MAJOR ARTICLE

Valganciclovir for Suppression of Human Herpesvirus–8 Replication: A Randomized, Double-Blind, Placebo-Controlled, Crossover Trial

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(See the editorial commentary by Crumpacker, on pages 6–7.)

Background. Human herpesvirus–8 (HHV-8) replication is critical in the induction and maintenance of Kaposi sarcoma, primary effusion lymphoma, and some cases of Castleman disease. In vitro and observational studies suggest that ganciclovir inhibits HHV-8 replication, but no randomized clinical trials have been conducted.

Methods. A total of 26 men infected with HHV-8 were randomized to receive 8 weeks of valganciclovir administered orally (900 mg once per day) or 8 weeks of placebo administered orally. After a 2-week washout period, participants in each group received the study drug they had not yet taken (either valganciclovir or placebo), for 8 additional weeks. Oral swab samples were collected daily during the study, and HHV-8 and CMV DNA were quantified by real-time PCR.

Results. A total of 16 human immunodeficiency virus (HIV)–positive men and 10 HIV-negative men enrolled in and completed the study. Of the 3439 swab samples that participants had been expected to provide, 3029 (88%) were available for analysis. HHV-8 was detected on 44% of swabs collected from participants who were receiving placebo, compared with 23% of swabs collected from participants who were receiving valganciclovir (relative risk [RR], 0.54 [95% confidence interval {CI}, 0.33–0.90]; $P = .02$). Valganciclovir reduced oropharyngeal shedding of cytomegalovirus by 80% (RR, 0.20 [95% CI, 0.08–0.48]; $P < .001$). Shedding of HHV-8 and shedding of cytomegalovirus were independent. Hematologic, renal, or hepatic toxicities were no more common among participants who received the active drug, compared with those who received placebo, though participants who received valganciclovir reported more days of diarrhea.

Conclusions. Valganciclovir administered orally once per day is well tolerated and significantly reduces the frequency and quantity of HHV-8 replication.

Human herpesvirus–8 (HHV-8) is the etiologic agent of Kaposi sarcoma (KS), primary effusion lymphoma (PEL), and multicentric Castleman disease (MCD) [1]. Although the incidence of KS has declined where the use of highly active antiretroviral therapy (HAART) is widespread [2], it remains the most common AIDS-associated malignancy in the United States [3], as well as the primary malignancy following transplantation in some geographic regions [4] and the most common cancer throughout the population in many parts of Africa [5]. The response of KS to treatment with chemotherapy or HAART is often incomplete [6], and no therapy for MCD or PEL has been proven effective in comparative trials.

The study of antiviral therapy for HHV-8 infection has been hampered by the lack of a traditional in vitro system to model HHV-8 replication. The virus does not sustain lytic replication in cell culture, which prohibits the use of antiviral susceptibility testing methods that rely on cytopathic effect, and no animal model of

Received 24 December 2007; accepted 28 December 2007; electronically published 20 May 2008.

Potential conflicts of interest: none reported.

Financial support: National Institutes of Health (grants K23 AI-054162 to C.C., K24 AI-071113 to A.W., P01 AI-30731 to A.W. and L.C., and U19 AI-31448 to A.W. and L.C.); Roche Laboratories (Investigator-Initiated Research Grant to A.W. and donation of study drug and placebo); Doris Duke Charitable Foundation (Clinical Scientist Development Award to C.C.).

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The Journal of Infectious Diseases 2008; 198:23–30

0022-1899/2008/19801-0007$15.00

DOI: 10.1086/588820

HHV-8 infection has been established. The in vitro susceptibility of HHV-8 to antiviral drugs has been supported by 2 findings. First, ganciclovir is phosphorylated in the presence of both the HHV-8 thymidine kinase at open reading frame (ORF) 21 and phosphotransferase at ORF36 [7]. Second, ganciclovir, cidofovir, and foscarnet inhibit the production of HHV-8 from latently infected cell lines upon stimulation, whereas antiviral medications such as acyclovir have been shown to have little or no activity against HHV-8 [8–12]. These preclinical studies offer strong support for the antiviral activity of valganciclovir against HHV-8.

