Evaluation of Sorivudine (BV-araU) versus Acyclovir in the Treatment of Acute Localized Herpes Zoster in Human Immunodeficiency Virus–Infected Adults

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The clinical efficacy and safety of sorivudine as treatment for acute cutaneous zoster in human immunodeficiency virus–infected adults was compared with that of acyclovir in a double-blinded randomized study. A total of 125 patients with laboratory-confirmed zoster rash present for ⩽72 h were assigned treatment with either 40 mg of sorivudine once daily or 800 mg of acyclovir five times daily, both taken orally for 7 days. Patients were assessed daily until all lesions crusted and then monthly for 6 months for postherpetic neuralgia (PHN) and for 12 months for recurrent or new episodes of zoster. Sorivudine significantly shortened the median period of new vesicle formation from 3.0 to 4.0 days (log rank $P = .0001$). Sorivudine was effective regardless of duration of rash before treatment. Zoster recurrences and new episodes were experienced by fewer patients assigned sorivudine (11%) than acyclovir (26%, $P = .037$). No differences were seen in incidence, severity, or duration of either acute neuritis or PHN. Both treatments were well tolerated.

Herpes zoster develops frequently in human immunodeficiency virus (HIV)–infected patients. Cohort studies of HIV-infected adults have resulted in incidence estimates of 29.4–51.5 zoster cases per 1000 person-years [1–3]. In contrast, large population-based studies have estimated incidence rates of 1.3 [4] and 3.4 [5] cases per 1000 person-years in immunocompetent adults. In patients with more advanced HIV infection, atypical, often chronic, skin lesions can develop, and cutaneous and visceral dissemination occurs, including encephalitis and retinitis [6–8]. Recurrences of zoster are also more frequent in HIV-infected patients [1–3, 9, 10]. In general, however, the natural history of varicella-zoster virus (VZV) infection in asymptomatic HIV-infected patients or in patients with less advanced disease appears to be similar to that in immunocompetent individuals of similar age.

The optimal therapy for VZV infection in HIV-infected patients remains unknown, although acyclovir has been widely used on the basis of data extrapolated from other immunocompromised populations [11]. High-dose intravenous acyclovir is often used to treat severe HIV-related VZV infections (such as ophthalmic zoster [12]), and oral acyclovir is routinely used for less severe episodes of localized cutaneous zoster. However, poor bioavailability (15%–25% after oral ingestion) [13] and, in some cases, resistance [14–16] limit efficacy, and acyclovir must be given orally five times daily. There are no previous controlled studies of oral or intravenous acyclovir therapy for zoster in HIV-infected persons.

Sorivudine (bromovinyl-arabinosyl uracil; BV-araU) is a pyrimidine nucleoside analogue with excellent in vitro activity against VZV. In VZV-infected cells, sorivudine is phosphorylated sequentially by the viral enzymes thymidine kinase and thymidylate kinase to the diphosphate, then once by a cellular kinase to produce sorivudine triphosphate. This contrasts with acyclovir, where only the first phosphorylation step is mediated by viral enzymes. Sorivudine triphosphate is a potent inhibitor of VZV DNA polymerase. Plaque-reduction assays show in vitro activity 2000–5000 times the potency of acyclovir [17, 18]. In one study of 101 clinical isolates of VZV using human fibroblast cultures, the ID_{50} of sorivudine was 0.0013 μg/mL versus 4.6 μg/mL of acyclovir [18]. Thymidine kinase–deficient VZV isolates resistant to acyclovir will also be cross-resistant to sorivudine; however, isolates with altered thymidine

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Each subject provided informed consent prior to participation in the study. The study was conducted in accordance with guidelines for human experimentation as designated by the Research Ethics Committee of the authors' respective institutions.

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kinase that are resistant to acyclovir may be sensitive to sorivudine [16]. In addition, ~50%–70% of sorivudine is bioavailable after oral ingestion. Peak serum levels of 1.5–2.0 μg/mL are achieved following a single 40-mg dose with 24-h trough levels of ~0.20 μg/mL or >100-fold the ID_{50} for VZV [19]. Once-daily oral dosing is therefore possible.

Because of the superior in vitro activity of sorivudine against VZV infection over that of acyclovir and its favorable pharmacokinetic profile allowing for once-daily dosing, the current study of sorivudine versus acyclovir for zoster in HIV-infected adults was conducted.

