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Safety and efficacy of Virend® for topical treatment of genital and anal herpes simplex lesions in patients with AIDS

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Abstract

Virend® (SP-303), a new topical antiviral agent with activity against herpesvirus, was evaluated in a multicenter, double-blind, placebo-controlled Phase II study for safety and effectiveness against recurrent genital herpes lesions in patients with AIDS. The primary endpoints of this study were complete healing of lesions and time to healing. Patients had a history of recurrent genital or anogenital herpes with at least one lesion and positive HSV culture at enrollment. Participants received Virend® (15% ointment; 24 patients) or matching placebo (21 patients) three times a day for 21 days. Excluding two patients in the Virend® group who received an initial treatment but were lost to follow-up, 9 of 22 (41%) patients treated with Virend® experienced complete healing of their lesions compared with three (14%) patients in the placebo group ($P = 0.053$). Viral culture revealed that 50% of Virend®-treated patients and 19% of placebo-treated patients became culture-negative during treatment ($P = 0.06$). Based on these preliminary clinical findings, further evaluation of Virend® for topical treatment of genital herpes in patients with AIDS is planned. © 1997 Elsevier Science B.V.

Keywords: Virend®; SP-303; Antiviral; Genital herpes; AIDS

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1. Introduction

Despite significant public awareness about sexually transmitted diseases, the incidence of genital infections with herpes simplex virus (HSV) continues to increase rapidly. Although information on the prevalence of genital herpes is not precise, recent reports indicate that 31–55 million individuals in the US are infected (Corey and Wald, 1995; Johnson et al., 1989). Similar rates of prevalence are seen in Canada and Europe (Corey and Wald, 1995; Sacks, 1995; Crooks, 1995). In individuals infected with human immunodeficiency virus (HIV), the incidence of infection with genital HSV is even higher (Corey and Wald, 1995; Holmberg et al., 1988; Hook et al., 1992; Stamm et al., 1988). Seroprevalence rates for HSV-2 in HIV-positive patients from different sexual transmitted disease clinics in the United States range from 47 to 77% (Corey and Wald, 1995; Kinghorn, 1994; Safrin et al., 1991; Sacks, 1995). Furthermore, compared with the immunocompetent population, individuals with acquired immunodeficiency syndrome (AIDS), especially those with advanced disease, generally have more frequent episodes of genital HSV, with longer times required for healing of lesions (de Ruiter and Thin, 1994; Pottage and Kessler, 1995; Shacker et al., 1993; Schacker and Corey, 1997). In fact, the surveillance case definition for AIDS devised by the Centers for Disease Control (1987) includes mucocutaneous herpes lesions of greater than 1 month duration.

Virend® is a topical formulation of the investigational antiviral agent, SP-303. SP-303 (Fig. 1) is isolated from the latex (sap) of the plant *Croton lechleri* and is a naturally occurring proanthocyanidin oligomer with an average molecular weight 2100 Da. The biological activities of SP-303 have previously been described (Ubillas et al., 1994). Briefly, SP-303 is active against both HSV-1 and HSV-2, and inhibits acyclovir-resistant HSV, including thymidine kinase mutants (Safrin et al., 1993, Ubillas et al., 1994). Time-of-addition studies and studies with radiolabelled SP-303 and virus indicate that SP-303 blocks viral infection of cells (Ubillas et al., 1994). The objective of this double-blind and placebo-controlled study was to assess the safety and efficacy of topically applied SP-303 in patients with AIDS who have recurrent genital and perianal herpes lesions to support testing Virend® in larger scale clinical studies.

2. Materials and methods

2.1. Patient population

Eligible patients were at least 18 years of age, were ELISA- or Western blot- positive for HIV antibody, satisfied the CDC surveillance case definition for AIDS (Centers for Disease Control, 1987), and had active-phase, culture-positive genital and/or perineal herpes lesions. Candidates who were receiving drug therapy for HIV disease, opportunistic infections, and other AIDS-related illnesses were eligible to participate if their drug dosages were stable and well-tolerated at study entry. Concomitant therapies were evaluated by the investigators throughout the study and changes in dosage were disallowed if they would have a negative impact on the overall health of a patient or if they had the potential to confound study results. Women of childbearing age had to have a negative urine pregnancy test and be will-