We hypothesized that valganciclovir will reduce HHV-8 replication in vivo. Ganciclovir therapy reduces the symptoms and signs of HHV-8–associated MCD in parallel with reductions of the HHV-8 load in plasma [13]. Early observations made during studies of ganciclovir therapy for cytomegalovirus (CMV) retinitis in HIV-positive patients found that ganciclovir reduced the rate of new KS development; the reduction was found to range from 40%, by Mocroft et al. [14], to 75%, by Martin et al. [15]. These studies suggest that inhibition of HHV-8 replication may be associated with clinical benefit, but data on HHV-8 replication were not collected. Additionally, HHV-8 replication may be activated by CMV [16], so it remains unclear whether the effect of ganciclovir on KS that has been observed in prior trials was a direct result of antiviral activity against HHV-8 or an indirect result of ganciclovir's suppression of CMV replication. To date, no randomized clinical trial has assessed the effect of antiviral medication on HHV-8 replication.

Replicating HHV-8 is found most frequently in the oropharynx, and the daily collection of saliva for the quantification of HHV-8 DNA provides a simple and accurate measure of the level of HHV-8 replication [17, 18]. We therefore sought to determine the safety and efficacy of valganciclovir on HHV-8 replication in the oropharynx in HIV-seropositive and HIV-negative persons who were asymptomatically infected with HHV-8, by use of a randomized, double-blind, placebo-controlled, crossover trial.

METHODS

Study participants. To define the potential antiviral effects of valganciclovir on HHV-8 replication, we selected 26 men for this study who had been observed in previous trials to shed HHV-8 from the oropharynx on ⩾40% of the days their saliva was sampled [18]. Subjects were recruited at the University of Washington Virology Research Clinic in Seattle between February 2003 and February 2005. Persons receiving medications known to have activity against human herpesviruses or who were known to have bone marrow suppression, a history of CMV disease, hypersensitivity to ganciclovir, or evidence of renal or hepatic dysfunction were excluded. Participants were eligible regardless of their HIV infection status, but HIV-positive participants who were receiving antiretroviral therapy (ART) could not change medications during the course of the study. The first 26 men who agreed to participate and who met the inclusion criteria were enrolled in the study.

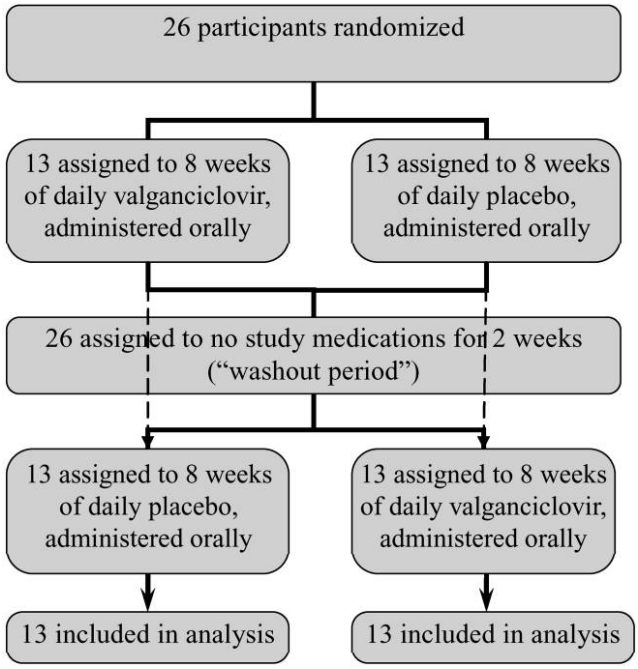

Figure 1. Study design for a trial of valganciclovir involving 26 participants asymptomatically infected with human herpesvirus–8.

Study procedures. On enrollment, participants were randomly assigned to initially receive either valganciclovir or placebo, 900 mg administered orally once per day for 8 weeks (figure 1). Participants were randomized by use of a computerized random number generator and stratified by HIV status. Participants, clinicians, laboratory personnel, and biostatisticians were blinded to treatment assignment throughout the trial. After a 2-week washout period during which no study medications were taken, participants then received the other treatment for another 8 weeks. Participants collected oropharyngeal swab samples daily and kept a symptom diary at home, as described elsewhere [18]. The diary surveyed common gastrointestinal complaints (nausea, vomiting, diarrhea, abdominal pain, and cramping) and constitutional symptoms (fever, night sweats, chills, and swollen glands), as well as sore throat, rash, headache, days missed from school or work, and visits to health-care professionals. Participants returned to clinic every 2 weeks for tests to assess drug safety (i.e., a complete blood count with differential, hepatic, and renal function tests), ascertainment of adherence to medication schedule by use of pill counts, and return of oropharyngeal swab samples. A data safety monitoring board reviewed all clinical and laboratory data when 50% of participants had completed the first arm of the study.

