A Randomized, Double-Blind Trial of Valaciclovir Prophylaxis for Cytomegalovirus Disease in Patients with Advanced Human Immunodeficiency Virus Infection

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Cytomegalovirus (CMV) disease is a common complication of advanced human immunodeficiency virus (HIV) infection. Administration of oral valaciclovir, a valine ester of acyclovir, achieves sufficient plasma acyclovir levels to inhibit many clinical isolates. Acyclovir has been associated with enhanced survival in AIDS but not with CMV disease prevention. CMV-seropositive patients (1227) with CD4 cell counts $<100/mm^3$ were enrolled in a randomized, double-blind trial. Valaciclovir, 8 g/day, was compared with acyclovir, 3.2 or 0.8 g/day, for CMV prevention; all three arms were compared for survival. The confirmed CMV disease rate was 11.7% among valaciclovir recipients and 17.5% in the pooled acyclovir arms, a 33% reduction in risk. Time to confirmed CMV disease was significantly longer for the valaciclovir group ($P = .03$). A trend toward earlier mortality for valaciclovir recipients was seen ($P = .06$). Toxicity and earlier medication discontinuation were more common in this group. Valaciclovir significantly reduces the risk of CMV disease. Further exploration of a better-tolerated dose is warranted.

Cytomegalovirus (CMV) end-organ disease, especially retinitis, is a common serious complication of advanced human immunodeficiency virus (HIV) infection, affecting ~25%–40% of those with very low CD4 cell counts [1–3]. CMV retinitis, which accounts for >80% of end-organ disease [2], causes retinal necrosis and may progress to blindness. Treatment of established disease requires lifelong parenteral or intraocular administration of virustatic agents (ganciclovir, foscarnet, and recently, cidofovir) that are toxic and expensive. Despite treatment, progression of retinal lesions typically occurs [4], making prevention of CMV end-organ disease a high priority.

High-dose acyclovir has been effective in reducing CMV disease in bone marrow, renal, and liver transplant recipients [5–7]. Valaciclovir, a valine ester of acyclovir, is rapidly and almost completely converted to acyclovir after oral administration, achieving 3- to 4-fold-higher total plasma acyclovir exposure than is possible with oral acyclovir [8]. Valaciclovir, 2 g four times daily, results in total acyclovir exposure similar to that achieved with intravenous dosing at 10 mg/kg three times

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Guidelines for human experimentation of the US Department of Health and Human Services as defined by the National Institutes of Health Office for the Protection of Research Risks (OPRR) were followed by all participating research sites, and informed consent according to OPRR guidelines was obtained from all participants.

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Valaciclovir is the International Non-proprietary Name–approved name and is used throughout; valacyclovir hydrochloride is the US Adopted Name–approved name.

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daily, which is sufficient to inhibit many clinical strains of CMV [9].

Oral acyclovir prophylaxis for recurrent herpes simplex virus (HSV) infections is commonly used in patients with advanced HIV disease. Two prospective randomized studies of such patient populations have shown a survival advantage associated with high-dose acyclovir compared with placebo [10, 11] but no significant effect on the development of CMV disease, and a third study failed to demonstrate an effect on CMV cultures [12]. Retrospective studies have demonstrated discordant results on mortality with acyclovir use [13, 14]. It is possible that clinically silent herpesvirus replication may up-regulate HIV replication [15, 16], an effect that could be mitigated by acyclovir.

We conducted a randomized, double-blind, comparative study of valaciclovir, 2 g four times daily, and two doses of oral acyclovir for the prevention of CMV end-organ disease and mortality in persons with advanced HIV disease. A pharmacokinetic study defined this valaciclovir dose as the maximum tolerated dose in AIDS patients [8]. A high dose of acyclovir, 800 mg four times daily, was the dose used in the placebo-controlled trials that reported a survival benefit without affecting CMV disease incidence [10, 11]. A lower dose, 400 mg twice daily, was chosen to suppress HSV recurrences and to prevent possible unblinding that might occur with a placebo. Use of three different delivered doses of acyclovir permitted exploration of a possible dose-effect relationship on survival.

