

THALIDOMIDE FOR THE TREATMENT OF ORAL APHTHOUS ULCERS
IN PATIENTS WITH HUMAN IMMUNODEFICIENCY VIRUS INFECTION

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ABSTRACT

Background In patients with advanced human immunodeficiency virus (HIV) infection, aphthous ulceration of the mouth and oropharynx can become extensive and debilitating. Preliminary reports suggest that thalidomide may promote the healing of oral aphthous ulcers.

Methods We performed a double-blind, randomized, placebo-controlled study of thalidomide as therapy for oral aphthous ulcers in HIV-infected patients. The patients received a four-week course of either 200 mg of thalidomide or placebo orally once per day. They were evaluated weekly for the condition of the ulcers, their quality of life, and evidence of toxicity. Assays were performed for plasma tumor necrosis factor α (TNF- α), soluble TNF- α receptors, and HIV RNA.

Results Sixteen of 29 patients in the thalidomide group (55 percent) had complete healing of their aphthous ulcers after four weeks, as compared with only 2 of 28 patients in the placebo group (7 percent; odds ratio, 15; 95 percent confidence interval after adjustment for group sequential testing, 1.8 to 499; unadjusted $P < 0.001$). Pain diminished and the ability to eat improved with thalidomide treatment. The adverse effects noted with thalidomide included somnolence and rash (7 patients each), and 6 of the 29 patients discontinued treatment because of toxicity. Thalidomide treatment increased HIV RNA levels (median increase, 0.42 log₁₀ copies per milliliter; increase with placebo, 0.05; $P = 0.04$). With thalidomide treatment there were unexpected increases in the plasma concentrations of TNF- α and soluble TNF- α receptors.

Conclusions Thalidomide is an effective treatment for aphthous ulceration of the mouth and oropharynx in patients with HIV infection. (N Engl J Med 1997;336:1487-93.)

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A PHTHOUS ulceration of the mouth, though painful and annoying, is usually a self-limited problem in immunocompetent persons.¹ In patients with human immunodeficiency virus (HIV) infection, however, aphthous ulcers frequently become progressive, destructive, and debilitating.¹⁻⁴ Extremely painful, enlarging necrotic lesions can develop, resembling the large aphthous ulcers often seen in patients with Behçet's syndrome. The hypopharynx and esophagus may

be involved. Aphthous ulcers can interfere with eating and lead to malnutrition and wasting. Even when the ulcers regress, they tend to recur.

Available treatments for aphthous ulcers in HIV-infected patients are unsatisfactory. Some success has been reported with topical, intralesional, and systemic corticosteroids, but the responses are not uniform and the relapse rate is high.² No controlled studies of this treatment have been performed, and long-term treatment with systemic corticosteroids may cause further immunosuppression in already immunocompromised patients.

Several groups have suggested that thalidomide, α -N-phthalimidoglutarimide, is effective for the severe forms of aphthous ulceration in HIV-infected and other patients.³⁻¹⁵ As part of AIDS Clinical Trials Group (ACTG) protocol 251 of the National Institute of Allergy and Infectious Diseases (NIAID), we performed a multicenter, double-blind, randomized, placebo-controlled study of the usefulness of thalidomide in treating oral aphthous ulcers in HIV-infected persons. In addition, since thalidomide has been reported to inhibit the production of tumor necrosis factor α (TNF- α),¹⁶⁻²⁰ a substance known to induce the expression of HIV by infected cells,²¹ we also evaluated the activity of the drug against TNF- α and HIV.

METHODS

Study Population

We enrolled patients in the study if they met the following criteria: an age of at least 13 years; documented HIV infection; oral aphthous ulceration of at least two weeks' duration, as confirmed by a biopsy that revealed no infectious, neoplastic, or other spe-

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*Additional investigators who participated in this trial are listed in the Appendix.

cific diagnosis; a surface diameter of at least 5 mm for the largest ulcer; a negative culture of the ulcer for herpes simplex virus; a hemoglobin concentration greater than 8 g per deciliter; an absolute neutrophil count greater than 500 per cubic millimeter; a platelet count greater than 50,000 per cubic millimeter; a serum bilirubin concentration no higher than 2.5 times the upper limit of normal; serum concentrations of aspartate aminotransferase and alkaline phosphatase less than 5 times the upper limit of normal; and a serum creatinine concentration of less than 2.5 mg per deciliter (221 μmol per liter).