Laboratory assessments. Serum samples were tested for antibodies to HIV and CMV by use of enzyme immunoassays (Ab-

bott Laboratories). DNA was extracted from oropharyngeal swab samples for the quantification of HHV-8 by real-time polymerase chain reaction (PCR) using primers to *orf73* [19], and for the quantification of CMV with a double-primer set to UL55 and UL123-exon 4 [20]. All samples with ⩾500 copies of HHV-8 DNA/mL or ⩾100 copies of CMV DNA/mL were characterized as positive [18, 20]. Several negative and positive controls were run with each reaction, including 2 reaction mixtures without DNA (negative controls) and at least 1 sample with a known quantity of HHV-8 DNA. An internal control was amplified with each specimen to assure that negative results were not attributable to inhibition of PCR [18, 20]. Specimens were run in batches of 560 swabs. They were grouped into these batches on the basis of when the specimens were received in the lab. Most participants submitted 14 days of swab samples at a visit; consequently, each run typically contained a mix of participants from both the active treatment and placebo arms of the trial.

Statistical analysis. The primary end point was the reduction in oropharyngeal replication of HHV-8 associated with valganciclovir use, as measured by HHV-8 shedding frequency, which was defined by the number of days on which HHV-8 was detected in samples analyzed by PCR divided by the total number of days for which samples were analyzed by PCR. The secondary end point was the safety of valganciclovir in persons with asymptomatic HHV-8 infection. In this crossover study design, each person acted as their own control to minimize the effect of variability in HHV-8 shedding rate on treatment efficacy measures and to optimize study power. Assuming a background shedding rate of 40% and allowing for a 20% dropout rate, we calculated that 26 participants would be required for the study to have an 80% chance of detecting a ⩾50% reduction in the rate of detection of HHV-8 in the oropharynx.

All data were collected and managed at the University of Washington and categorized and initially analyzed without knowledge of the participants' treatment assignment. The first day of that a participant received either valganciclovir or placebo and the days of the washout period were excluded from treatment efficacy analyses. Generalized linear mixed models using the Poisson distribution and log link with person-level random effects were used to test the efficacy of valganciclovir in reducing the frequency of HHV-8 and CMV replication. The quantity of HHV-8 was analyzed for days on which HHV-8 was detected, and the quantity was $\log_{10}$ transformed prior to analysis. Linear mixed effects models with person-level random intercepts compared the mean quantity of HHV-8 detected in participants in the active treatment arm and the placebo arm. Covariates for time period and the interaction between time period and treatment were created to test for period and carryover effects [21]. To summarize both frequency and quantity data graphically, the mean $\log_{10}$ copies per milliliter of HHV-8 DNA detected was calculated by using all days, assigning the value 0 to days on which HHV-8 was not detected.

Safety was monitored by clinical and laboratory evaluation of the participants. Transaminitis was defined by a serum alanine aminotransferase level >250 U/dL, renal insufficiency was defined by a serum creatinine level ⩾1.5 mg/dL, anemia was defined by a hematocrit <30%, thrombocytopenia was defined by a platelet count of <20,000 cells/mL, and neutropenia was defined by a neutrophil count of <1500 cells/mL. Person-level comparisons of adverse events in participants who received active drug and practicableness who received placebo used McNemar's test, and day-level comparisons of adverse events used generalized linear mixed effects models. SAS statistical software (version 9.1; SAS Institute) was used for all analyses.

Adherence rates, calculated as the number of unreturned pills divided by the total pills each participant should have taken, were compared between active treatment and placebo arms by using generalized linear mixed models. The Spearman rank correlation coefficient was used to estimate the correlation between adherence rates and treatment efficacy, as well as the relationship between treatment efficacy for HHV-8 and CMV.