Methods

Subjects. Eligible subjects were $\geq$13 years old, with laboratory evidence of HIV infection or a clinical diagnosis of AIDS, an absolute CD4 lymphocyte count $<100/mm^3$, serologic evidence of prior CMV infection, a Karnofsky performance score $\geq$60, and no evidence of CMV end-organ disease. All participants were evaluated for possible retinitis within 21 days before entry by an experienced ophthalmologist who used dilated indirect fundoscopy. Patients with symptoms associated with extraocular CMV syndromes were required to undergo additional medical evaluation as indicated to rule out preexisting CMV disease. Participants had to be receiving all medications for HIV and opportunistic infections for at least 30 days before entry; there were no restrictions on these therapies.

Patients were ineligible if they had chronic nausea or vomiting, ocular media opacities, or necrotizing retinopathy, were pregnant or breast-feeding, had a history of hypersensitivity to acyclovir or known lactose intolerance, had received immunomodulators within 30 days before entry, had previously received anti-CMV agents, or had any of the following laboratory values: absolute neutrophil count $<500/mm^3$, estimated creatinine clearance $<$50 mL/min, total bilirubin $>$5 mg/dL, or serum aminotransferase $>$5 times the upper limit of normal.

Randomization and treatment. Participants were randomized in a 3:2:2 ratio to valaciclovir, 2 g four times daily, high-dose acyclovir, 800 mg four times daily, or low-dose acyclovir, 400 mg twice daily. Patients were stratified by baseline CD4 cell count: <50 and $50-100/mm^3$. Double-blinding required administration of 18 pills per day. All medications considered essential for optimal care were permitted, except anti-CMV agents and immunomodulators. Simultaneous enrollment in other studies of HIV disease management was encouraged.

Design and study conduct. Comparison of the valaciclovir arm with the pooled acyclovir arms for the prevention of CMV end-organ disease, provided the acyclovir arms were not different, was specified in the protocol. The higher acyclovir dose (3.2 g/day) had been shown in two previous placebo-controlled trials to be ineffective for preventing CMV disease in patients with advanced HIV infection [10, 11], and it was anticipated that the lower dose of acyclovir would also be ineffective. The 3.2 g/day dose was associated with a survival advantage in these studies, so investigation of the effect of both lower and higher delivered doses of acyclovir was planned to explore a possible dose-effect relationship. This analysis would compare the survival experience of the three arms in pairwise fashion. A target sample size of 1200 patients, with 12 months of planned follow-up after entry of the last subject, was selected to provide at least 82% power to detect an approximate doubling of the median CMV-free time for valaciclovir relative to the pooled acyclovir arms and to detect a 55% increase in median survival for pairwise comparison among the three arms.

Participants were evaluated at baseline, week 4, and week 8 and every 8 weeks thereafter. At each visit, blood was obtained for routine laboratory tests, serum and plasma specimens were banked, urine was cultured for CMV according to local methods, and quality-of-life measures were assessed. CD4 cell counts and HIV p24 antigen determinations were obtained every 24 weeks.

As this was a collaborative effort of the AIDS Clinical Trials Group (ACTG) and investigators in Europe, Canada, and Australia, an International Steering Committee was formed with appropriate representation. The committee met semiannually and provided overall governance to the diverse study sites.

Dose modification and toxicity management. Since acyclovir is generally well-tolerated, even by patients with advanced HIV disease, study drug dosing was modified only for diminished renal function (estimated creatinine clearance, $<$50 mL/min) that would impair acyclovir elimination. When significant toxicity (grade 3 or higher according to the standard ACTG toxicity grading scheme) occurred, a trial of interruption, dose reduction, or discontinuation was advised for potentially toxic nonstudy medications. If the toxicity did not resolve, study drug was then interrupted. If toxicity attributed to study drug did not resolve within 30 days, study medication was permanently discontinued until a protocol amendment (July 1994) allowed patients to restart study drug after an interruption of up to 6 months for any reason. Study drug formulation included 3.6, 10.9, and 13.4 g of lactose/day for valaciclovir, high-dose acyclovir, and low-dose acyclovir, respectively. Symptoms suggestive of lactose intolerance were managed with dietary modification or a trial of lactase (or both).