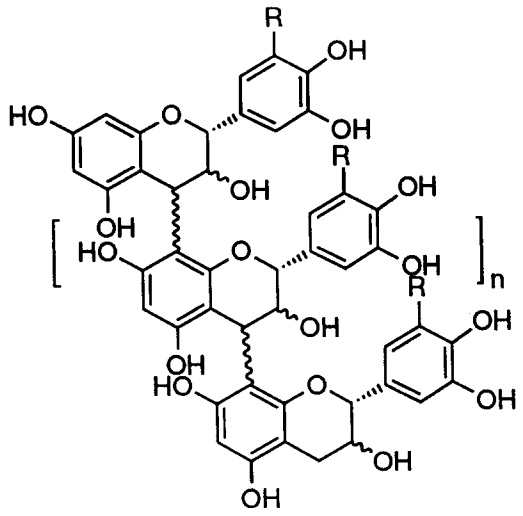

Fig. 1. Chemical structure of SP-303. The value of n ranges from four to 11 with seven being the average number of subunits.

ing to use a medically accepted method of contraception during the study. Other ineligible individuals included those being treated with known anti-HSV or investigational drugs and lactating women. Also individuals with an absolute neutrophil count < 750 cells/μl, platelet count $< 50\,000$ cells/μl, hematocrit < 25 g/dl, serum transaminase values greater than two times the upper limit of normal, total bilirubin ≥ 2.0 mg/dl, or serum creatinine ≥ 2.0 mg/dl were not eligible.

2.2. Study design

Patients at eight medical centers in Mexico were enrolled for this clinical investigation which was conducted in two phases: (i) a double-blind and placebo-controlled phase in which participants were randomly assigned to treatment with Virend® or placebo for 21 days; and (ii) an optional second phase in which patients originally treated with Virend® or placebo were treated only with Virend® under open-label conditions for an additional 21 days. Pre-enrollment screening (day -7) included a medical history, physical examination (including vital signs), and clinical laboratory evaluation (hematology, blood chemistry, urinalysis, and a pregnancy test). Evaluation of HSV lesions during pre-enrollment screening, at baseline (study entry, day 1), and at each clinic visit, included documentation of the number and location of lesions, total lesion area, collection of a specimen for HSV culture, and an assessment of the severity of lesion pain. In addition, specimens were obtained for HSV serotyping at day 1. At the completion of the 21 day double-blind and placebo-controlled phase of treatment, some patients were selected to participate in an open-label phase with Virend®. Selection of these patients was based on the opinion of the investigator as to whether treatment with Virend® might be beneficial, and neither patient nor physician were aware of the original treatment group to which these patients had been assigned. At the end of the 21- or 42- day treatment period, all patients were scheduled to participate in a 2-week follow-up period. All patients signed an informed consent form prior to enrollment and the study was approved by the institutional review board at each center. In addition, the study was conducted according to United States Food and Drug Administration guidelines.

Patients were dispensed one or two appropriately labeled 7 g tubes of Virend or placebo which were indistinguishable to investigators. They were requested to apply the ointment (Virend® [15% SP-303, w/w] in USP hydrophilic ointment or matched placebo in an ointment base) to their herpes lesions three times daily for 21 days. Patients were instructed to cleanse lesions with mild soap and water, gently blot them dry, and then cover the entire lesion area with a thin layer of ointment. They were also requested to evenly space ointment applications during waking hours (morning, afternoon, and evening) and to time bathing to occur just before one of the applications. To receive a new supply of medication, patients were required to return each used or unused tube.

2.3. Virology

Specimens for HSV culture were obtained from lesions at each clinic visit according to standard methods for obtaining virus samples (Mattison et al., 1988; Wentworth et al., 1973). Identification of herpesviruses from cultured specimens using HSV type-specific monoclonal antibody has also been described (Lafferty et al., 1987). Where there were multiple lesions, culture specimens were obtained from the largest lesion that was present on day 1. Patients who had two successive specimens from which no virus was isolated were considered culture-negative.

2.4. Safety

Patients were instructed to report all adverse clinical events that occurred during the treatment or post-treatment period. In addition, study personnel carefully monitored each participant for the occurrence of serious or unanticipated clinical events. Vital signs, including blood pressure, temperature, pulse, and respiration rate were assessed, and hematology and serum chemistry values were evaluated for clinically significant abnormalities using National Cancer Institute toxicity grades (Miller et al., 1981).