RESULTS

Participant characteristics. The median age of study participants was 42 years (range, 24–66 years), and 17 (65%) of 26 participants reported their race as white (table 1). All participants identified themselves as men who have sex with men. Sixteen (62%) of 26 participants were HIV-positive, with a median CD4 T cell count of 434 cells/mm^3 (range, 49–936 cells/mm^3) and a mean HIV RNA plasma level of $\log_{10}$ 3.8 copies/mL (range, 2.2–5.3 copies/mL). Eight (50%) of 16 HIV-positive participants were receiving ART during the course of the study, including 7 who were receiving HAART, which was defined as any combination of ⩾3 antiretroviral agents that included at least 1 nonnucleoside reverse transcriptase or protease inhibitor.

Effect of valganciclovir on the detection of HHV-8 in the oropharynx. Of 3439 oropharyngeal swab samples that participants had been expected to provide, 3029 (88%) were available for analysis. Valganciclovir reduced the frequency with which HHV-8 was detected in saliva as well as the quantity detected. HHV-8 was detected on 583 (44%) of 1333 days among patients who were receiving placebo and on 318 (23%) of 1360 days among patients who were receiving valganciclovir Thus, the use of valganciclovir was associated with a 46% reduction in the frequency with which HHV-8 was detected in the oropharynx, with a relative risk (RR) of 0.54 for the detection of HHV-8 during administration of valganciclovir, compared with placebo (95% confidence interval [CI], 0.33–0.90; $P = .02$).

Next, we analyzed the quantity of HHV-8 detected in the oropharynx on the days on which HHV-8 was detected. The mean $\log_{10}$ copies per milliliter detected for participants who were receiving placebo was 5.0 copies/mL (range, 2.7–7.9 copies/mL),

Table 1. Demographic and clinical baseline characteristics of 26 participants asymptomatically infected with human herpesvirus–8.

Characteristic	HIV infection status		
	Negative ($n = 10$)	Positive ($n = 16$)	Total ($n = 26$)
Age, median (range), years	45 (37–66)	40 (24–54)	42 (24–66)
Race or ethnicity			
White	8 (80)	9 (56)	17 (65)
Non-white	2 (20)	7 (44)	9 (35)
CMV infection status			
Positive	9 (90)	16 (100)	25 (96)
Negative	1 (10)	0 (0)	1 (4)
CD4 T lymphocyte count, median (range), cells/mm^3	NA	434 (49–93)	NA
Plasma HIV RNA level, mean (range), $\log_{10}$ copies/mL	NA	3.8 (2.2–53)	NA
Receipt of antiretroviral drugs			
None	NA	8 (50)	NA
Non-HAART	NA	1 (6)	NA
HAART	NA	7 (44)	NA

NOTE. Data are no. (%) of participants, unless otherwise indicated. CMV, cytomegalovirus; HAART, highly active antiretroviral therapy; NA, not applicable.

compared with 4.7 copies/mL for participants who were receiving valganciclovir (range, 2.7–7.6 copies/mL). Valganciclovir significantly reduced the quantity of HHV-8 by 0.44 logs (95% CI, 0.12–0.75 logs; $P = .007$).

Reductions in oropharyngeal shedding of HHV-8 were seen among both HIV-positive and HIV-negative participants. Person-level comparison showed that 15 (94%) of 16 HIV-positive participants had HHV-8 detected on at least 1 day during the time they were receiving placebo, compared with 11 (69%) of 16 HIV-positive participants during time they were receiving valganciclovir. We also observed a reduction in day-level rates of HHV-8 detection in HIV-positive participants, with HHV-8 detected on 438 (53%) of 822 days during the time these participants received placebo versus 246 (29%) of 854 days during the time they received valganciclovir. Among HIV-negative participants, 9 (90%) of 10 had HHV-8 detected in saliva on at least 1 day during the time they received placebo versus 8 (80%) of 10 during the time they received valganciclovir. However, for the HIV-negative subgroup, HHV-8 was detected on 145 (28%) of 511 days during placebo use versus 72 (14%) of 506 days during valganciclovir use.