CMV disease end-point evaluations. Study ophthalmologists performed dilated indirect funduscopy in all subjects every 24 weeks and whenever new visual complaints arose. Retinal photographs were taken to document CMV retinitis and were verified by an independent fundus photograph reading center that was masked to study drug assignment. Participants were evaluated at both scheduled and symptom-driven visits for signs and symptoms of possible extraocular CMV disease by use of a standardized questionnaire. Additional medical assessment was directed by the

site investigator. Diagnostic criteria for confirmed extraocular disease, as defined in the protocol, were based on a compatible clinical syndrome with histologic evidence of invasive CMV disease. Data pertaining to all extraocular disease, including presentation, radiologic evaluation, and results of diagnostic procedures and laboratory testing, were reviewed by an international committee of seven investigators blinded to site and study drug assignment. Neither CMV viremia nor a positive culture from any site without clinical and histologic evidence of invasive disease was considered an end point.

Statistical methods and interim analyses. Primary analyses included all eligible participants according to their randomized treatment assignment (intent-to-treat principle). The Kruskal-Wallis test was used for comparisons of ordinal data and the χ^2 test for nominal data. Product-limit estimates were used to summarize time-to-event data [17]. The log rank test was used for comparing time-to-event distributions [18, 19]. Cumulative incidence analysis was done to assess the risk of developing CMV disease in the face of competing mortality [20]. All tests of significance were two-sided. All *P* values reported are nominal *P* values, unadjusted for interim analyses or for multiple comparisons.

The study was monitored by an independent data and safety monitoring board, following an O'Brien-Fleming group sequential approach [21]. At the third scheduled interim analysis for efficacy, with 57% of the total end points reported, significantly earlier mortality was seen in the valaciclovir arm, with only a trend toward a CMV preventive effect. The study was terminated at that time, with all follow-up visits completed by May 1995 and data collection completed by August 1995.

Results

Study population. Enrollment of 1227 subjects at 72 sites began in December 1992 and ended in October 1994. Sixty-six percent were enrolled at ACTG sites in the United States and 34% at sites in Canada, Australia, and Europe. Seventy participants (5.7%) had 73 eligibility exemptions, primarily for laboratory values out of range or out of date. Participants were primarily white, non-Hispanic (79.8%) men (93.9%) who had never injected drugs (92.3%). The treatment arms were comparable with respect to selected baseline characteristics (table 1). Fewer than half (44.6%) had urine cultures positive for CMV at entry. The median CD4 cell count was 32/mm^3, and 67.9% had $<$50 cells/mm^3. Prophylaxis for *Pneumocystis carinii* pneumonia, *Mycobacterium avium* complex (MAC) infection, and fungal infections were used by 96.5%, 26.2%, and 53.3%, respectively, and was balanced among the arms. There were no significant differences in the use of one or more antiretroviral agents (zidovudine, didanosine, zalcitabine, stavudine, or nevirapine), taken by 79.2% overall, or for prior diagnoses of HSV or varicella-zoster virus infection, Kaposi's sarcoma, *P. carinii* pneumonia, or disseminated MAC infection. The median duration of study treatment was 29, 36, and 40 weeks for valaciclovir, high-dose acyclovir, and low-dose acyclovir, respectively; however, the median duration of follow-up was comparable at 57, 56, and 60 weeks. Loss to follow-up rates by study arm (7.1%, 7.9%, and 4.3% for valaciclovir, high-dose acyclovir, and low-dose acyclovir, respectively) or by drug (7.1% for valaciclovir and 6.1% for acyclovir) were similar.

CMV disease end points. One hundred eighty-four patients (15% overall) had confirmed CMV end-organ disease (table 2). Forty-eight patients (3.9%) had end points reported that could not be confirmed because of missing critical data, such as retinal photographs or tissue histology. Eighteen end points (1.5%) were rejected because they failed to meet predefined criteria; all but 2 of these were cases of extraocular disease. Most confirmed end points (77.2%) occurred in patients with $<$50 CD4 cells at entry.