2.5. Efficacy

The variables evaluated for primary efficacy were complete healing of HSV lesions (total lesion area = 0 cm^2) and time (days) to healing. Secondary variables for efficacy included reduction in severity of pain associated with HSV lesions, percentage of individuals becoming HSV culture negative, and reduction in total lesion area of evaluable lesions compared to baseline. A lesion was considered evaluable if it was measurable (i.e. area > 0 cm^2) at randomization (day 1) and had not coalesced with a lesion that was not present at the time of randomization. Thus, a lesion present at day 1 that coalesced with a new lesion (i.e. not present at day 1) was not further evaluated, but the area of the original lesion prior to coalescence was carried forward for each assessment to the end of the study. However, a lesion present at day 1 that coalesced with another lesion, which also was present at day 1, was measured like individual lesions and the newly coalesced lesion was monitored to the end of the study. Total lesion area was determined by photographing lesions using a Polaroid camera (Model CU-5) with a fixed length tripod to maintain a constant distance between the lesion and the camera lens. This system, which was used at all study centers, ensured that the method for lesion measurement was comparable between successive visits and between different patients. From the photographs, total lesion area was determined by measuring the lesion across its longest axis and then perpendicular to that axis at its midpoint. The two values were multiplied and expressed as cm^2. Where there was more than one lesion, areas from the individual lesions were added to derive total lesion area. In addition, patients subjectively assessed the severity of lesion pain using a 10 cm visual analogue scale, in which 10 indicated severe pain, 5 indicated moderate pain, and 0 indicated no pain.

2.6. Statistical analyses

Response rates were analyzed using Fisher's Exact test. Time to lesion healing was determined using the Kaplan-Meier product-limit estimate of time to resolution and comparisons between the two groups were made using the log rank test (Kaplan and Meier, 1958; Turnbull, 1976). Percent change from baseline in total lesion area and pain scores were compared at each time point using the Wilcoxon Rank Sum test. Correlations among $CD4^+$ cell count, lesion size, and healing used the unpaired t-test. All statistical tests employed two-tailed analyses. Statistical methods are described by SAS Institute (1990).

3. Results

3.1. Study population

A total of 45 patients were randomly assigned to receive treatment with Virend® ($n = 24$) or placebo ($n = 21$). Of these, 12 (27%) withdrew from the study prematurely: 5 of 24 (21%) in the Virend® group and 7 of 21 (33%) in the placebo group. Three patients discontinued because of adverse events associated with advancing HIV disease (two Virend® and one placebo) and one Virend®-treated patient discontinued because of burning at the application site. Except for two patients assigned to the Virend® group, all patients who discontinued prematurely had at least one follow-up evaluation prior to discontinuation. The two patients in the Virend® group that did not have any follow-up assessment of their lesions after day 1 included one patient who died of a probable spontaneous pneumothorax on day 2 of the study and another who did not return to the clinic for any follow-up assessment. Details regarding study discontinuations are presented in Table 1.

The demographics, HIV, and HSV history of the treatment groups at baseline (day 1) are presented in Table 2A. The mean $CD4^+/mm^3$ was 71 and 34 for patients treated with Virend® and placebo, respectively, and was statistically indistinguishable ($P = 0.13$). All patients had a history of prior HSV episodes, with patients in the Virend® group experiencing a mean of four episodes of genital/perianal herpes in the year prior to enrollment compared with a mean of 3.1 episodes for those in the placebo group. Prior to entering the study, 13 (29%) patients had received

Table 1
Summary patients who discontinued from the study prematurely

Reason for premature discontinuation	No. patients	
	Prematurely Discontinuing	
	Virend® ($n = 24$)	Placebo ($n = 21$)
Adverse event:		
Esophagitis	1	0
Herpes zoster	0	1
Wasting syndrome	1	0
Burning at application site	1	0
Treatment failure	0	1
Patient refusal	0	2
Concomitant drug therapy	0	1
Death	1[a]	1[b]
Other	1[c]	1[d]
Total premature discontinuations	5 (21%)	7 (33%)

[a] Patient died of probable pneumothorax on day 2.
[b] Patient died of AIDS wasting syndrome and anemia 1 day after end of double-blind phase.
[c] Patient lost to follow-up.
[d] Patient stopped treatment because of alteration in color of placebo test substance.