Analyses that adjusted for HIV and HAART status showed that receipt of valganciclovir significantly reduced the risk of HHV- 8 being detected in the oropharynx, by 46% (RR, 0.54 [95% CI, 0.33–0.90]; $P = .02$), and it reduced the HHV-8 DNA copy number by a mean of 0.44 logs (95% CI, 0.12 to 0.76 logs; $P = .007$) (table 2). Small numbers of participants precluded detailed analyses of the effect of valganciclovir in subgroups defined by HIV infection status and HAART use, but modeling suggested differential effects of valganciclovir within HIV and HAART categories ($P = .053$ for interaction), with the greatest treatment effect occurring among the HIV-positive participants who were receiving HAART (RR, 0.30 [95% CI, 0.19–0.47]; $P < .001$).

In analyses that adjusted for valganciclovir use, HIV-positive participants who were not receiving HAART (RR, 2.36 [95% CI,

Table 2. Effect of valganciclovir on the frequency and quantity of oropharyngeal shedding of human herpesvirus–8 (HHV-8).

Outcome measure	Study arm		Estimated measure of effect[a] (95% CI)	*P*
	Placebo	Valganciclovir		
Days on which HHV-8 was detected in saliva, proportion (%)	583/1333 (44)	318 /1360 (23)	Relative risk, 0.54 (0.33 to 0.90)	.02
Quantity of HHV-8 in saliva (range), mean $\log_{10}$ copies/mL [b]	5.0 (2.7–7.9)	4.7 (2.7–7.6)	Coefficient, −0.44 (−0.76 to −0.12)	.007

NOTE. CI, confidence interval.

[a] Adjusted for treatment arm, HIV infection status, and use of highly active antiretroviral therapy.

[b] Calculated only for days during which HHV-8 was detected in saliva.

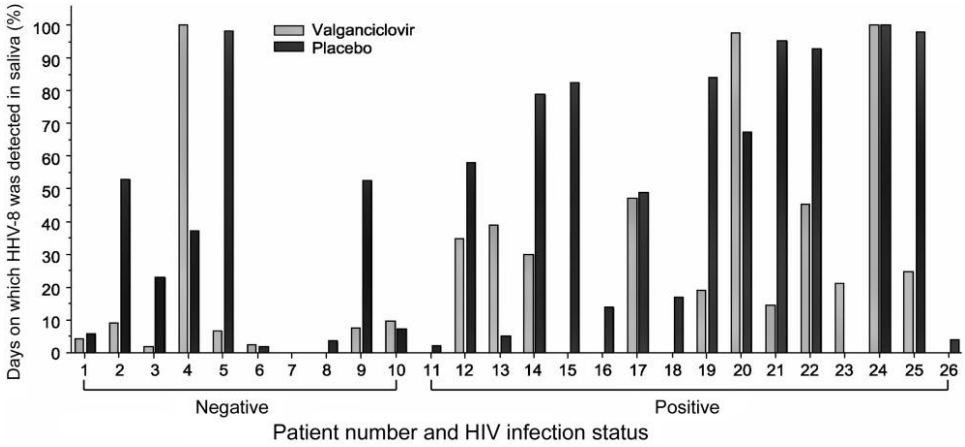

Figure 2. Comparison of the rate of human herpesvirus–8 shedding in the oropharynx among participants who received valganciclovir and participants who received placebo.

1.00–5.53]) and those who were receiving HAART (RR, 1.59 [95% CI, 0.58– 4.34]) tended to shed HHV-8 more frequently than HIV-negative men, although this comparison was not statistically significant overall ($P = .14$). HHV-8 shedding was more common among HIV-positive persons with higher CD4 T cell counts (RR, 6.0 for participants with CD4 cell count >200 cells/mm^3 vs. <200 cells/mm^3 [95% CI, 2.0–17.7]; $P = .003$). The effect of valganciclovir on the quantity of HHV-8 did not vary greatly by HIV infection status or HAART use ($P = .98$ for interaction).

Kinetics of HHV-8 inhibition with valganciclovir. During the time participants received valganciclovir, minimal HHV-8 shedding (<10%) was observed in approximately half of the participants (figure 2). On average, lower levels of HHV-8 shedding were observed after the first 1–2 weeks of valganciclovir treatment (figure 3). As participants switched to the washout period and receipt of placebo, the frequency and amount of viral shedding rebounded. We did not find significant period effects (i.e., the effect of valganciclovir was the same whether it was given before or after placebo) or carryover effects (i.e., treatment with valganciclovir first did not affect shedding in patients who subsequently received placebo) for either the frequency of shedding ($P = .83$ and $P = .76$, respectively) or the quantity of shedding ($P = .90$ and $P = .59$, respectively) (figure 3*A* compared with 3*B*).