The valaciclovir arm was compared with the two pooled acyclovir arms for prevention of CMV disease, according to the protocol, because the two acyclovir arms were similar ($P = .67$). The confirmed end-point rates were 11.7% and 17.5% for valaciclovir and acyclovir, respectively, representing a 33% reduction for those randomized to valaciclovir. Time to confirmed CMV disease was significantly longer for the valaciclovir group than for those assigned to acyclovir ($P = .03$; figure 1). The hazard ratio (HR) for valaciclovir relative to acyclovir was 0.71 (95% confidence interval [CI], 0.52–0.97), consistent with a significant reduction in the risk for CMV disease. The estimated 12-month rates for confirmed end points were 10% for valaciclovir and 14.6% for acyclovir.

A number of secondary analyses were done. When all reported (confirmed plus presumptive) end points were considered, the protective effect of valaciclovir in delaying time to first CMV disease persisted ($P = .009$; table 2). Considering only the 122 end points (66%) that occurred while participants were receiving assigned study medication or within 14 days of its discontinuation (as-treated analysis), valaciclovir was significantly more effective than acyclovir ($P = .006$). In a cumulative incidence analysis of CMV end points that accounted for the competing risk of death, valaciclovir significantly reduced the risk of CMV disease relative to acyclovir ($P = .006$).

Baseline positive urine cultures were predictive of future CMV disease. Seventy-nine CMV end points (23.9%) occurred among those with positive cultures at entry, whereas only 46 (11.2%) occurred among those with negative cultures ($P < .001$). In multivariate analyses that included baseline demographics, laboratory values, urine culture results, time of urine culture conversion, other diagnoses, and antiretroviral use, valaciclovir was significantly protective ($P < .05$). A greater protective effect was seen in the higher CD4 cell count stratum ($\geq$50) at entry, with rates of 4% and 16%, respectively, for valaciclovir and the pooled acyclovir arms ($P = .001$) compared with 15% and 18%, respectively, for those with entry CD4 cell count $<$50 ($P = .57$).

CMV retinitis accounted for 79.3% of end points and gastrointestinal disease for 15.2%; other diagnoses were relatively infrequent (table 3). Despite small numbers, a proportional reduction in all CMV diagnoses was seen for valaciclovir. There were no significant differences among the arms with

Table 1. Selected baseline characteristics of patients with advanced HIV infection participating in valaciclovir CMV prophylaxis study.

	VACV (n = 523)	HACV (n = 353)	LACV (n = 351)	Total (n = 1227)	P*
Male (%)	93.9	94.3	93.4	93.9	0.89
Age, years (median)	38	37	37	37	0.42
Race/ethnicity (%)					
White, non-Hispanic	80.3	81.0	77.8	79.8	0.57
Black, non-Hispanic	11.7	9.9	11.4	11.1	
Hispanic	5.7	7.4	9.1	7.2	
Other	2.3	1.7	1.7	2.0	
No injection drug use (%)	92.5	92.4	91.7	92.3	0.91
Karnofsky score (median)	90	90	90	90	0.59
CD4 cells/mm^3 (median)	31	33	33	32	0.95
% with <50/mm^3	66.9	68.6	68.7	67.9	
Hemoglobin ⩾7 g/dL (%)	99.2	99.4	98.9	99.2	0.29
Urine CMV culture-positive (%)†	48.9	42.5	40.1	44.6	0.10
Any antiretroviral use	78.2	79.9	80.1	79.2	0.75
Prophylaxis (%)					
PCP	96.7	96.3	96.3	96.5	0.92
MAC	27.2	23.5	27.6	26.2	0.38
Fungal	53.5	52.7	53.6	53.3	0.96
Prior diagnosis (%)					
HSV or VZV	45.5	45.6	44.7	45.3	0.97
Kaposi's sarcoma	14.0	10.2	11.7	12.2	0.23
PCP	26.8	26.1	26.5	26.5	0.97
MAC	5.7	7.6	5.7	6.3	0.45

NOTE. VACV = valaciclovir; HACV = high-dose acyclovir; LACV = low-dose acyclovir. PCP = *Pneumocystis carinii* pneumonia; MAC = *Mycobacterium avium* complex; HSV = herpes simplex virus; VZV = varicella zoster virus.

* All tests of significance were Pearson's χ^2 test, except for age, CD4 cell count (Kruskal-Wallis test).

† Based on total of 742 evaluable cultures: VACV, 323; HACV, 212; LACV, 207.

regard to the development of varicella-zoster virus or HSV infections or for new diagnoses of Kaposi's sarcoma.