oral and/or topical ACV therapy for recurring genital herpes lesions. The wash-out period for ACV was at least 2 weeks, and patients were not permitted to take ACV (or any other anti-HSV treatment) during the study. The characteristics of HSV lesions evaluable at baseline are summarized in Table 2B. At baseline, patients randomized to receive Virend® had 61 evaluable lesions, whereas patients in the placebo group had 48 lesions. The difference in the total number of lesions between the two groups is due to a few patients with many lesions having been randomized to receive Virend® (e.g. one patient had 11 lesions). Most patients (Virend®, 20/24 [83%]; placebo, 18/21 [86%]) had three or fewer lesions; only five patients had five or more lesions (Virend®, three patients; placebo, two patients). The majority of the lesions were in the anal area and the anatomical distribution of the other lesions are given in Table 2B. The mean total lesion area for patients who received Virend® was 8.01 cm^2 and for those who received placebo, it was 4.36 cm^2. This difference in total lesion area between the groups occurred because two patients in the Virend® group had lesion areas > 40 cm^2. Differences in lesion number and area between the two groups can be attributed to the fact that randomization of patients was not stratified for either lesion number or lesion size at the outset of the study. Although baseline data for lesion size and area appear to indicate that Virend® patients had more severe herpes disease, these differences were not statistically significant when these parameters were compared between the two patient populations: $P = 0.69$ for lesion number and $P = 0.22$ for total area of lesions.

As expected in this patient population, all but one patient (98%) received concomitant medication during the study. Anti-infective agents, including antibiotics, antituberculous agents, antiretrovirals (AZT, ddI, and ddC), and sulfonamides were taken by 31 (69%) of the 45 patients; some patients were taking more than one of these agents. Drugs for the treatment of disorders relating to the gastrointestinal tract (e.g. diarrhea, nausea and vomiting, and constipation) were taken by 24 (53%) patients. Vitamin B complex was another frequently used concomitant medication (ten patients, 22%).

3.2. Safety results

None of the 21 patients who received placebo had a cutaneous reaction at the application site on day 1, although one of the 24 Virend®-treated patients experienced moderate erythema at the application site. As discussed previously, three patients were discontinued from the study because of complications due to HIV infection (Table 1). In addition, one patient treated with Virend® withdrew because of burning at the site of application. A second Virend® patient reported burning at the application site but continued in the study. The remainder of adverse events were thought by the investigators to be unrelated to the study drug. Overall, 13 (54%) patients treated with Virend® and 10 (48%) who received placebo experienced adverse events in this study. Diarrhea was the most frequently reported event, occurring

Table 2
Summary of demographic and baseline characteristics of patients

Characteristic	Treatment group	
	Virend® ($n = 24$)	Placebo ($n = 21$)
A. Demographics, HIV, and HSV history		
Age (years)		
Mean (range)	32 (21–50)	35 (20–54)
Gender (no. of patients)		
Male	23	19
Female	1	2
Weight (kg)		
Mean (range)	61 (44–80)	57 (40–97)
$CD4^+/mm^3$		
Mean (range)[a]	71 (0–465)	34 (8-84)
Median	34	26
No. patients with AIDS-defining opportunistic infections at enrollment (excluding recurrent herpes)	13	15
No. genital/anogenital HSV episodes during last 12 months		
Mean (range)	4 (1–20)	3.1 (1–8)
Median	2	2
No. patients receiving ACV prior to enrollment		
Oral ACV	4	3
Topical ACV	3	2
Oral and topical ACV	0	1
B. Evaluable lesions		
Total number of lesions[b]	61	48
Median (range)	2 (1–11)	1 (1–9)
Location of lesions		
Anal	40	25
Genital	15	10
Perianal	3	13
Supra-anal	3	0
Total lesion area (cm^2)[c]		
Mean (per group)	8.01	4.36
Median (per group)	2.71	2.30
Minimum (per patient)	0.13	0.09
Maximum (per patient)	45.00	15.75

[a,b,c] $CD4^+$ cell count, total number of lesions, and total lesion area were not statistically different between the Virend® and placebo groups at baseline. Refer to text for details.

in seven (16%) patients (Virend®, four patients; placebo, three patients). Another frequently occurring event included infection, which was reported in four (9%) patients (Virend®: 1 patient and placebo: 3 patients). Of all the adverse events, only those associated with pain at the site of application were considered by investigators as likely to be related to study drug. However, this conclusion is somewhat mitigated since one patient receiving placebo treatment also experienced pain at the site of application. All other adverse events, including laboratory abnormalities and abnormal findings on physical examination, were considered to be due to a concurrent illness, a concomitant medication, or some other known cause related to these patients' underlying HIV disease. There was an equal distribution between the groups of hematologic and serum chemistry

toxicities, suggesting that Virend® does not exhibit systemic toxicity. The death of one patient treated with Virend® on day 2 of the study was attributed to progression of HIV disease, and the death of one placebo patient on the day after the double-blind phase was completed was due to AIDS wasting syndrome and anemia. In summary, with the exception of two patients treated with Virend® who experienced pain or burning at the site of application, no adverse effects were attributable to treatment with Virend®.