Effect of valganciclovir on CMV replication and relation to HHV-8 replication. Twenty five (96%) of 26 men were seropositive for CMV, and 14 (56%) shed CMV from the oropharynx on at least 1 day of the study (9 HIV-positive participants and 5 HIV-negative participants). Valganciclovir reduced CMV shedding by 80%, compared with shedding among participants who were not receiving the drug (RR, 0.20 [95% CI, 0.08–0.48]; $P < .001$); CMV was detected on 163 (13%) of 1255 days that placebo was used, compared with 33 (3%) of 1215 days that valganciclovir was used. Valganciclovir's effect on CMV was seen in both HIV-positive participants (109 [14%] of 798 days of placebo use vs. 23 [3%] of 821 days of valganciclovir use with CMV-positive samples) and HIV-negative participants (54 [12%] of 457 days of placebo use vs. 10 [3%] of 394 days of valganciclovir use with CMV-positive samples).

Among the 11 participants who were never observed to shed CMV, valganciclovir still reduced HHV-8 shedding (56% shedding rate during placebo use vs. 29% shedding rate during valganciclovir use [RR, 0.53 {95% CI, 0.29–0.97}; $P = .04$]). We found no significant correlation between the effect of valganciclovir on HHV-8 and the effect of valganciclovir on CMV ($r = 0.15$; $P = .47$).

Adherence to medication regimen and safety of valganciclovir. Of 5560 pills, 5274 (94.9%) were not returned, yielding an estimated median adherence rate of 97.1% (range, 73%–100%). Adherence rates were not significantly different during the time participants received placebo arm and the time they received active drug ($P = .68$), and these rates were not related to the effect of valganciclovir on HHV-8 shedding ($r = -0.16$; $P = .44$).

No participant who was receiving either active study drug or placebo experienced anemia, thrombocytopenia, or renal insufficiency. No serious adverse events were observed during the study. One participant had a transient elevation in serum levels of alanine aminotransferase during administration of placebo. Three participants were neutropenic during the time they received placebo (2 HIV-positive participants and 1 HIV-negative participant), compared with 2 participants during the time they received valganciclovir (both of whom were HIV-positive). Among a subset of 22 participants who provided data on gastrointestinal symptoms during the study, nausea was reported by 2 HIV-positive participants while taking valganciclovir and reported by 3 while taking placebo; abdominal cramps were reported by 3 HIV-positive participants during the time they were taking valganciclovir and reported by 4 during the time they were taking placebo. Diarrhea was reported by 6 HIV-positive participants and 1 HIV-negative participant while taking valgan-