Antiviral activity. The effect of valaciclovir on recovery of CMV from urine cultures was analyzed according to whether the baseline culture result was negative or positive. Valaciclovir both significantly delayed the time to first positive culture among the 411 patients who were culture-negative at entry ($P < .001$) and decreased the duration of viral shedding among the 331 who were culture-positive at entry ($P = .003$; figure 2). Although viral shedding may be intermittent in the absence of specific anti-CMV therapy, these results suggest that valaciclovir had a greater antiviral effect than acyclovir. Antiviral

Table 2. CMV disease end points in patients with advanced HIV infection: valaciclovir versus pooled acyclovir groups.

End point	VACV (n = 523)	HACV + LACV* (n = 704)	Total (n = 1227)
Reported	83 (16.8)	167 (23.7)	250 (20.4)†
Confirmed‡	61 (11.7)	123 (17.5)	184 (15.0)
Rejected	4 (0.8)	14 (2.0)	18 (1.5)
Unevaluable	18 (3.4)	30 (4.3)	48 (3.9)

NOTE. Data are no. (%). VACV = valaciclovir; HACV = high-dose acyclovir; LACV = low-dose acyclovir.

* Planned analysis for efficacy of prophylaxis was comparison of VACV with pooled ACV arms.

† 29 patients had multiple end points reported, for total of 285 CMV end points.

‡ Only patients' first confirmed end point was considered for primary analysis.

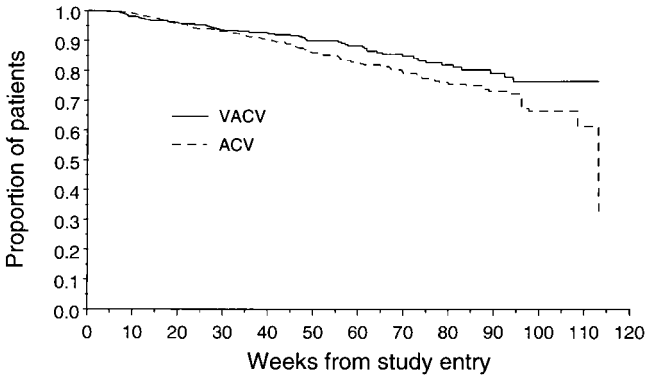

Figure 1. Kaplan-Meier plot of time to first confirmed CMV end-organ disease in valaciclovir CMV prophylaxis study. Valaciclovir (VACV) significantly delayed time to first confirmed CMV disease compared with pooled acyclovir (ACV) arms ($P = .03$, log rank test).

Table 3. Distribution of CMV syndromes among participants with confirmed end points in CMV prophylaxis trial.

Syndrome	VACV (n = 523)	HACV + LACV (n = 704)	Total (n = 1227)
Retinitis	51 (9.75)	95 (13.5)	146 (11.9)
Upper GI disease*	4 (0.8)	11 (1.6)	15 (1.2)
Lower GI disease†	3 (0.6)	10 (1.4)	13 (1.1)
CNS disease‡	2 (0.4)	7 (1.0)	9 (0.7)
Pneumonitis	1 (0.2)	0 (0.0)	1 (0.1)

NOTE. Data are no. (%). VACV = valaciclovir; HACV = high-dose acyclovir; LACV = low-dose acyclovir. GI, gastrointestinal tract; CNS, central nervous system.

* Mouth ulcer, esophagitis, gastritis, duodenitis.

† Colitis, proctitis.

‡ Encephalitis, radiculomyopathy.

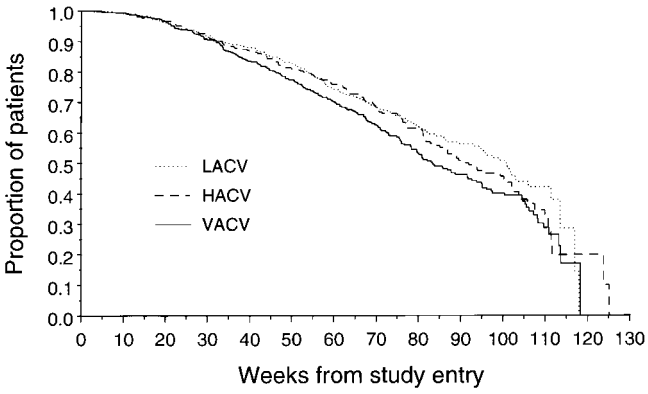

Figure 3. Kaplan-Meier plot of time to death. For survival, each treatment arm was compared with other 2 arms. There was trend to earlier mortality in valaciclovir (VACV) group (P = .06, log rank test) compared with high- and low-dose acyclovir (HACV, LACV).

activity as assessed by polymerase chain reaction is described in the companion paper by Griffiths et al. [22].