Patients were excluded from the study if they had bilateral peripheral neuropathy more severe than grade 1 or a history of such neuropathy, a known allergy to thalidomide, or prior treatment of aphthous ulcers with thalidomide; if they were pregnant or lactating; if they were receiving short-term therapy for opportunistic infections; if they were receiving radiation to the head or neck; if they had been treated with systemic or oral topical corticosteroids within one week before the first set of blood tests; if they were treated with other putative immunomodulators within the two weeks before entry into the study and during the study; if they were undergoing systemic cancer chemotherapy; if they were treated with antiinfective mouthwashes; and if they were receiving zalcitabine, pentoxifylline, methotrexate, trimetrexate, or antineoplastic alkylating agents. If a patient had received any of the latter group of medications within eight weeks before entering the study, the patient's aphthous ulcers had to have persisted for at least four weeks after the medication was discontinued. Anti-HIV therapy was held constant beginning four weeks before study entry. Antimicrobial prophylaxis against opportunistic infections was permitted.

Patients were recruited at 19 sites in the United States. The study was approved by the institutional review board of each medical center. The patients gave written informed consent to participate. Precautions were taken to prevent and detect pregnancy, as described in the Discussion section.

Treatment Regimens

The patients were randomly assigned to receive a four-week course of either two 100-mg capsules of thalidomide or two placebo capsules orally once a day at bedtime (the study medications were kindly provided by Andrus Pharmaceuticals, Beltsville, Md.). Patients whose aphthous ulcers had not completely healed by the end of the four weeks were offered the option of taking two 100-mg capsules of open-label thalidomide daily for the next four weeks. If the healing was still not complete after that period, 200 mg of thalidomide could be given twice a day for an additional four weeks as tolerated.

As specified in the study protocol, in the event of sedation or other adverse effects, depending on their nature and grade (as defined according to the NIAID criteria), the dose was reduced, the study medication was permanently discontinued, or the medication was withheld until the adverse effect had resolved, at which point the treatment was resumed at a reduced dose.

Criteria for Response

One end point of the study was the complete absence of oral aphthous ulcers after four weeks of study treatment (a complete response). If a patient discontinued the study treatment before the end of four weeks because of toxicity, the response was not considered complete unless there was complete healing at the time of the discontinuation and the complete healing lasted until the four-week visit. A partial response at week 4 was defined as a decrease of 50 percent or more in the combined surface area of the three largest ulcers, as compared with the area of the three largest ulcers at base line, with no formation of new ulcers. (The surface area was defined as the product of the ulcer's largest surface diameter and its largest perpendicular surface diameter.) A lack of response was defined as a decrease of less than 50 percent or the occurrence of a new ulcer.

An additional, independent end point was the change in the

HIV load, as measured by the plasma HIV RNA level, from base line to week 4.

Evaluation of Patients and Follow-up

After the screening and base-line evaluations, the patients were seen weekly by site investigators unaware of the patients' treatment status and the results of measurements of TNF- α and the HIV load, in order to assess the healing of oral ulcers and toxic effects of the study medication. At base line and at each weekly visit, a quality-of-life questionnaire was administered to assess pain and eating ability; neuropathy was assessed; and there were laboratory evaluations of blood cells, serum chemistries, serum thalidomide levels, and hepatic and renal function. Plasma samples for the measurement of TNF- α , soluble TNF- α receptor type II, and HIV RNA were obtained at base line and every two weeks. CD4 and CD8 lymphocyte counts were performed at base line and week 4. A pregnancy test for the β subunit of human chorionic gonadotropin in serum was performed weekly on women with childbearing potential and was repeated four weeks after the discontinuation of the study medication.

Quality-of-Life Measurements

The quality-of-life questionnaire contained 15 items that measured general health, pain, and eating ability during the study. Two of the items, from the Medical Outcomes Study: HIV,²² assessed general perceptions of health and pain; they were supplemented by an item assessing the patient's pain while eating. Two scales with six items each assessed discomfort while eating and the actual consumption of food (the latter scale was modified from the Sickness Impact Profile²³). The responses to these questions were scored on scales ranging from 1 to 5 or 1 to 6, with higher numbers indicating poorer health or more severe symptoms.

