randomized in error and discontinued from the study due to a prolonged QT interval that was noted prior to initiating therapy with pritelivir. One participant receiving pritelivir developed urticaria without angioedema and was discontinued on day 10, and one participant receiving valacyclovir discontinued treatment on day 7 because of a constellation of mild symptoms that included headache, insomnia, and anxiety; these treatment-emergent adverse events were considered probably or possibly related to the trial medication. The percentage of participants with skin and subcutaneous tissue disorders were similar during pritelivir (10.4%) and valacyclovir (9.0%) treatment.

Discussion

Among adults with frequent recurrences of genital HSV-2, the use of pritelivir compared with valacyclovir resulted in a lower percentage of swabs with HSV detected over 28 days.

Pritelivir decreased the number of days of overall genital shedding, subclinical shedding, and genital lesions over the total number of positive swabs and days with lesions, respectively, compared with valacyclovir in intent-to-treat analysis. The frequency of pain was also reduced. In addition, in per-protocol analysis, quantity of virus shed was also decreased significantly during pritelivir treatment compared with valacyclovir treatment. No sequence variation in the UL5 and UL52 regions associated with resistance to pritelivir in vitro was detected in genital swabs obtained during pritelivir therapy.

A crossover design of the trial allowed participants to be their own controls. This design is more efficient relative to a parallel group study of the same size because in patients with established genital HSV-2 infection, shedding and recurrence rates have been shown to be stable over months and shedding rates are highly variable between persons; thus, studying within-person changes allows for a more precise estimate of treatment efficacy. In addition, each study participant in a crossover trial is treated with both drugs. A potential drawback to this design occurs if either there are temporal trends that affect shedding rates over time, if the effect of the first drug remains after the second drug is initiated, or if there are high dropout rates, which would make within-participant comparisons unfeasible. The placebo-controlled trial of pritelivir[7] suggested that a month-long washout period is sufficient because shedding rates returned to baseline within 2 weeks of drug cessation.

Currently available nucleoside analogues improve the clinical outcomes in genital herpes and improve the quality of life of those who choose suppressive therapy.[16,17] However, breakthrough viral shedding and recurrences still occur, as well as sexual and perinatal transmission. Furthermore, nucleoside analogues only partly mitigate the more severe HSV syndromes such as neonatal HSV or HSV encephalitis, and the options for immunocompromised patients who develop resistance to acyclovir are severely limited.[18] In addition, the availability of nucleoside analogues has not affected the prevalence of HSV-2, likely because most patients are not diagnosed or not treated and because the drugs are insufficiently potent to completely abrogate viral shedding and transmission. Whether a more potent regimen would have the potential to reduce HSV-2 infection on the population level requires further study, akin to the work currently conducted on HIV incidence by lowering the community viral load.[19]

The comparison between pritelivir to valacyclovir early in the drug development process aimed to understand the balance between efficacy and safety. Few prescription medications have a safety profile comparable with the nucleoside analogues for HSV. This safety is likely driven by the requirement for virally mediated phosphorylation by thymidine kinase, and thus the drug is activated only in cells that are already infected. However, this may also limit the efficacy of the drug because viral replication must already be ongoing in order for the drug to be effective. In contrast, pritelivir is also very specific for HSV but does not require activation or ongoing viral replication. The drugs also have a difference in their half-lives, with acyclovir having a half-life of 3 hours and pritelivir of 50 to 80 hours.[20] Dose-ranging studies have consistently shown that frequent dosing of acyclovir and valacyclovir is more effective for clinical HSV disease, and continuous infusion of acyclovir can even overcome in vitro resistance.[21,22] Thus treatment with a drug that maintains a steady level throughout the dosing interval may result in fewer opportunities for HSV to reactivate.[23]

The trial was placed on clinical hold by the FDA and terminated by the sponsor based on findings in monkeys in a 39-week toxicity study. These findings included skin related findings such as dry skin, crusty skin lesions, and alopecia as well as anemia (decreases in hemoglobin and in most animals an increase in the percentage of reticulocytes). So far the mechanism of dermatologic and hematologic findings is not understood. However, in the present study participants did not experience any similar adverse events (eg, anemia), although one person developed a rash (hives). The changes observed in lymphocyte count and creatinine levels were small, and longer duration of therapy will be needed to assess their clinical significance.