Methods

Patient Population

HIV-infected adults at least 18 years of age were eligible for enrollment if they presented with a clinical diagnosis of localized herpes zoster within 72 h of rash onset. Excluded were pregnant or lactating women and patients with an acute life-threatening opportunistic infection, a Karnofsky performance status score of <60, concurrent visceral or cutaneous zoster dissemination (defined as >20 vesicles in noncontiguous dermatomes), chickenpox, bacterial superinfection of zoster lesions, or significant anemia (hemoglobin, <7.0 g/dL), thrombocytopenia (<50,000 cells/mm^3), neutropenia (<500 cells/mm^3), renal insufficiency (creatinine >2.5 mg/dL), or hepatic dysfunction (bilirubin more than twice the upper limit of normal, and aspartate aminotransferase or alanine aminotransferase more than three times the upper limit of normal). Patients were also excluded if they had received antiviral therapy (other than zidovudine, didanosine, or zalcitabine) or any immune globulin or immunomodulatory agents within 2 weeks of study entry. Also disallowed were patients receiving concurrent or recent (≤72 h) treatment with fluorinated pyrimidines (5-flucytosine, 5-fluorouracil, or its derivatives), anticoagulants, probenecid, or cimetidine. Patients with involvement of the ophthalmic branch of the trigeminal nerve were enrolled at selected sites following protocol amendment.

Patients were recruited from 31 sites in Canada, the United Kingdom, Australia, France, the Netherlands, Belgium, New Zealand, Switzerland, and Spain. The median enrollment at each site was 3 patients.

Study Design and Treatments

Protocol AI458-049 was a multicenter, randomized, double-blind, acyclovir-controlled study. Participants were randomized to receive either 40 mg of sorivudine once daily or 800 mg of acyclovir five times a day for 7 days. Matching sorivudine placebo capsules were given once daily to patients receiving acyclovir; matching acyclovir placebo tablets were given five times daily to patients receiving sorivudine. There was no stratification in treatment allocation.

Patient Evaluation

Acute phase (days 1–28). All patients were to be evaluated daily (home or office visit) until all lesions had crusted and also on days 7, 10, 14, 21, and 28, regardless of lesion status. If all lesions had not crusted by day 14, patients were to be seen every other day until 100% crusting. At each visit, assessment was made of rash progression, acute neuritis, zoster-related sleep and activity impairment, zoster-related analgesic use, cutaneous or visceral dissemination, other zoster-related complications, recurrent and new episodes of zoster, HIV-related events, and adverse events.

Rash progression was evaluated by counting the number of new vesicles that had developed in the primary and adjacent dermatome(s) since the previous visit, together with recording the percentage of lesions that were maculopapular, vesicular, pustular, crusted, and healed (defined as loss of crust or regression of lesions from an earlier stage). Topical antivirals, anesthetics, and other applications that might interfere with lesion assessment were prohibited.

Acute neuritis was defined as discomfort, paresthesia, or pain in the involved dermatome ≤28 days from commencing study medication and was assessed at each visit on the following scale: 0 = none, 1 = mild, 2 = moderate, 3 = severe, and 4 = incapacitating. Similar scales were used at each visit to assess sleep interruption and activity impairment due to zoster. Zoster-related analgesic use was reported on a scale of 0–5 (0 = none; 1 = nonnarcotic analgesic, antidepressant, or antipsychotic; 2 = oral narcotic; 3 = any oral analgesic plus antidepressant; 4 = parenteral narcotic; and 5 = nerve block).

Physical examination (including CDC HIV staging and Karnofsky performance status) was performed on days 1, 7, and 28. Lesions were cultured for virus every other day until all lesions had crusted. Rapid VZV direct fluorescent antibody (DFA) stain of lesion scrapings was to be performed daily for up to 3 days until positive or another diagnosis was made. Routine hematologic and biochemical tests and urinalyses were to be performed on days 1, 3, 7, and 14; VZV serology was to be done on days 1 and 28. CD4 cell count was to be obtained on day 1. Zoster serology was considered positive if there was a 4-fold rise in VZV IgG antibody titer, a positive VZV IgM titer, or a single VZV IgG titer of >20,000.