TNF Measurements and Virologic Assays

The laboratory assays for TNF- α , soluble TNF- α receptor type II, and HIV-1 RNA were performed at the end of the study. Plasma levels of TNF- α were measured with TNF- α enzyme amplified-sensitivity immunoassay kits (Medgenix, Incstar, Stillwater, Minn.), and levels of soluble TNF receptor II were measured with HyCult enzyme-linked immunosorbent assay kits (Caltag, San Francisco). The assays were performed in an ACTG Advanced Technology Laboratory (University of California at Los Angeles). The samples from each patient were batch-tested in a single run. For quality control, 15 percent of the samples were retested in a subsequent run to confirm the results of the first run.

HIV-1 RNA levels in plasma collected in acid-citrate-dextrose were determined in a single ACTG-certified laboratory by the HIV-1 Amplicor Monitor assay (Roche Diagnostics, Branchburg, N.J.)²⁴ with the Viral Quality Assurance Program standards of the National Institutes of Health. Each patient's samples were batch-tested in a single run with detection on the same microtiter plate to minimize variability.

Statistical Analysis and Interim Data Monitoring

The study was designed to have 80 percent power and type I error rates of 0.05 for the independent end points of complete ulcer resolution and change in HIV load at week 4. The study was not designed for the formal testing of hypotheses about other end points; we present those findings for exploratory purposes only, without adjusting the type I error rates for multiple testing. All the analyses were performed on an intention-to-treat basis, except that three patients who did not begin the study treatment were excluded.

For continuous and ordinal variables, appropriate two-tailed Wilcoxon nonparametric rank-sum or signed-rank tests were used.²⁵ Two-by-two classifications of ulcer-related and other dichotomous end points were tested by Fisher's exact test.²⁶ The strength of the association between the variables used in the analysis was estimated with Spearman's rank-correlation coefficient.²⁵

The distributions of the time to ulcer healing were estimated by the Kaplan–Meier product-limit method.²⁷

The study design included a group sequential interim analysis of the ulcer-healing end point for the first 45 of 82 intended patients, with an O'Brien–Fleming stopping boundary.²⁸ The results of the interim analysis were presented to an ad hoc interim-review committee. On the basis of these findings, enrollment in the placebo group was closed, by which time 12 more patients had completed four weeks of randomized study treatment. Results for all 57 patients (which were virtually identical to the results of the interim analysis) are presented here.

RESULTS

Study Population

Between February 1994 and October 1995, 60 patients were enrolled. Three patients were excluded from the analysis because they never received treatment according to the study protocol. The ulcers of two of the three patients healed between the time of the screening visit and the time the study treatment was scheduled to begin; the third patient was found after randomization to be ineligible for the study. Of the 57 patients included in the analysis, 28 were randomly assigned to receive placebo and 29 were assigned to receive thalidomide. The patients in the two groups had similar base-line characteristics (Table 1). Almost all had substantial pain that impaired their eating and overall health. Only one patient in each group missed the final study visit at week 4.

Clinical Data

Among the 29 patients in the thalidomide group, 16 (55 percent) had responded to therapy completely at week 4, as compared with 2 of the 28 patients in the placebo group (7 percent; odds ratio, 15; 95 percent confidence interval after adjustment for group sequential testing, 1.8 to 499; unadjusted $P < 0.001$) (Fig. 1). For the patients in the thalidomide group who had complete responses, the median time to complete ulcer healing was 3.5 weeks (95 percent confidence interval, 2 to 4). Once the patients randomly assigned to placebo were offered open-label thalidomide after week 4, their rate of complete response was similar to the initial rate of complete response in the thalidomide group (Fig. 2).

If one combines complete and partial responses, the results show a similar pattern. Of the 29 patients in the thalidomide group, 26 (90 percent) had complete or partial responses at the end of week 4, as compared with only 7 of 28 patients in the placebo group (25 percent; odds ratio, 24; 95 percent confidence interval, 5.2 to 162; $P < 0.001$).

Seven patients received the higher dose of thalidomide (200 mg twice a day) because their ulcers were still present. Five of these patients had complete healing.