Survival. There were 488 deaths overall (39.8%). A trend toward earlier mortality was seen for patients randomized to valaciclovir (P = .06; figure 3). Mortality rates were 42.6%, 38.2%, and 37.0% for valaciclovir, high-dose acyclovir, and low-dose acyclovir, respectively, with estimated 12-month rates of 24.1%, 19.5%, and 18.8%. Pairwise comparisons suggested that the risk of death was greater for valaciclovir than for low-dose acyclovir (HR, 1.28; 95% CI, 1.03–1.59), with no significant difference between valaciclovir and high-dose acyclovir (HR, 1.17; 95% CI, 0.94–1.45) or between the two acyclovir arms (HR, 1.10; 95% CI, 0.87–1.40).

Only 57 deaths (11.7%) occurred in patients who were still receiving assigned study medication or within 14 days of its discontinuation. In an as-treated analysis, survival was significantly shorter in the valaciclovir arm (P = .002). Mortality was similar among those who had positive or negative urine CMV cultures at entry, with 137 (41.4%) and 148 (36.0%) deaths, respectively (P = .13). Multivariate analyses revealed an increased risk of death in patients receiving valaciclovir when baseline demographics, laboratory values, diagnoses, antiretroviral use, and time of elevated serum creatinine were considered ($P < .05$).

The most common principal cause of death, in 44 patients (9.0% of all deaths), was non-Hodgkin's lymphoma, evenly divided between systemic and primary central nervous system disease. Other common causes of death were non–*P. carinii* pneumonia (8.8%), disseminated MAC infection (8.6%), wasting (7.8%), *P. carinii* pneumonia (7.4%), sepsis (6.8%), and Kaposi's sarcoma (6.6%). CMV disease was listed as the principal cause of death for 16 patients (3.3%). There were no significant differences in the primary causes of death among the three arms.

Tolerance. Of all adverse events grade 3 or higher, only gastrointestinal complaints occurred significantly more often and earlier in the valaciclovir arm (P = .03). Grade 2 or greater increases in serum creatinine (>1.5 times the upper limit of normal) occurred earliest in the valaciclovir group (P = .03), although there were no differences among the arms for grade 1 or higher increases (P = .11). Sixty-five patients had an estimated creatinine clearance <50 mL/min while receiving study medication; 58.5% were randomized to valaciclovir (P = .03).