Viral culture susceptibility testing was conducted at 2 laboratories: the General Virology Laboratory at the University of British Columbia and the Department of Virology at the Swedish Institute for Infectious Disease Control in Stockholm. The Canadian group used the Hybriwix Probe Systems (Diagnostic Hybrids, Athens, OH) for determining VZV antiviral susceptibility. The susceptibility range for sorivudine and acyclovir using this method was up to 0.00031 μg/mL and 0.76 μg/mL, respectively. The viral culture susceptibilities were analyzed by ELISA by the Swedish group: 0.00011–0.00035 μg/mL for sorivudine and 0.23–2.3 μg/mL for acyclovir.

Long-term phase (day 29–12 months). Following the acute phase, patients were to be assessed monthly for 5 months by telephone or visit for the development of postherpetic neuralgia (PHN) defined as paresthesia, abnormal sensation or pain experienced in a previously involved but currently healed dermatome occurring >28 days after study enrollment. Severity of PHN was assessed using the same scoring system as for acute neuritis.

In addition, patients were followed for 12 months after enrollment for zoster-related complications, recurrent (same dermatome) or new (different dermatome) episodes of zoster, HIV-related events, and death. Other than deaths, information on adverse events

was recorded after day 28 only if considered by the investigator to be related to study medication.

Statistical Methods

All statistical analyses were performed using SAS (SAS Institute, Cary, NC). The reported nominal *P* values were based on two-sided tests. The nominal significance level was calculated using the O'Brien and Fleming group sequential procedure [20]. Treatment differences were declared statistically significant at $\alpha = .05$ only if the nominal *P* value was $<.0471$ according to this procedure.

The primary efficacy end point was time from first day of study medication to cessation of new vesicle formation. Prospectively defined secondary efficacy end points included time until 50% and 100% crusting of lesions; time until 50% and 100% healing of lesions; incidence, intensity, and time to cessation of acute neuritis; and incidence, intensity, and time to cessation of PHN. The incidence and type of zoster-related complications, scarring, and zoster recurrences or new episodes were specified as tertiary efficacy end points.

Intent-to-treat analyses were conducted on the 125 patients who had a clinical diagnosis and laboratory-confirmed VZV infection (DFA, culture, and/or serology).

The 2 treatment groups were compared with respect to demographic and baseline characteristics using Fisher's exact test for categorical data and the Wilcoxon test for ordinal and continuous data.

All end points defined by time to event were analyzed using time-to-failure methods for censored observations. Patients not achieving end points were censored at their last available observation. Analyses using the Kaplan-Meier product limit method provided the mean and median time to event and standard error for each treatment arm.

A proportional hazard (Cox) model was used to estimate relative risk, 95% confidence intervals (CIs), and *P* values for the time-to-event end points. Risk estimates and 95% CIs were adjusted for demographic and significant prognostic factors. Sixteen demographic and baseline factors of possible prognostic and clinical relevance, including age, rash duration, CD4 cell count, severity of zoster pain, and acyclovir use prior to the current episode of zoster, were considered for the regression model. Forward stepwise regression was used to identify significant factors. All significant prognostic factors identified by this step together with variables with significant differences between treatment arms at baseline and treatment arm were all included in the final model. All reported *P* values associated with relative risk were based on this covariate-adjusted analysis.

End points other than time to event, including incidence of progression of disease, incidence and type of zoster-related complications, incidence of zoster recurrence or new episode, incidence of scarring, incidence and severity (maximum score on-study for each patient) of acute neuritis, incidence and severity of PHN, incidence and severity of zoster-associated pain, and proportion of patients with positive cultures after day 1 were analyzed using Fisher's exact test for categorical data and the Wilcoxon rank sum test for ordinal data.

Safety analyses were performed on 136 patients who received at least one dose of study medication. The proportions of patients experiencing clinical adverse events and developing laboratory abnormalities were compared using Fisher's exact test.

Results

Patient Population

A total of 137 patients with a clinical diagnosis of acute, localized herpes zoster were randomized between November 1991 and August 1993. The study was terminated when the second interim analysis of the first 112 patients who completed the acute phase revealed a significant difference in the time to cessation of new vesicle formation at the $P = .001$ level, thereby satisfying the prospectively defined sequential stopping rules for the primary efficacy parameter (O'Brien-Fleming group sequential procedure). At the time the study closed, 69 patients had been randomized to receive sorivudine and 68 to receive acyclovir. Twelve patients (5 receiving sorivudine, 7 receiving acyclovir) had other diagnoses, including herpes simplex virus infection (6), psoriasis (1), scabies (1), and rashes of undetermined etiology (4). The intent-to-treat analyses presented here are based on the experience of the 125 patients with laboratory-documented zoster.