The quality-of-life data showed that the patients

TABLE 1. BASE-LINE CHARACTERISTICS OF 57 HIV-INFECTED PATIENTS WITH APHTHOUS ULCERS TREATED WITH THALIDOMIDE OR PLACEBO.*

CHARACTERISTIC	PLACEBO (N=28)	THALIDOMIDE (N=29)
Age — yr	34.4±1.3	36.2±1.5
Weight — kg	61.9±2.1	66.2±3.0
Sex — no. (%)		
Male	24 (86)	26 (90)
Female	4 (14)	3 (10)
Race or ethnic group — no. (%)		
Non-Hispanic white	10 (36)	9 (31)
Non-Hispanic black	6 (21)	7 (24)
Hispanic	10 (36)	9 (31)
Asian or Pacific Islander	2 (7)	2 (7)
American Indian	0	2 (7)
CD4 cells		
No./mm ³		
Median	27.8	17.0
Interquartile range	16.8, 83.5	6.0, 80.0
Percentage†		
Median	4.3	2.0
Interquartile range	1.8, 8.0	1.0, 8.0
Copies of HIV RNA — ×10 ⁻³ /ml‡		
Median	83.3	120.6
Interquartile range	37.1, 254.1	67.6, 206.0
Area of ulcers — mm ²	194.3±43.5	193.6±41.5
Mean quality-of-life score§	3.0±0.2	3.1±0.2

*Plus-minus values are means ±SE.

†Percentages shown are percentages of all lymphocytes.

‡Data are based on 26 patients in each group.

§Data are based on 27 patients in the placebo group and 28 patients in the thalidomide group.

in the thalidomide group succeeded much more than those in the placebo group in attaining a relatively problem-free status (responses of ≤ 2 on all measures [$P < 0.03$] except general health). The improvement was greatest with regard to the patients' discomfort while eating ($P < 0.001$).

The patients in the thalidomide group gained a median of 1.8 kg (4 lb) during the first four weeks of the study, whereas there was no weight gain in the placebo group ($P = 0.07$). The study had only 27 percent power to detect a difference of 1.8 kg.

Immunologic Data

The median plasma levels of TNF- α and soluble TNF- α receptor type II were elevated in both groups before the study treatment began (Table 2). After two weeks of treatment, both levels increased significantly more in the thalidomide group than in the placebo group (Table 2). The increases in plasma TNF- α levels correlated with the increases in levels of soluble TNF- α receptor type II from base line to week 2 ($r = 0.64$, $P = 0.001$) and from base line to week 4 ($r = 0.47$, $P = 0.005$). There were no important changes in CD4 or CD8 lymphocyte counts or percentages from base line to week 4.