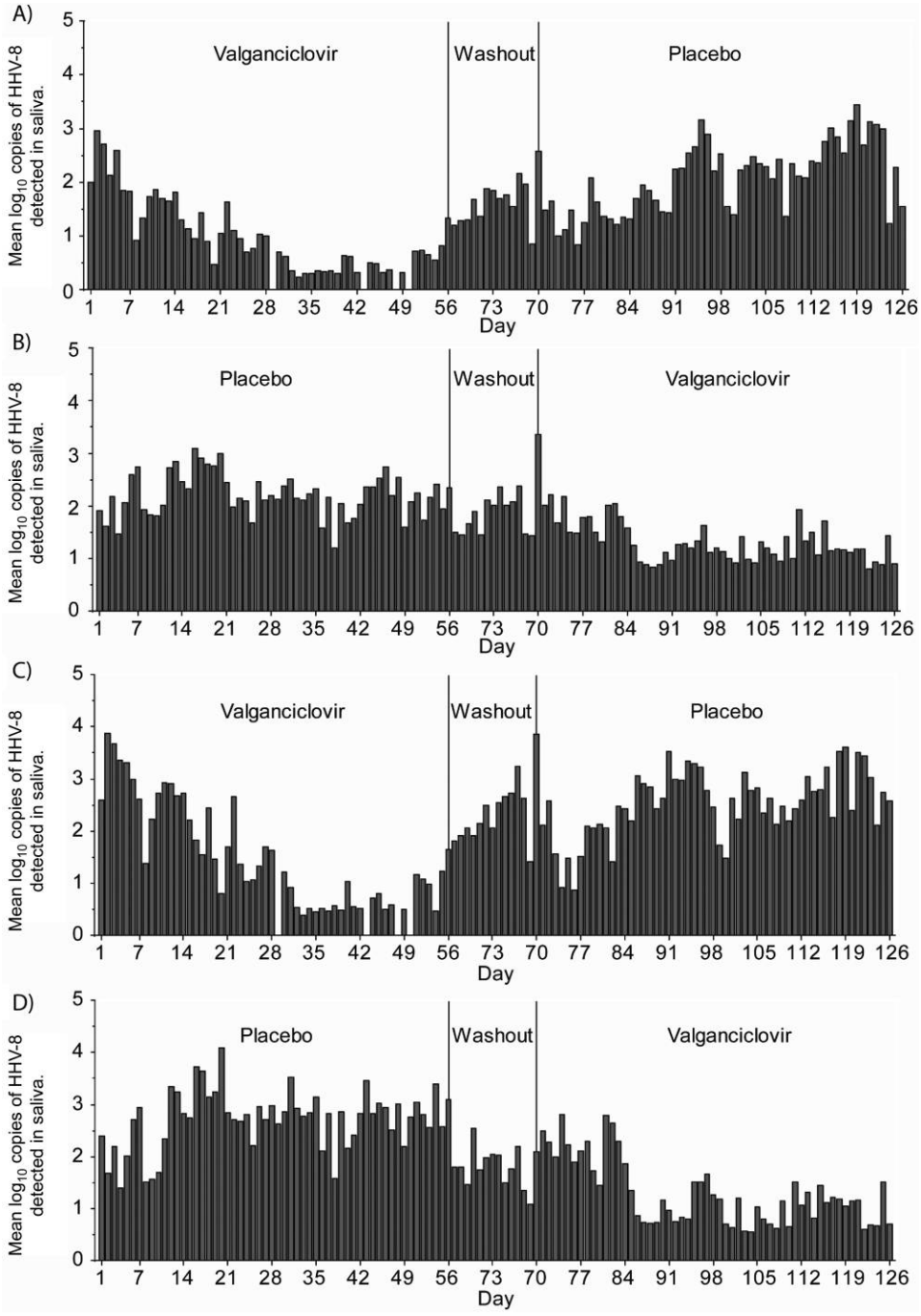

Figure 3. Oropharyngeal shedding of human herpesvirus– by day of study. Mean $\log_{10}$ copies of HHV-8 DNA detected in saliva is summarized for all participants who provided data for each study day. Zero copies were assigned a log value of 0. *A,* All participants who received valganciclovir followed by placebo ($n = 13$). *B,* All participants who received placebo followed by valganciclovir ($n = 13$). *C,* HIV-positive participants who received valganciclovir followed by placebo ($n = 8$). *D,* HIV-positive participants who received placebo followed by valganciclovir ($n = 8$).

ciclovir and reported by 3 HIV-positive participants and 1 HIV-negative participant while taking placebo, though this person-level difference was not significant ($P = .50$). Day-level or visit-level comparison showed that participants reported a total of 132 days of diarrhea, including 9% of days on valganciclovir and 2% of days on placebo ($P = .02$).

DISCUSSION

We found that valganciclovir administered orally effectively inhibits mucosal HHV-8 replication. The frequency and with which HHV-8 was detected in the oropharynx and the quantity detected were significantly reduced during valganciclovir ther-

apy. The antiviral effect was reasonably prompt and appeared to be independent of the drug's substantial reduction in CMV replication. HHV-8 replication resumed on discontinuation of the drug, indicating the need to use daily dosing to achieve effective virologic control. This study also corroborates previous findings that oropharyngeal shedding of HHV-8 is frequent among HIV-positive persons asymptomatically infected with HHV-8 (especially those with high CD4 T cell counts) [19, 22], as well as asympotomatically infected men without HIV infection [18].