3.3. Efficacy results for double-blind, placebo-controlled study

3.3.1. Effect of treatment on resolution of lesions

Excluding the two patients who were lost to follow-up from the 24 patients enrolled in the Virend® group (see above), nine patients (9/22, 41%) experienced complete resolution of all their lesions during the 21 day study. Compared with these patients, three patients (3/21, 14%) who received placebo had complete healing of all their lesions ($P = 0.053$) (Table 3A). In an intent-to-treat analysis in which the two patients who were lost to follow-up are included in the calculations, 9/24 (37.5%) of the patients treated with Virend® had complete healing of their lesions. Under these circumstances, the level of significance compared with placebo patients was $P = 0.077$. The percentages of patients exhibiting complete healing at 7, 14, and 21 days is shown in Table 3B. Using the Kaplan-Meier product-limit method of analysis (Kaplan and Meier, 1958; Turnbull, 1976), a greater percentage of patients treated with Virend® had complete healing compared to placebo-treated patients during all three time points, however, these results were not statistically significant ($P = 0.079$ for day 21 comparison).

Table 3
Effect of Virend® on healing of herpes lesions

	Treatment Group	
	Virend® ($n = 22$[a])	Placebo ($n = 21$)
A. Number (%) of patients with complete healing at end of the 21 day study		
Complete healing of lesions (total lesion area = 0 cm^2)	9 (41%)[b]	3 (14%)
B. Percentage of patients with complete healing by day 7, 14 or 21 of study[c]		
Study Day:		
7	18.2	9.8
14	33.9	9.8
21	44.9	16.7

[a] Two patients which had no follow-up assessment after enrollment are excluded from this analysis.
[b] $P = 0.053$ compared to placebo-treated patients. For the intent-to-treat analysis which includes the two Virend®-treated patients that had no follow-up evaluation, $P = 0.077$.
[c] Kaplan-Meier product-limit estimate.

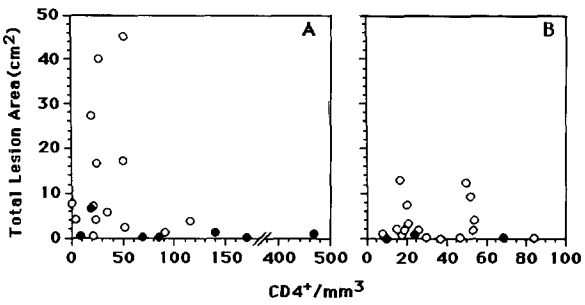

Fig. 2. Relationship between complete healing in Virend®- (A) and placebo-treated (B) patients and $CD4^+/mm^3$ and total lesion area at baseline. Patients with complete healing of lesions are denoted by solid circles. ($CD4^+$ counts were not available for three patients in the Virend® group and two patients in the placebo group.)

The mean $CD4^+$ cell count for Virend®-treated patients who had complete healing of their lesions was $136/mm^3$. This compared to a value of $38/mm^3$ for Virend® patients whose lesions did not heal ($P = 0.03$). When the size of lesions is factored into the correlation, the mean total lesion area at baseline for patients who experienced complete resolution of their lesions was 1.14 cm^2, whereas those patients whose lesions failed to heal started the study with a mean total lesion area of 12.21 cm^2 ($P = 0.03$). The relationship between $CD4^+$ levels and size of lesions at baseline in patients who were treated with Virend® and who had complete healing of their lesions is shown in Fig. 2A. For comparative purposes, the same relationships are shown for patients treated with the placebo (Fig. 3B). All of the three placebo

patients who experienced complete healing of their lesions had small lesions (< 0.90 cm^2) and two of these patients had relatively low CD4$^+$ counts (10 and 24 CD4$^+$/mm^3).