This study was limited by early termination and therefore, fewer participants than planned were treated. However, because of greater viral suppression during pritelivir therapy than assumed in power calculations and because few participants were lost to follow-up, a statistically significant difference in viral shedding and genital lesions was seen during the treatment with the 2 regimens. The persons enrolled had agreed to obtain very frequent genital samples and thus may differ from the general population. However, these differences should not affect the biological activity of the drugs.

Conclusions

Among adults with frequently recurring genital HSV-2, the use of pritelivir compared with valacyclovir resulted in a lower percentage of swabs with HSV detection over 28 days. Further research is needed to assess longer-term efficacy and safety.

ARTICLE INFORMATION

Correction: This was corrected online on January 26, 2017, to fix 2 ommissions in the abstract and several rows in Table 2.

Author Contributions: Drs Wald and Magaret had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Ruebsamen-Schaeff and Birkmann are cosenior authors.
Concept and design: Wald, Timmler, Magaret, Johnston, Stobernack, Corey, Birkmann, Ruebsamen-Schaeff.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Wald, Magaret, Warren, Corey, Birkmann.
Critical revision of the manuscript for important intellectual content: Wald, Timmler, Magaret, Tyring, Johnston, Fife, Selke, Huang, Stobernack, Zimmermann, Corey, Birkmann, Ruebsamen-Schaeff.
Statistical analysis: Wald, Magaret.
Administrative, technical, or material support: Wald, Timmler, Huang, Birkmann.
Study supervision: Wald, Warren, Tyring, Johnston, Fife, Selke, Birkmann, Ruebsamen-Schaeff.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Wald reports consulting for Aicuris, Amgen, and GSK; serving on data, safety, and monitoring board for Merck, and receiving clinical trial support through

University of Washington from Gilead, Vical, and Genocea, and travel funds from Admedus. Dr Magaret reports consulting for Aicuris and Immune Design. Ms Warren and Drs Fife and Tyring report receiving clinical trial support through their institutions from Aicuris. Dr Johnston reports receiving clinical trial support through her institution from Aicuris and Sanofi Pasteur. Dr Corey reports holding stock in Immune Design and being a coinventor on several patents associated with the development of an HSV-2 vaccine. Dr Birkmann reports contributing to patents related to galenics and the synthesis of drug substances through AiCuris. Drs Timmler, Stobernack, Zimmermann, Birkmann, and Ruebsamen-Schaeff are employees of AiCuris. DrsTimmler, Zimmermann, Birkmann, and Ruebsamen-Schaeff report holding stock options in AiCuris. No other disclosures are reported.

Funding/Support: This study was supported by AiCuris GmbH & Co KG.

Role of the Funder/Sponsor: The study was designed collaboratively by investigators at University of Washington and AiCuris. AiCuris had a role in the conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. The sponsor did not have the right to prevent submission or publication of the data. The statistical analyses reported herein were conducted independently at the University of Washington.

Previous Presentation: Presented in part at the Interscience Conference on Antimicrobial Agents and Chemotherapy, 2014, Washington, DC, abstract L-419.

REFERENCES

1. Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep*. 2015;64(RR-03):1-137.

2. Corey L, Wald A, Patel R, et al; Valacyclovir HSV Transmission Study Group. Once-daily valacyclovir to reduce the risk of transmission of genital herpes. *N Engl J Med*. 2004;350(1):11-20.

3. Johnston C, Saracino M, Kuntz S, et al. Standard-dose and high-dose daily antiviral therapy for short episodes of genital HSV-2 reactivation: three randomised, open-label, cross-over trials. *Lancet*. 2012;379(9816):641-647.

4. Celum C, Wald A, Hughes J, et al; HPTN 039 Protocol Team. Effect of aciclovir on HIV-1 acquisition in herpes simplex virus 2 seropositive women and men who have sex with men: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2008;371(9630):2109-2119.