Patients randomized to receive acyclovir were more likely to report incapacitating pain at baseline (11%) than those assigned to receive sorivudine (0%; $P = .014$). However, the number presenting with severe or incapacitating pain was similar in the sorivudine (22%) and acyclovir (26%) groups. Although there appeared to be differences in CD4 cell count and acyclovir use in the past, these differences were not statistically significant; otherwise, there were no significant differences in demographic, clinical, or zoster characteristics at baseline between treatment groups (tables 1 and 2).

Study Medication Compliance

Compliance regarding study medication was carefully monitored by pill counts, and compliance was excellent. Only 6 patients (3/treatment group) completing the 7-day dosing period failed to take all 7 ''sorivudine'' tablets and $\geqslant$124 ''acyclovir'' capsules (equivalent to 6 days plus one dose of therapy), and 9 patients (5 randomized to receive sorivudine and 4 to receive acyclovir) withdrew or were lost to follow-up during the dosing period.

Study Discontinuations

Nine patients (6%) discontinued the study during the dosing period for the following reasons: cutaneous dissemination (1 receiving sorivudine, 2 receiving acyclovir); lost to follow-up (2 receiving sorivudine); patient request (1 receiving sorivudine, 1 receiving acyclovir); progression of VZV disease (1 receiving sorivudine); and never received study medication (1 receiving acyclovir). No patient discontinued because of an

Table 1. Sorivudine versus acyclovir for zoster in HIV infection: baseline characteristics of study population by treatment group.

	Sorivudine $n = 64$	Acyclovir $n = 61$	Total $n = 125$
Age (years)			
Median	33	34	34
Mean ± SE	33.9 ± 0.92	36.0 ± 0.94	34.9 ± 0.66
Range	17–55	24–55	17–55
Gender *n* (%)			
Male	60 (94)	56 (92)	116 (93)
Female	4 (6)	5 (8)	9 (7)
Race *n* (%)			
White	56 (88)	54 (89)	110 (88)
Non-white	8 (12)	7 (11)	15 (12)
CD4 cell count (mm^3)			
n	62	60	122
Median	233.5	174	209
Mean ± SE	244.1 ± 21.69	214.6 ± 25.26	229.6 ± 16.59
Stratum, *n* (%)			
⩽50	9 (14)	16 (26)	25 (20)
50–100	7 (11)	10 (16)	17 (14)
101–200	12 (19)	6 (10)	18 (14)
201–300	11 (17)	11 (18)	22 (18)
>300	23 (36)	17 (28)	40 (32)
Unknown	2 (3)	1 (2)	3 (2)
Previous zoster (%)	12 (19)	16 (26)	28 (22)
Previous acylocvir therapy (%)	16 (25)	25 (41)	41 (33)

adverse event. An additional 17 patients discontinued before completing the acute phase for the following reasons: need for prohibited medication (1 receiving sorivudine, 1 receiving acyclovir); dissemination (1 receiving acyclovir); death (1 receiving sorivudine); lost to follow-up (3 receiving sorivudine); recurrence (2 receiving sorivudine, 7 acyclovir); and zoster-related event (1 receiving sorivudine).

Progression of Rash

The median time to cessation of new vesicle formation was significantly less for patients randomized to sorivudine (3.0 days) compared with that in patients assigned to acyclovir (4.0 days, unadjusted log rank $P = .0001$) (figure 1, table 3). Of all the baseline variables, only acyclovir use (prior to the current episode of zoster) was a significant prognostic factor, but the difference was maintained after adjustment for this baseline difference (adjusted $P = .0002$). The difference in favor of sorivudine remains significant in the subgroups of patients enrolled ⩽48 h (unadjusted log rank $P = .001$) and >48 h (unadjusted log rank $P = .019$) of rash onset.

Resolution of Rash

The median time to 100% crusting of lesions was also significantly shorter in the sorivudine group (8 days) compared with that in the acyclovir group (9 days) (unadjusted log rank $P = .041$, table 3). A similar difference was seen in the subgroup of patients receiving study medication within 48 h of rash onset (log rank $P = .032$). No significant difference between the treatment groups was observed in time to 100% healing of lesions (median time to healing was 21 days in both groups).