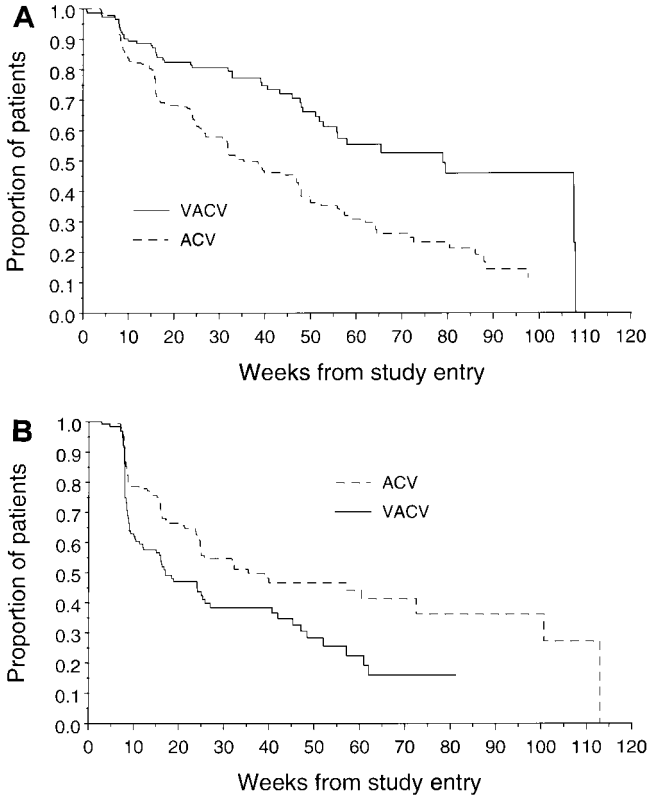

Figure 2. Antiviral effect of valaciclovir (VACV) on recovery of CMV from urine compared with pooled acyclovir (ACV) arms according to baseline culture status (**A**, culture-negative; **B**, culture-positive).

Eighteen patients developed an illness with features suggestive of thrombotic microangiopathy (TMA), reported as thrombocytopenic purpura or hemolytic-uremic syndrome, 8 of whom were still receiving assigned study medication. Most cases failed to meet established criteria for classical thrombocytopenic purpura or hemolytic-uremic syndrome, with milder thrombocytopenia and anemia, rare neurologic abnormalities, poor response to plasma therapy when administered, and prolonged survival without plasma therapy. The reported events occurred a median of 54 weeks after enrollment (range, 8–84). TMA-like syndromes were reported more frequently in the valaciclovir arm (14) than in either of the acyclovir arms (high-dose acyclovir, 1; low-dose acyclovir, 3; $P = .008$). Those randomized to valaciclovir had received doses of 8 g/day for a median of 54 weeks (range, 8–77), and 12 had been treated for >35 weeks. Patients with TMA-like syndromes received multiple medications, and most had intercurrent illnesses that could explain the hematologic and renal abnormalities. The relative risk of a TMA-like event was increased among recipients of a number of concomitant medications, including clofazimine, fluconazole, ciprofloxacin, ethambutol, and trimethoprim-sulfamethoxazole, as well as valaciclovir. These cases and associated risk factors are more fully described elsewhere [23].

Treatment discontinuation. The treatment arms differed in time to permanent discontinuation of study medication for reasons other than death or the development of CMV disease, with those assigned to valaciclovir discontinuing earlier ($P = .01$). The overall estimated 12-month discontinuation rate was 46.6%. The respective rates for valaciclovir, high-dose acyclovir, and low-dose acyclovir were 50.5%, 46.2%, and 41.0%. Patients randomized to valaciclovir discontinued dosing significantly more often for protocol-defined toxicity ($P = .001$), with a trend toward earlier discontinuation for subjective complaints ($P = .07$), while those assigned to acyclovir discontinued treatment significantly more often for the development of CMV disease ($P = .001$). Participants cited pill burden (8.4%) and gastrointestinal complaints (7.1%) as their most common reasons for self-initiated discontinuation, with no significant differences among the arms.

Discussion

This study was designed to compare valaciclovir, 2 g four times daily, with high- and low-dose acyclovir (arms combined) for the prevention of CMV disease in patients with advanced HIV infection and for pairwise comparison of the three different delivered acyclovir doses for survival. A significant protective effect for valaciclovir against CMV disease was demonstrated, with a 33% reduction in the rate of confirmed CMV end-organ disease and significant prolongation of the time to development of CMV disease ($P = .03$). A 49% reduction in the rate of confirmed CMV end-organ disease has previously been demonstrated in a placebo-controlled study of oral ganciclovir, 1 g three times daily [24]. A second placebo-controlled trial using the same dose of ganciclovir failed to confirm this result [25]. Secondary analyses that included presumptive diagnoses and end points that occurred while patients were receiving treatment or within 14 days of its discontinuation, as well as evidence of an antiviral effect on recovery of virus from urine, support the superiority of valaciclovir in delaying CMV disease compared with acyclovir.

This is the first randomized trial of CMV prophylaxis in which all end points were independently confirmed. Cases of retinitis were evaluated by an independent retinal photograph reading center, and extraocular disease was assessed by a panel of blinded investigators. Protocol criteria for confirmed extraocular disease were stringent, requiring a compatible clinical syndrome and evidence of CMV-related tissue invasion. Forty-eight patients who received a clinical diagnosis of CMV end-organ disease lacked key data for independent confirmation, and 18 cases that were fully evaluated failed to meet predetermined criteria. Sixteen of these were presumptive diagnoses of extraocular disease, which may reflect the difficulty in establishing an unequivocal diagnosis in clinical practice or the strict case definitions used. In contrast, clinical diagnosis of CMV retinitis by experienced ophthalmologists appears sufficient for future trials.