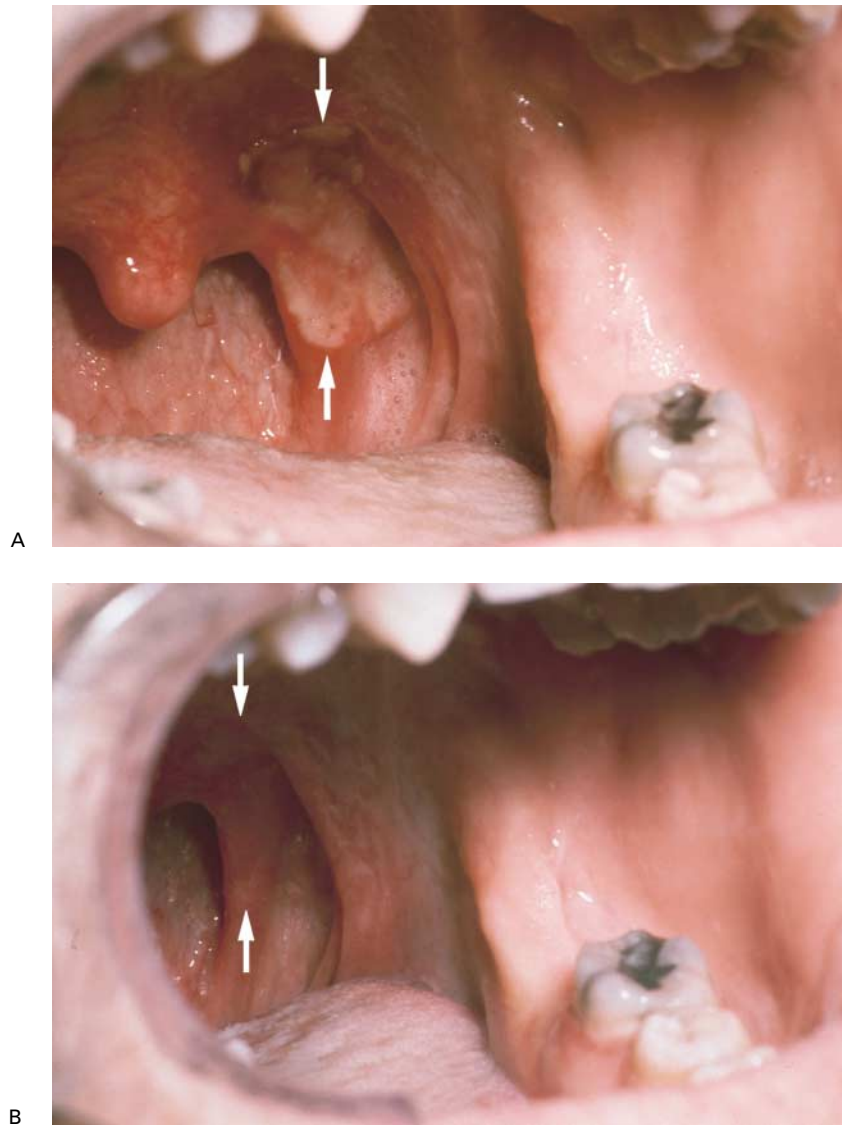


Figure 1. Major Aphthous Ulcer of Six Weeks' Duration on the Palatopharyngeal Arch of a 30-Year-Old Man with the Acquired Immunodeficiency Syndrome (AIDS).

AIDS was diagnosed on the basis of CD4 cell counts of less than 200 per cubic millimeter. The ulcer healed completely, with little scarring, after four weeks of thalidomide therapy. In the photograph in Panel A, obtained at the start of the study, the arrows indicate the location of the upper and lower ulcer margins. In the photograph in Panel B, obtained after four weeks' treatment with thalidomide, the arrows indicate where the ulcer margins had been at the start of the study.

Virologic Data

The patients in the thalidomide group had a significantly greater increase in HIV RNA from base line to week 4 than the patients in the placebo group (median increase in the thalidomide group, 0.42 \log_{10} copies per milliliter; in the placebo group, 0.05; $P=0.04$). During the same interval, the increases in HIV RNA were weakly associated with the increases in plasma levels of TNF- α ($r=0.34$, $P=0.05$) and soluble TNF- α receptor type II ($r=0.42$, $P=0.01$).

Safety

Six patients in the thalidomide group discontinued the study medication because of toxic effects of treatment. One of the 28 patients assigned to placebo requested an early discontinuation of treatment. The estimated probability of remaining in the study to day 28 without a dose reduction was 52 percent in the thalidomide group and 89 percent in the placebo group.

Twelve patients assigned to thalidomide and 11

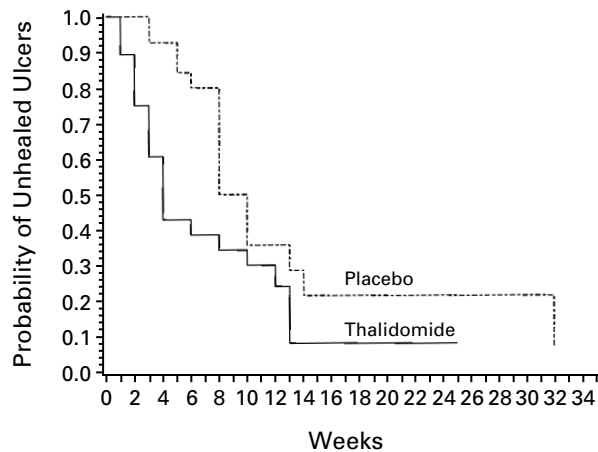


Figure 2. Estimated Distribution of the Time Needed for Complete Healing of Aphthous Ulcers in the 57 Patients, According to Treatment Group. Open-label thalidomide was offered at week 4.

patients assigned to placebo had new adverse events of grade 3 or higher (as classified according to the NIAID criteria) during the four weeks of randomized treatment. Grade 4 neutropenia occurred in two thalidomide-treated patients who had severe neutropenia before therapy. One patient in the thalidomide group and two patients in the placebo group had grade 3 neutropenia. Somnolence was reported in seven patients in the thalidomide group (24 percent) and two patients in the placebo group (7 percent, $P=0.144$). Seven patients in the thalidomide group (24 percent) had rashes, as compared with one patient in the placebo group (4 percent,