Virology

Sixty-five patients (32 receiving sorivudine, 33 receiving acyclovir) had a positive VZV culture at baseline. Isolates from 22 patients (12 receiving sorivudine, 10 receiving acyclovir) were recovered following shipment to one of two central virology laboratories and were available for sensitivity testing. The mean ID_{50}s of the 22 pretherapy isolates was 0.000327 μg/mL for sorivudine (range, 0.0007–0.001 μg/mL) and 0.626 μg/mL for acyclovir (range, 0.01–1.74 μg/mL). All isolates were in the susceptibility range for both sorivudine (0.00031 μg/mL) and acyclovir (0.76 μg/mL).

Seventy-four patients (37 receiving sorivudine, 37 receiving acyclovir) had serial cultures done through day 5. The proportion of patients with serial cultures positive for VZV after day 1 was significantly lower in the sorivudine group (1/37) compared with that of the acyclovir group (11/37, $P = .003$). All tested isolates were fully susceptible to both sorivudine and acyclovir.

Table 2. Sorivudine versus acyclovir for zoster in HIV infection: baseline zoster characteristics by treatment group.

	Sorivudine $n = 64$	Acyclovir $n = 61$	Total $n = 125$
Duration of rash (h)			
n	64	60	124
Median	45	37	43.5
Mean ± SE	41.8 ± 2.73	36.2 ± 2.78	39.1 ± 1.95
Stratum (%)			
⩽24	17 (27)	19 (31)	36 (29)
24 to ⩽48	20 (31)	17 (28)	37 (30)
48 to ⩽72	25 (39)	23 (38)	48 (38)
>72	2 (3)	1 (2)	3 (2)
Unknown	0	1 (2)	1 (1)
No. of discrete vesicles			
Median	95	90	90
Mean ± SE	148.3 ± 19.11	150.0 ± 23.41	149.1 ± 14.98
Intensity of discomfort or pain (%)			
None	4 (6)	7 (11)	11 (9)
Mild	22 (34)	12 (20)	34 (27)
Moderate	24 (38)	26 (43)	50 (40)
Severe	14 (22)	9 (15)	23 (18)
Incapacitating	0	7 (11)	7 (6)

Recurrent and New Episodes of Zoster

The incidence of first recurrent or new episodes of zoster over 12 months of follow-up was less frequent among sorivudine-treated subjects (11% vs. 26%, $P = .037$; acute phase, 3% vs. 12%; long-term phase, 8% vs. 15%). The time to first recurrence or new episode was significantly longer in the sorivudine group (relative risk = 0.40 [95% CI = 0.163–0.968], log rank $P = .035$). Ten of the 23 zoster recurrences or new episodes were confirmed by DFA or culture (or both); 4 were DFA- or culture-negative. No DFA or culture was done for 9 patients.

Zoster Pain

Acute neuritis. The mean maximum pain intensity score during the acute phase was 2.27 for patients receiving sorivudine and 2.36 for those receiving acyclovir. The median time to cessation of acute neuritis was similar in both groups (sorivudine-treated = 31 days, acyclovir-treated = 30 days). There was also no difference in the incidence of analgesic use for acute neuritis (77% for both groups), in mean maximum analgesic scores (sorivudine-treated = 1.50, acyclovir-treated = 1.59), and in proportion of patients reporting sleep interruption (sorivudine-treated = 81%, acyclovir-treated = 74%). Overall, 44% of patients had maximum pain intensity scores of ⩾2 (sorivudine-treated = 40%, acyclovir-treated = 46%).

PHN. Twenty-six patients were discontinued prior to entering the long-term phase of the study. Of the 99 patients who entered the 6-month follow-up phase, 51% of sorivudine and 58% of acyclovir recipients had PHN. The treatment groups were similar during the long-term phase in terms of mean maximum pain intensity scores (sorivudine-treated = 0.78, acyclovir-treated = 0.91); median time to complete cessation of PHN (sorivudine-treated = 55 days, acyclovir-treated = 64 days); incidence of analgesic use for PHN (sorivudine-treated = 22%, acyclovir-treated = 35%); and mean maximum analgesic scores (sorivudine-treated = 0.39, acyclovir-treated = 0.57).