3.3.2. Other assessments on the effect of treatment on lesions

With regard to lesions that did not resolve, six (25%) patients treated with Virend® and five (24%) patients treated with placebo had lesions that were improved (total lesion area decreased by $\geq 25\%$, but was > 0 cm^2, compared to baseline). Three (13%) Virend®-treated patients and five (24%) placebo-treated patients had lesions that were worse compared with baseline (total lesion area had increased $\geq 25\%$). Patients with unchanged lesions (total lesion area increased or decreased by $< 25\%$) included six (25%) treated with Virend® and eight (38%) treated with placebo. The median percentage decrease in total lesion area from baseline measurements is shown in Fig. 3. The value of the last measurement was carried forward to replace missing evaluations during treatment, and for this intent-to-treat analysis, the baseline value was carried forward if there were no evaluations after randomization. The difference between the Virend® and placebo groups is not statistically significant despite the fact that the Virend® group exhibited a greater percentage of patients whose lesions completely resolved (Table 3A). Lack of significance in this analysis (Fig. 3) is attributable to several Virend® patients who had large lesions with only slight improvement. Of the 16 (36%) patients who developed new lesions prior to day 21, nine (38%) were in the Virend® group and seven (33%) were in the placebo group. This lack of activity of Virend® in preventing new lesions was anticipated, since Virend® was applied only to lesions existing at baseline and not to surrounding areas.

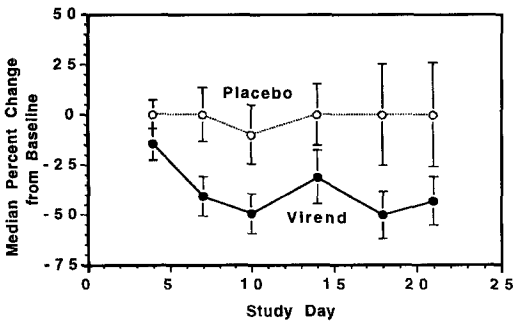

Fig. 3. Comparison of median percent change from baseline based on total area of lesions in Virend®- and placebo-treated patients (intent-to-treat analysis). Errors bars represent standard error of the mean.

3.3.3. Effect of treatment on lesion pain

Compared with patients given placebo, there was a trend towards significance in decreased lesion pain severity on day 4 in the patients treated with Virend® ($P = 0.09$). However, overall there were no significant differences between the treatment groups for the sum of pain intensity values or for the proportion of patients who experienced either complete, 50%, or no pain relief.

3.3.4. Effect of treatment on virus shedding

Serotyping of specimens from patients prior to enrollment indicated that all patients were infected with HSV-2. Fifty percent of Virend®-treated patients became culture-negative during treatment compared with 19% of those in the placebo group ($P = 0.06$).

3.4. Efficacy results during 21 day open-label extension period

Following the treatment period, 15 patients (Virend®, 7; placebo, 8) were treated with Virend® during the open-label extension period. Two (29%) patients originally treated with Virend® and 5 (62%) originally treated with placebo experienced complete healing of lesions by day 42. The investigators' ratings of lesions during the extended treatment period are presented in Table 4.

4. Discussion

The active component of Virend® is SP-303, a naturally occurring oligomer which is isolated from the latex of a medicinal plant (*Croton lechleri*) common to Central and South America. For centuries, indigenous people in this area have used the latex from this plant to treat a variety of illnesses including infections of the skin such as

Table 4
Effect of Virend® on herpes lesions during open-label 21 day extension period compared with baseline

Lesion appearance	No. (%) patients according to response to Virend® treatment	
	Treatment Group	
	Original Virend® Patients (n = 7)	Original Placebo Patients (n = 8)
Resolved[a]	2 (29%)	5 (62%)
Improved[b]	1 (14%)	1 (13%)
Worse[c]	1 (14%)	1 (13%)
Unchanged[d]	3 (43%)	1 (13%)

[a] Complete healing of lesion (total lesion area = 0 cm^2).
[b] Total lesion area had decreased by ≥25%, but was >0 cm^2.
[c] Total lesion area had increased by ≥25%.
[d] Total lesion area had increased or decreased by <25%.

those caused by herpes simplex virus (Ubillas et al., 1994). Based on the results of preclinical studies showing SP-303 inhibits replication of HSV in cell culture and exhibits efficacy in rodent models of HSV-2 vaginitis, clinical evaluation of SP-303 in patients with genital herpes was initiated. A patient population comprising individuals with AIDS who had recurrent genital herpes was selected because of the desire to test SP-303 in a individuals who generally have more severe herpes disease than the normal population. Moreover, it was felt that the thymidine kinase-independent antiviral mechanism of SP-303 might prove advantageous in a patients with AIDS who were acyclovir (ACV)-resistant. Finally, marketing considerations suggested that an effective topical agent would provide an alternative therapy to a patient population heavily dependent on a variety of oral medications. While results from the present study are preliminary and do not provide evidence to prove the utility of Virend® in effectively treating genital herpes in this population, these results serve as the impetus for further clinical evaluation of Virend®. To this end, a multicenter placebo-controlled, double-blind clinical study with Virend® is scheduled to begin in early 1997 in the US.