$P=0.052$). Other adverse events in the thalidomide group, each observed in three patients or fewer, included chest pain, respiratory difficulties, fever, confusion, headaches, fatigue, dizziness, irregular heart-beat, lethargy, nausea, syncope, elevated levels of hepatic aminotransferases, and elevated levels of alkaline phosphatase. In the placebo group, the adverse events included headaches, anemia, elevated levels of γ -glutamyltransferase, elevated levels of hepatic aminotransferases, fever, diarrhea, fatigue, and hallucinations. Seven patients in the thalidomide group and five in the placebo group had new or worsened peripheral sensory neuropathy.

During the first four weeks of study treatment, there were no deaths or new episodes of opportunistic infections. No pregnancies occurred.

DISCUSSION

This double-blind, randomized, placebo-controlled study shows that thalidomide is effective in healing aphthous ulceration of the mouth and oropharynx in HIV-infected patients. The ulcers healed completely by week 4 in 55 percent of the patients in the thalidomide group, as compared with 7 percent of the patients in the placebo group. Almost all the patients taking thalidomide (90 percent) had at least partial healing. There was complete resolution in some patients within as little as one week after the start of therapy, but the median time to complete healing among the patients who responded was 3.5 weeks. Quality-of-life measures clearly showed that thalidomide reduced the pain from the aphthous lesions and improved the ability to eat.

There were no significant differences between the groups in the incidence of serious adverse events,

TABLE 2. CHANGES IN PLASMA LEVELS OF TNF- α AND SOLUBLE TNF- α RECEPTOR TYPE II, ACCORDING TO TREATMENT GROUP.*

VARIABLE AND GROUP	NO. OF PATIENTS	BASE-LINE VALUE median (interquartile range)	P VALUE	NO. OF PATIENTS	CHANGE, BASE LINE TO WEEK 2† median (interquartile range)	P VALUE	NO. OF PATIENTS	CHANGE, BASE LINE TO WEEK 4† median (interquartile range)	P VALUE
TNF- α (pg/ml)									
Placebo	22	37.09 (22.32, 75.85)	0.870	20	-0.31 (-5.60, 3.55)	0.001‡	20	-0.91 (-9.49, 6.66)	0.090
Thalidomide	20	36.97 (25.97, 48.62)		16	12.16§ (5.63, 22.98)		14	4.04 (0.14, 8.83)	
Soluble TNF- α receptor type II (ng/ml)									
Placebo	22	3.60 (2.81, 5.59)	0.890	20	-0.17 (-0.43, 0.27)	0.002‡	20	-0.05 (-0.50, 0.28)	0.007‡
Thalidomide	20	3.75 (2.85, 5.12)		16	1.46§ (0.53, 1.87)		14	0.53§ (0.31, 1.06)	

*P values are for the difference between groups.

†Positive values indicate that the level increased from base line to the week shown; negative values indicate that the level decreased. The levels during a specified period around the date of the visit were averaged (in the case of base-line values, the measurements considered were made at or before the base-line visit). Changes from base line are the differences between the average values. Mean (\pm SD) normal values for TNF- α are 9.5 ± 5.7 pg per milliliter; and for soluble TNF- α receptor type II, 2.1 ± 0.7 ng per milliliter. Data on 42 of the 57 patients were used in the analysis.

‡ $P < 0.05$ by the two-sample Wilcoxon rank-sum test for the comparison of the difference in changes between groups.

§ $P < 0.05$ by the Wilcoxon signed-rank test for the comparison of the base-line and post-base-line values within the group.

but not all the patients could tolerate the initial therapeutic regimen (200 mg per day) for the entire four weeks of the randomized study. Approximately half the patients either discontinued the study medication permanently or had their doses reduced before the four-week course ended. Half of these treatment changes were due to rash or excessive sedation.

Peripheral sensory neuropathy was not found with greater frequency in the thalidomide group. However, such neuropathy is a known complication of longer-term thalidomide treatment.²⁹ Given the other neuropathic insults to which HIV-infected patients are exposed, patients receiving thalidomide must be monitored carefully for this potential toxic effect.