Dissemination and Other Zoster-Related Complications

Eight patients, 4 in each treatment group, experienced zoster-related complications. Four had cutaneous dissemination (1 sorivudine-treated, 3 acyclovir-treated). There were no cases of visceral dissemination. One patient in the sorivudine group developed Ramsay-Hunt syndrome 6 days into the study, was treated with open-label acyclovir, and recovered uneventfully. One patient in the acyclovir group reported loss of motor activity of the right quadriceps 6 months into the study, which had not resolved by the end of the 12-month follow-up. At entry, he presented with zoster involving dermatomes L3 and L4 of the right leg. One patient in the sorivudine group developed a bacterial superinfection on study day 9. The infection resolved 1 day later, after the patient began treatment with erythromycin for bronchitis. A patient in the sorivudine group presented with alopecia in the healed dermatome 2 months into the study. The alopecia had diminished in severity but was still present at the end of the 12-month follow-up. Incidence of scarring between the treatment groups was also similar (sorivudine-treated = 39%, acyclovir-treated = 34%).

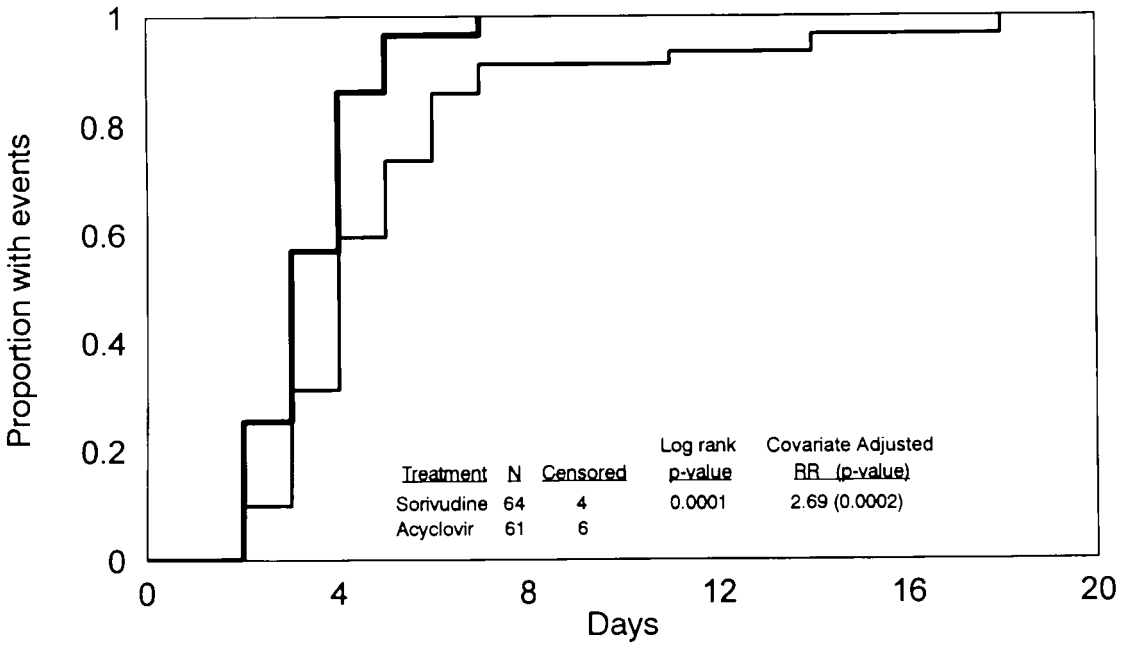

Figure 1. Sorivudine vs. acyclovir for zoster in HIV infection. Time to cessation of new vesicle formation (sorivudine [thick line], acyclovir [thin line])

Safety Data

One patient randomized to the acyclovir group never received study medication. This patient is not included in the analyses of safety data.

No patients discontinued study medication due to an adverse event or laboratory abnormality. The most frequently reported adverse events were nausea or vomiting or both (22%), headache (11%), diarrhea (7%), abdominal pain (6%), fever (6%), and musculoskeletal pain (4%, table 4). With the exception of dyspepsia or heartburn (or both), which were more common in the acyclovir group ($P = .024$), there were no significant differences in any adverse event between treatment groups. Sorivudine recipients tended to report rash more frequently (7%) than those assigned to receive acyclovir (0%, $P = .058$). However, these rashes were localized, mild to moderate in severity, and often attributed to other causes by the investigators.