The topical formulation of Virend® used in the present study resulted in complete healing of genital lesions in 41% (9/22) of treated patients. An agent producing this frequency of resolution of lesions would not likely represent a feasible alternative to presently available oral antiviral therapies. However, a new topical formulation of SP-303 has been developed which may increase the percentage of patients experiencing complete healing. The topical formulation used in the present study was an ointment which was viscous and therefore difficult to apply, and it did not readily dissolve at the site of application. A new formulation of SP-303 comprising a water-soluble gel overcomes these problems and will be used in future clinical trials. This new formulation has shown efficacy by inhibiting the development of lesions and viral shedding in the HSV-2 model of guinea pig vaginitis (unpublished data).

At present, oral acyclovir (ACV) is the standard therapy for genital HSV infections, both in immunocompetent and immunocompromised patients, including individuals with HIV infection and AIDS. Although little formal investigational data are available on use of oral ACV specifically for patients with AIDS who have genital herpes, ACV is recognized as the drug of choice by clinicians caring for this population of patients. A 5% topical ACV ointment is available for treating genital herpes, but it is not considered to be highly effective in HIV-infected individuals (Masur, 1995). Genital HSV infection in individuals with advanced HIV disease can be refractory to ACV. Some HIV-infected patients respond to higher than normal dosages of oral and/or intravenous ACV (Wagstaff et al., 1994; Engel et al., 1990) while those whose lesions are caused by ACV-resistant HSV require alternative chemotherapy, such as foscarnet. Although resistance to ACV is currently infrequent, the incidence of ACV resistance in patients with AIDS is increasing (Corey et al., 1992; Englund et al., 1990; Pottage and Kessler, 1995). Attesting to the variety of efforts underway to develop new anti-HSV drugs, famciclovir, an orally administered nucleoside, was approved in late 1995, and other herpes drugs, such as cidofovir, a topical nucleotide analogue active in treating ACV-resistant genital herpes lesions (Naesens et al., 1997), are in development. Unlike these drugs, which act intracellularly to disrupt the replication of HSV DNA, SP-303 inhibits HSV replication by interacting

with cell-free virus to prevent infection of susceptible cells (Ubillas et al., 1994). This might be considered to be a disadvantage since it is expected that an extracellular mechanism affords a smaller 'window of opportunity' for an antiviral agent compared to an intracellularly mediated process. However, if Virend® treatment is initiated sufficiently early in an infection, Virend® may be as effective as ACV in inhibiting viral replication. This is based on the results of a study in which the new gel formulation of SP-303 was tested in HSV-2-infected guinea pigs: Vaginal application of SP-303, begun 6 h after intravaginal infection, demonstrated that SP-303 and topical ACV were equivalent in inhibiting virus shed into vaginal secretions (unpublished data). The final verdict on the effectiveness of the extracellular mechanism of SP-303 will derive from the next clinical study.

Correlations between the size of genital herpes lesions and response to Virend® treatment indicate that Virend® is more active in patients with smaller overall lesion areas: 1.14 cm^2 for complete healers vs. 12.21 cm^2 for non healers (total lesion areas at baseline). Of three Virend®-treated patients with the largest total lesion areas at enrollment (27.4, 40, and 45 cm^2), only one patient showed improvement (decrease in size $\geq 25\%$) while the lesion areas in the other two were unchanged or worse. Based on the limited information available on the natural history of genital herpes in patients with AIDS, it seems reasonable that patients with smaller lesion areas would more readily respond to a topical antiviral agent than patients with larger lesions. When $CD4^+$ count is considered as a factor for complete healing, it was found that Virend® is generally more effective in patients with relatively higher $CD4^+$ levels: 136/mm^3 and 38/mm^3 for complete healers and non healers, respectively. This should not to be interpreted as suggesting that Virend® was wholly ineffective in patients with relatively low $CD4^+$ cell counts. In fact, if 30 $CD4^+/mm^3$, the approximate median $CD4^+$ count at baseline for both Virend® and placebo patients, is selected to distinguish patients with relatively low and high $CD4^+$ counts, two Virend®-treated patients with completely healed lesions had $CD4^+$ counts less than 30. This type of analysis implies that total lesion area and $CD4^+$ cell count are the two most important factors influencing the ability of Virend® to resolve lesions. In reality, it is likely that other factors, such as age and overall health of a patient and severity of opportunistic infections, also play significant roles in healing of herpes lesions.