5. Elion GB, Furman PA, Fyfe JA, de Miranda P, Beauchamp L, Schaeffer HJ. Selectivity of action of an antiherpetic agent, 9-(2-hydroxyethoxymethyl) guanine. *Proc Natl Acad Sci U S A*. 1977;74(12):5716-5720.

6. Kleymann G, Fischer R, Betz UA, et al. New helicase-primase inhibitors as drug candidates for the treatment of herpes simplex disease. *Nat Med*. 2002;8(4):392-398.

7. Wald A, Corey L, Timmler B, et al. Helicase-primase inhibitor pritelivir for HSV-2 infection. *N Engl J Med*. 2014;370(3):201-210.

8. Mark KE, Wald A, Magaret AS, et al. Rapidly cleared episodes of herpes simplex virus reactivation in immunocompetent adults. *J Infect Dis*. 2008;198(8):1141-1149.

9. US Department of Health and Human Services. Division of AIDS (DAIDS) table for grading the severity of adult and pediatric adverse events, version 2.0. http://rsc.tech-res.com/docs/default-source/safety/daids_ae_grading_table_v2_nov2014.pdf. Published November 2014. Accessed November 21, 2016..

10. Ashley RL, Militoni J, Lee F, Nahmias A, Corey L. 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(4):662-667.

11. Jerome KR, Huang ML, Wald A, Selke S, Corey L. Quantitative stability of DNA after extended storage of clinical specimens as determined by real-time PCR. *J Clin Microbiol*. 2002;40(7):2609-2611.

12. Magaret AS, Wald A, Huang ML, Selke S, Corey L. Optimizing PCR positivity criterion for detection of herpes simplex virus DNA on skin and mucosa. *J Clin Microbiol*. 2007;45(5):1618-1620.

13. Field HJ, Biswas S. Antiviral drug resistance and helicase-primase inhibitors of herpes simplex virus. *Drug Resist Updat*. 2011;14(1):45-51.

14. Edlefsen PT, Birkmann A, Huang ML, et al. No evidence of resistance of HSV-2 to pritelivir following four weeks of daily therapy. *J Infect Dis*. 2016;214(2):258-264.

15. Magaret A. Models for HSV shedding must account for two levels of overdispersion. Collection of biostatistics Research Archive. http://biostats.bepress.com/uwbiostat/paper410. Published January 2016. Accessed November 10, 2016.

16. Patel R, Tyring S, Strand A, Price MJ, Grant DM. Impact of suppressive antiviral therapy on the health related quality of life of patients with recurrent genital herpes infection. *Sex Transm Infect*. 1999;75(6):398-402.

17. Workowski KA, Berman S; Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases treatment guidelines, 2010. *MMWR Recomm Rep*. 2010;59(RR-12):1-110.

18. Piret J, Boivin G. Resistance of herpes simplex viruses to nucleoside analogues: mechanisms, prevalence, and management. *Antimicrob Agents Chemother*. 2011;55(2):459-472.

19. Dieffenbach CW. Preventing HIV transmission through antiretroviral treatment-mediated virologic suppression: aspects of an emerging scientific agenda. *Curr Opin HIV AIDS*. 2012;7(2):106-110.

20. Zovirax (acyclovir) [prescribing information]. Research Triangle Park, NC: 2007.

21. Engel JP, Englund JA, Fletcher CV, Hill EL. Treatment of resistant herpes simplex virus with continuous-infusion acyclovir. *JAMA*. 1990;263(12):1662-1664.

22. Mindel A, Faherty A, Carney O, Patou G, Freris M, Williams P. Dosage and safety of long-term suppressive acyclovir therapy for recurrent genital herpes. *Lancet*. 1988;1(8591):926-928.

23. Schiffer JT, Swan DA, Magaret A, et al. Mathematical modeling of herpes simplex virus-2 suppression with pritelivir predicts trial outcomes. *Sci Transl Med*. 2016;8(324):324ra15.