Serious adverse events (i.e., resulting in or prolonging hospitalization, or death) during the acute phase were reported for 3 patients: acute paranoia or depression (or both) in an acyclovir recipient, severe diarrhea in a second acyclovir recipient, and malaise and *Cryptosporidium* enteritis in a sorivudine recipient who entered the study with 4 CD4 cells/mm^3. The sorivudine recipient who was hospitalized for malaise and *Cryptosporidium* enteritis died on study day 24 of pneumonia and cachexia. Death was attributed to underlying advanced HIV disease.

Death was the only adverse event that required data collection after study day 28. Nine deaths occurred during the long-term phase of the study, 1 during the acute phase. In all, 10 deaths (3 sorivudine recipients, 7 acyclovir recipients), all attributed to underlying HIV progression, were reported.

The incidence of modified World Health Organization grade 3 or 4 laboratory toxicities was infrequent in both treatment groups (table 4).

Discussion

This report presents the results of the first published, double-blind study of therapy for acute, localized, herpes zoster in HIV-infected adults and the first controlled study of sorivudine for the treatment of zoster.

Given that vesicles appear as a consequence of continuing viral replication, the ability of an agent to stop new vesicle formation is perhaps the best clinical measure of antiviral activity. The results of this study clearly demonstrate that the potent in vitro activity of sorivudine translates into enhanced clinical benefit. Compared with acyclovir, sorivudine significantly shortened the median times to cessation of new vesicle formation (4 vs. 5 days) and to complete crusting of lesions (8 vs. 9 days).

It is possible that as a result of previous acyclovir use, low-level or otherwise inapparent acyclovir resistance may have affected the response to acyclovir therapy in our patient population. A greater proportion of patients randomized to the acyclovir group reported prior therapy with acyclovir (41% vs. 25%). Any previous acyclovir treatment was a significant negative prognostic factor in predicting treatment response (time to cessation of new vesicles) for the whole population.

Table 3. Sorivudine versus acyclovir for zoster in HIV infection: progression of rash.

Time (days) to	Sorivudine	Acyclovir	Unadjusted analysis *P*	Covariate-adjusted analysis RR (95% CI)	Covariate-adjusted analysis *P*
Cessation of new lesion formation					
All patients					
n	64	61			
Median	3	4			
Mean ± SE	3.4 ± 0.15	5.1 ± 0.46	.0001	2.69 (1.600–4.512)	.0002
Duration of rash ⩽48 h					
n	37	36			
Median	3	4			
Mean ± SE	3.5 ± 0.21	5.1 ± 0.47	.001		
Duration of rash >48 h					
n	27	24			
Median	3	4			
Mean ± SE	3.3 ± 0.21	5.1 ± 0.90	.019		
Complete (100%) crusting					
n	64	61			
Median	8	9			
Mean ± SE	8.0 ± 0.37	9.6 ± 0.64	.041	1.72 (1.082–2.724)	.022

NOTE. RR = relative risk; CI = confidence interval.

However, all of the examined baseline VZV isolates had IC_{50}s within the range of susceptibility for acyclovir. Although sorivudine will not be active against acyclovir-resistant thymidine kinase–deficient viruses, it is active against many isolates with altered thymidine kinase [16].

Zoster recurrences are >10 times more frequent in HIV-infected persons [1–3, 10]. In this study, sorivudine therapy was associated with a significantly lower rate of first recurrent or new episodes of zoster during the 12-month follow-up period (11% vs. 26% for the acyclovir group, respectively). The rate in the acyclovir group was similar to that reported in epidemiologic studies [1, 3, 10] of HIV-infected persons, but these reports did not include details on antiviral therapy. Although the criteria for a recurrence included the requirement that active VZV disease was no longer present (DFA- or culture-negative) between the first episode of zoster and the recurrence, it is possible that some of the early recurrences were relapses, rather than real recurrences. Regardless, fewer zoster episodes may improve quality of life and decrease costs for antiviral and analgesic treatments.

Sorivudine was as effective as acyclovir for amelioration of acute neuritis and PHN. This study was powered to detect a significant difference in the time to cessation of new vesicle formation (the primary end point). A much larger study with more frequent assessments of zoster-related pain would likely be necessary to determine whether sorivudine offers any significant advantage over acyclovir in the management of zoster pain.