That Virend® appears to be less effective in individuals with lower $CD4^+$ levels and larger lesions is not surprising since ACV is often less effective in this population of HIV-infected patients. Clearly, one explanation for the lack of activity of ACV in this group is viral resistance to the drug (Pottage and Kessler, 1995; Schacker and Corey, 1997). However, in other cases, the lack of response is not attributable to ACV resistance. In these instances, it has been suggested that ACV treatment may result in culture-negative lesions, but the lesions do not readily heal because the patient is too ill to harness the anabolic resources needed for the healing process. In light of this possibility, it is noteworthy that the Virend®-treated patient with the largest lesion area (45 cm^2) did not completely heal during the 21 day treatment regimen, but became culture-negative for HSV on day 7 and remained culture-negative to the end of the study. Although wound healing in patients with AIDS is a controversial issue (Fisher and Gomey, 1991; Pankhurst et al., 1994; Robinson et al., 1992), reports exist indicating that this population can experience delayed healing compared to immunocompetent patients (Abrahamson, 1995; Consten et al., 1995). At least one report provides data which show that low $CD4^+$ levels correlate with delayed healing of some types of anorectal lesions following surgical repair (Consten et al., 1995). Thus, it seems possible that patients with late stage or advanced HIV disease who are treated with anti-HSV therapy will have some lesions that are free of HSV, yet fail to readily heal.

In HIV-infected individuals with recurrent genital HSV, low $CD4^+$ levels (e.g. ≤ 50 cells/mm^3) are associated with an increased incidence of resistance to ACV (Schacker and Corey, 1997) and an increase in the frequency of genital shedding of HSV-2 (Augenbraun et al., 1995; Bagdades et al., 1992). Since susceptibility testing was not per-

formed in the present study, no conclusion can be reached regarding the ability of Virend® to effect lesions caused by ACV-resistant HSV. Possible correlation between viral shedding and $CD4^+$ count is irrelevant in this study because all enrollees were required to be culture-positive for HSV at the outset. Several investigators indicate that genital HSV disease in HIV-positive patients can be more severe than in the normal population (Chaisson and Volberding, 1995; de Ruiter and Thin, 1994; Pottage and Kessler, 1995; Sacks, 1995; Schacker and Corey, 1997; Skoldenberg, 1995; Wagstaff et al., 1994). Increased severity may be manifest by extensive mucocutaneous lesions and by lesions that have longer than normal duration. With the exception of large, persistent lesions due to ACV-resistant HSV, possible correlation between $CD4^+$ cell count and severity of genital HSV as measured by size or duration of lesions, for example, is only implied. Therefore, in the present study, an analysis was done to ascertain if a correlation between area of lesions at baseline and $CD4^+$ count existed. Based on regression analysis using Virend® and placebo patients, no correlation is evident. However, this conclusion is limited by the small sample size of the study population and by the fact that, except for one patient, all patients had $CD4^+$ cell counts less than $200/mm^3$. Thus, until a larger study is conducted using individuals with a broader range of $CD4^+$ counts, it should not be generally concluded that a correlation between $CD4^+$ count and size of HSV lesions does not exist.

Finally, it must be considered that treatment of HIV-infected individuals with new and effective anti-HIV drugs may indirectly impact on the severity of their herpes disease. New drugs that inhibit the HIV protease, used as a monotherapy or in combination with drugs like zidovudine and didanosine, produce reduction in the plasma viral RNA load and increase the number of circulating $CD4^+$ cells (Hirsch et al., 1997). Although $CD4^+$ levels are not considered to be as accurate an indicator as the plasma viral load in predicting the outcome of HIV disease, the concentration of $CD4^+$ cells may correlate with the severity of HSV disease and the frequency of recurrences. Certainly, the $CD4^+$ cell concentration correlates closely with the risk of *Pneumocystis carnii* pneumonia (Decker and Masur, 1997). Whether or not the $CD4^+$ level proves to be an important factor contributing to the severity of HSV disease, it seems likely that the response to anti-HSV therapy in HIV-infected patients will be enhanced as more individuals respond to the newer and effective HIV treatments.

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