The role that direct antiviral chemotherapy will play in preventing HHV-8–associated infection or disease remains to be determined. The reduced incidence of KS observed in the aforementioned studies of HIV-positive persons treated with ganciclovir suggested that the prevention of KS with antiviral medications was possible. Although latent HHV-8 is the predominant form of viral infection in KS tissue, HHV-8 replication is essential to the initiation or maintenance of HHV-8–associated disease. Lytic HHV-8 replication is necessary for the persistence of KS lesions [23, 24], and the detection of HHV-8 in plasma has been associated with the subsequent development of KS in prospective studies of patients with HIV infection [25–30]. Additionally, HHV-8 produces angiogenic and inflammatory factors during lytic replication, including an interleukin-6 analogue and a viral G-protein–coupled receptor [31]. These data suggest the potential for antiviral medication to mitigate some of these viral replication–related sequelae.

We felt it was important to establish the antiviral activity of valganciclovir prior to embarking on a study to demonstrate its clinical efficacy. Given the current expense of valganciclovir and the potential toxicities associated with long-term use, its role in the prevention of KS in areas where the condition is endemic remains to be explored. One potential strategy would be intermittent administration to persons predicted to be at high risk for developing KS on the basis of previously described risk factors, such as HHV-8 viremia [25–30], absence of neutralizing antibodies to HHV-8 [32], or profound immunosuppression [33]. Alternatively, valganciclovir may be useful for the prevention of KS in high-risk transplant patients, as it has been shown that it can be used safely for the prevention of CMV disease in this setting. Although lytic replication may play a role in some aspects of KS, antiviral therapy is not likely to be of benefit when used as a single agent for the treatment of KS, as the role of persistent viral replication after malignant transformation is less clear [34].

Antiviral therapy may also be useful in the treatment of some HHV-8–related disease. For example, almost all cells infected with HHV-8 in MCD harbor lytically replicating virus [35], and the quantity of HHV-8 in the peripheral blood closely parallels the acuity of disease [36]. The results of this randomized trial lend support to our previous clinical observations documenting reductions in HHV-8 viremia and concomitant clinical improvement among patients with MCD who received valganciclovir [13]. The amount of HHV-8 replication in patients with PEL is intermediate between that in patients KS and that in patients with MCD, but evidence for an adjunctive role for antiviral medication in the treatment of PEL offers hope that the treatment of this high-mortality disease could be improved [37]. Studies to optimize the dose and duration of valganciclovir therapy for patients with MCD and patients with PEL should be undertaken.

Our study design was an efficient approach for defining the antiviral activity of orally administered valganciclovir against HHV-8 replication in vivo. However, this study design also had a number of important limitations. First, the population was highly selected, having been previously observed to have HHV-8 frequently detected in the oropharynx. Future studies using less-selected patient populations and defining the antiviral effects in other body sites should be pursued. Similarly, additional trials to define the optimal dose for prevention of HHV-8–associated diseases are needed. Valganciclovir is initially administered at 900 mg twice per day for the treatment of cytomegalovirus ("induction"), after which it is often reduced to 900 mg once per day ("maintenance"). Given that the toxicity of valganciclovir is in part dose related and that this study was an exploratory trial, we elected to use the lower dose. It was gratifying that we were able to demonstrate an effective antiviral effect with minimal toxicity, suggesting the possibility of trials of longer duration that might result in true clinical benefit. The observed reductions in HHV-8 shedding were limited in both magnitude and duration. It is unclear whether higher doses would have resulted in greater efficacy, greater toxicity, or both.

In conclusion, to our knowledge valganciclovir is the first antiviral agent shown to reduce HHV-8 replication in a randomized clinical trial, . Antiviral medications have been shown to be useful in the prevention of other virus-associated malignancies, including hepatocellular carcinoma [38] and posttransplant lymphoproliferative disease [39]. The prevention of KS with valganciclovir in persons judged to be at high risk on the basis of immunosuppression and the presence of frequent and sustained HHV-8 replication could be an important strategy in areas where KS is endemic. Additional research is needed to define the optimal use of antiviral drugs for persons infected with HHV-8, but this study offers hope that the prevention of HHV-8–associated malignancies might be feasible.

Acknowledgments

We thank the men who participated in this study and the members of the Data Safety Monitoring Board, Drs. Kathy Neuzil, Timothy Dellit, and John Pauk.

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