Sorivudine therapy was well tolerated in this immunocompromised population. Other than dyspepsia or heartburn, which were more common in the acyclovir group, there were no statistically significant differences in clinical or laboratory toxicities between the 2 treatment groups. It is important to note that a metabolite of sorivudine, bromovinyl uracil (BVU), is a potent inhibitor of an enzyme required for the metabolism of 5-fluorouracil (5FU) [21]. Deaths from 5FU toxicity with resultant severe myelosuppression have been reported from Japan in individuals receiving concomitant 5FU and sorivudine therapy [22]. Treatment with 5FU, derivatives of 5FU, or the related 5-flucytosine was prohibited within 72 h before or after completion of sorivudine treatment in this study. Data from subsequent studies on the duration of inhibition of dihydro-pyrimidine dehydrogenase by BVU have lead to the current recommendation not to administer fluorinated pyrimidines 4 weeks before, during, or 4 weeks after completion of sorivudine.

This was the first prospective study of zoster in HIV infection. Overall, the median time of new lesion formation was only 3–4 days, and most patients had completely crusted or healed their rashes by day 9. Moreover, only 4 patients experienced cutaneous dissemination, and there were no cases of hepatitis, pneumonitis, or other serious zoster-related complications. These observations suggest that patients with less advanced HIV disease (median CD4 cell count, >209/mm^3) recover fully from an episode of acute zoster, and their clinical course resembles that of immunocompetent patients with zoster. Patients with more advanced HIV disease are probably at greater risk of complications, including VZV myelitis, encephalitis, and progressive outer retinal necrosis syndrome [23, 24]. In this study, patients who had recurrences tended to have low CD4 cell counts and lower Karnofsky performance scores at entry. The number of patients with zoster-related complications was too small to be able to analyze for any prognostic factors.

Table 4. Sorivudine versus acyclovir for zoster in HIV infection: adverse events.

	Sorivudine $n = 69$	Acyclovir $n = 67$	Total $n = 136$*
Adverse event during acute phase, *n* (%)			
Any adverse event	40 (58)	35 (52)	75 (55)
Events occurring in ⩾3% of all patients			
Nausea/vomiting	12 (17)	15 (22)	27 (20)
Headache	7 (10)	9 (13)	16 (12)
Diarrhea	3 (4)	7 (10)	10 (7)
Abdominal pain	4 (6)	5 (7)	9 (7)
Fever	5 (7)	3 (4)	8 (6)
Musculoskeletal pain	2 (3)	4 (6)	6 (4)
Constipation	1 (1)	4 (6)	5 (4)
Dyspepsia/heartburn	0	6 (9)	6 (4)
Rash	5 (7)	0	5 (4)
Cough	2 (3)	2 (3)	4 (3)
Fatigue	0	4 (6)	4 (3)
Insomnia	2 (3)	2 (3)	4 (3)
Malaise	1 (1)	3 (4)	4 (3)
Serious adverse events,† *n* (%)	1 (1)	2 (3)	3 (2)
Deaths (all due to underlying disease, *n*)			
Acute phase	1 (1)	0	1 (<1)
Long-term phase	2 (3)	7 (10)	9 (7)
Laboratory toxicities,‡ *n* (%)			
Neutropenia (<1.5 cells × 10^3/mm)	0	2 (4)	2 (2)
ALT/SGPT (⩾1.25 × upper limit of normal)	1 (2)	0	1 (1)
Hyperkalemia	0	1 (2)	1 (1)
Hypoglycemia	1 (2)	0	1 (1)

NOTE. ALT = alanine aminotransferase; SGPT = serum glutamate-pyruvate transaminase.
* Safety analyses included all patients who took ⩾1 dose of study drug.
† During acute phase resulting in hospitalization or death (see text for details).
‡ Patients with grade 3/4 on-study laboratory toxicities/patients with normal baseline results.

In conclusion, the results of this first clinical trial of sorivudine in HIV-infected patients with localized zoster demonstrate clinical efficacy superior to that of acyclovir in terms of duration of new lesion formation, time to complete crusting, persistence of positive viral cultures, and incidence of recurrent disease. Sorivudine was as effective as acyclovir in decreasing the severity and duration of acute neuritis and PHN. The drug was well tolerated in this study population. We believe this study provides evidence that the potent in vitro activity of sorivudine against VZV translates into a significant advance in the clinical management of VZV infection.

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Appendix

The following members of the Multinational Sorivudine Study Group participated in this study, enrolled research subjects, or both.

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Virologic studies were performed by A. Linde and H. Dahl, Swedish Institute for Infectious Disease Control, Stockholm; S. Sacks, University Hospital, Vancouver, Canada; and D. Dwyer, Westmead Hospital, Sydney, Australia.