A trend to earlier mortality was seen in the valaciclovir group compared with the acyclovir arms. Two randomized double-blind trials that compared high-dose acyclovir with placebo in patients with advanced HIV disease (median CD4 cell count, 39 and 32/mm^3) reported annual mortality estimates of 23% and 27% for the high-dose acyclovir recipients compared with 39% and 46%, respectively, for the placebo groups [10, 11]. The current study, which lacked a placebo arm, had similar annual mortality rates, with 18.8%, 19.5%, and 24.1% for low-dose acyclovir, high-dose acyclovir, and valaciclovir, respectively. Differences that may have an impact on mortality, such as baseline HIV load, are not available. Patients with less advanced HIV disease (CD4 cell count, 100–300/mm^3) treated with high-dose acyclovir or placebo for a median of 365 days had no difference in survival, although median time to death was long (945 days) [26]. Additional support for the concept that inhibition of herpesvirus replication may improve survival in AIDS has come from a recent well-designed observational study [14], although a second observational study did not find a survival advantage [13]; this discordance may result from methodologic concerns [27]. Two placebo-controlled studies of oral ganciclovir prophylaxis for CMV disease demonstrated a trend to enhanced survival for ganciclovir recipients [24, 25].

The results of the study reported here may provide some insight into which herpesviruses are responsible for this effect. As there was no significant difference between high- and low-dose acyclovir, improved survival may be due to suppression of the most sensitive herpesviruses, such as HSV-1 or -2. Further support for this possibility comes from evidence that HSV infection in human skin is associated with increased numbers of HIV virions, possibly HIV/HSV pseudotypes, and that reactivation of HSV-2 can increase HIV plasma RNA levels [28,

29]. However, the possible involvement of other herpesviruses, such as Epstein-Barr virus or human herpesvirus 8, cannot be discounted.

There was an association between treatment with valaciclovir and moderate nephrotoxicity. Although the time to grade 3 or greater renal impairment was not significantly different among the arms, there was a difference for more modest impairment (grade 2 or higher). Acyclovir is excreted renally. High serum concentrations of acyclovir can lead to precipitation in renal tubules; resultant renal impairment is generally reversible when treatment is withdrawn [30]. Because oral valaciclovir can result in acyclovir concentrations previously attainable only with intravenous dosing, it is possible that prolonged use of high-dose valaciclovir may have contributed to renal insufficiency in this patient population.

Thrombotic microangiopathies are being recognized with increasing frequency in patients with advanced HIV disease. One study reported 15 cases (2.9%) among 521 patients with CD4 cell counts $<100/mm^3$ [31]. That study identified both CMV disease and fluconazole use as risk factors. Administration of high doses of valaciclovir also appeared to be a risk factor for TMA-like syndromes in the present study. The precise relationship to valaciclovir is unclear, since 8 of 14 patients treated with valaciclovir had discontinued treatment at least 1 week before their first abnormal serum creatinine value. TMA and microangiopathic hemolytic anemia have also been reported in clinical trials of high-dose valaciclovir for CMV prophylaxis in renal and bone marrow transplant recipients, but not at rates exceeding the baseline levels for these patient populations, and no cases have been noted in HIV-seropositive or -seronegative patients treated with lower doses of valaciclovir (1–3 g/day) for herpes zoster or genital herpes for periods up to 1 year [32]. Additional data are required for a better understanding of the role of valaciclovir and other medications for TMA-like conditions in HIV disease.

This study demonstrated that valaciclovir can significantly reduce the risk of CMV end-organ disease in patients with advanced HIV disease. The fact that patients assigned to valaciclovir discontinued treatment earlier, had more adverse effects, and exhibited a trend to earlier mortality indicates that a dose of 2 g four times daily was too high. Further studies are needed to identify a dose of valaciclovir that is better-tolerated while maintaining a CMV protective effect to determine its ultimate role in the prevention of CMV disease in patients with advanced HIV infection.

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