Thalidomide is notorious for its teratogenic effects.³⁰⁻³² During the period of pregnancy when there is known sensitivity to the effects of thalidomide (21 to 35 days after conception), even a single dose of thalidomide is dangerous.³¹ If thalidomide is given to women with childbearing potential, the treatment should be accompanied by cautionary measures, including careful informed-consent procedures, a requirement that effective birth control be used, testing for pregnancy every two weeks, warning labels on packages and vials, and preestablished procedures for counseling and monitoring in the event of pregnancy. We believe that this approach should be used so that women with childbearing potential can receive this treatment and other potentially beneficial therapies of known or uncertain teratogenic risk.

Recently, the immune-modulating and angiogenesis-inhibiting activities of thalidomide have been recognized.³³⁻³⁵ The drug has shown evidence of effectiveness in treating graft-versus-host disease in transplant recipients³⁴ and in treating erythema nodosum leprosum.³⁵ Most descriptions of the use of thalidomide to treat aphthous ulcers in HIV-infected patients and others have been case reports and retrospective series.³⁻¹⁴ However, one placebo-controlled, double-blind, crossover trial with no wash-out period reported success with 100 mg of thalidomide per day in presumably non-HIV-infected subjects.¹⁵ End points related to both prophylaxis and treatment were combined in that trial.

The cause of aphthous ulceration has not been established. Viral, immunologic, hormonal, and stress-related factors have all been suggested.³⁶ Evidence of HIV RNA or protein has been found in some macrophages at the bases of esophageal ulcers in some patients with the acquired immunodeficiency syndrome (AIDS).³⁷ However, it is likely that the direct cause of aphthous ulceration is immunologic^{36,37} and that the mechanism of action of thalidomide, like that of corticosteroids, is based on its immunomodulating properties.

Our study failed to elucidate the putative immuno-

logic mechanism, however. Although thalidomide was reported to inhibit the production of TNF- α ,^{16-20,38,39} our data did not show that TNF- α was inhibited, at least not systemically. Plasma levels of both TNF- α and soluble TNF- α receptor type II increased in the thalidomide-treated patients as compared with those receiving placebo. This suggests either that TNF- α is not important in the pathogenesis of aphthous ulcers or that if it is, the effect may occur locally in the tissues. It is more likely that other mechanisms are involved.

Our data suggest that thalidomide enhances the production of HIV. This contradicts *in vitro* findings¹⁸ but is consistent with the results of our measurements of TNF- α and lends support to the proposed relation between the activation of TNF- α and viral expression from HIV-infected cells.²¹ TNF- α induces the expression of HIV from chronically infected cell lines by stimulating nuclear factor- κ B, a cellular transcription factor used by HIV.²¹ Because of the effect of thalidomide on the HIV load and on the levels of soluble TNF- α receptor type II, two measures associated with the clinical progression of HIV disease,⁴⁰⁻⁴³ we urge caution in using thalidomide in HIV-infected persons after the two to four weeks of short-term treatment.

Our data indicate that when large, nonhealing aphthous ulcers of the gastrointestinal tract develop in HIV-infected patients, the patients usually have advanced immunosuppression. The median absolute CD4 cell count in our patients was 25 cells per cubic millimeter; 89 percent had CD4 counts of less than 200 cells per cubic millimeter. Thus, such ulceration should probably be considered an AIDS-defining event.

Few data are available on the incidence of severe aphthous ulcers among HIV-infected patients. They are certainly uncommon, but when they do occur they are often devastating. Our study shows that thalidomide is clearly effective in treating this condition.

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APPENDIX

In addition to the study authors, the ACTG protocol 251 team included: D. Greenspan and F. Aweeka, University of California, San Francisco; C. Trapnell and L. Purdue, Division of AIDS, NIAID; J. McFarland and W. Levy, ACTG Operations Center, Social and Scientific Systems, Rockville, Md.; G. Jones, Data Management Center, Frontier Science Technology and Research Foundation, Amherst, N.Y.; D. Simpson, Mount Sinai School of Medicine, New York; A. Bardequez, New Jersey Medical School, Newark; R. Clark, Tulane University, New Orleans; N. Quesada, University of California, Los Angeles; and P.J. Andrusis, Jr., and M.W. Drulak, Andrusis Pharmaceuticals, Beltsville, Md.

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