

A RANDOMIZED TRIAL OF ENHANCED THERAPY FOR EARLY SYPHILIS IN PATIENTS WITH AND WITHOUT HUMAN IMMUNODEFICIENCY VIRUS INFECTION

ROBERT T. ROLFS, M.D., M. RIDUAN JOESOEF, M.D., PH.D., EDWARD F. HENDERSHOT, M.D., ANNE M. ROMPALO, M.D., MICHAEL H. AUGENBRAUN, M.D., MICHAEL CHIU, M.D., GAIL BOLAN, M.D., STEVEN C. JOHNSON, M.D., PAMELA FRENCH, M.D., ERIC STEEN, M.D., JUSTIN D. RADOLF, M.D., AND SANDRA LARSEN, PH.D.,
FOR THE SYPHILIS AND HIV STUDY GROUP

ABSTRACT

Background Reports of neurosyphilis and invasion of cerebrospinal fluid by *Treponema pallidum* in patients with human immunodeficiency virus (HIV) infection have led to doubts about the adequacy of the recommended penicillin G benzathine therapy for early syphilis.

Methods In a multicenter, randomized, double-blind trial, we assessed two treatments for early syphilis: 2.4 million units of penicillin G benzathine and that therapy enhanced with a 10-day course of amoxicillin and probenecid. The serologic and clinical responses of patients with and without HIV infection were studied during one year of follow-up.

Results From 1991 through 1994, 541 patients were enrolled, including 101 patients (19 percent) who had HIV infection but differed little from the uninfected patients in their clinical presentations. The rates at which chancres and rashes resolved did not differ significantly according to treatment assignment or HIV status. Serologically defined treatment failures were more common among the HIV-infected patients. The single clinically defined treatment failure was in an HIV-infected patient. Rates of serologically defined treatment failure did not differ according to treatment group (18 percent at six months with usual therapy; 17 percent with enhanced therapy). *T. pallidum* was found at enrollment in the cerebrospinal fluid of 32 of 131 patients (24 percent) and after therapy in 7 of 35 patients tested. None had clinically evident neurosyphilis, and the rate of detection of *T. pallidum* did not differ according to HIV status.

Conclusions After treatment for primary or secondary syphilis, the HIV-infected patients responded less well serologically than the patients without HIV infection, but clinically defined failure was uncommon in both groups. Enhanced treatment with amoxicillin and probenecid did not improve the outcomes. Although *T. pallidum* was detected in cerebrospinal fluid before therapy in a quarter of the patients tested, such a finding did not predict treatment failure. The current recommendations for treating early syphilis appear adequate for most patients, whether or not they have HIV infection. (N Engl J Med 1997;337:307-14.)

©1997, Massachusetts Medical Society.

SINCE 1987, several reports have described neurosyphilis and other complications of syphilis in patients infected with the human immunodeficiency virus (HIV),¹⁻⁷ often after the patients have been treated with penicillin G benzathine, as recommended by the Centers for Disease Control and Prevention (CDC). Also, in 1987 viable treponemes were identified in the cerebrospinal fluid of two HIV-infected patients after this therapy.⁸ These observations have prompted questions about the adequacy of the CDC-recommended treatment for HIV-infected patients with early syphilis.^{3,9-11} The efficacy of the recommended therapy for patients with early syphilis who are not infected with HIV was also questioned¹²; after this therapy neurosyphilis was reported and *Treponema pallidum* was isolated from the cerebrospinal fluid of patients not known to be HIV-infected.¹³⁻¹⁶ Although experience suggested that syphilis treatment rarely failed in patients not infected with HIV, data on the matter had not been systematically collected.^{17,18}

We evaluated the effectiveness of the CDC-recommended treatment for early syphilis in patients with and without HIV infection by comparing that treatment with the same regimen enhanced by the addition of amoxicillin and probenecid. The enhanced regimen was chosen because the occurrence of neurosyphilis and the isolation of *T. pallidum* from cerebrospinal fluid after treatment with benzathine penicillin, which does not provide treponemi-

From the Division of STD Prevention, National Center for HIV, STD, and Tuberculosis Prevention (R.T.R., M.R.J.), and the Division of STD Laboratory Research, National Center for Infectious Diseases (S.L.), Centers for Disease Control and Prevention, Atlanta; the Philadelphia Department of Public Health and the Medical College of Pennsylvania-Hahnemann University, Philadelphia (E.F.H., P.F.); the Baltimore Health Department and Johns Hopkins University Medical Center, Baltimore (A.M.R.); State University of New York Health Sciences Center at Brooklyn, Brooklyn (M.H.A.); the University of Texas Southwestern Medical Center, Dallas (M.C., E.S., J.D.R.); the San Francisco Department of Public Health, San Francisco (G.B.); Walter Reed Army Medical Center, Washington, D.C. (S.C.J.); and the National Naval Medical Center, Bethesda, Md. (S.L.). Address reprint requests to the Communications Office, National Center for HIV, STD, and Tuberculosis Prevention, Centers for Disease Control and Prevention, Mailstop E-06, Atlanta, GA 30333.

Other authors were William E. Brady, M.P.H. (National Center for HIV, STD, and Tuberculosis Prevention, Atlanta), Kenneth F. Wagner, D.O. (National Naval Medical Center, Bethesda, Md.), and Debra A. D'Aquila, M.D. (Philadelphia Department of Public Health and Medical College of Pennsylvania-Hahnemann University, Philadelphia).

cidal levels of antibiotic coverage in cerebrospinal fluid,¹⁹⁻²² suggested that such coverage may improve therapeutic efficacy.²⁰ The enhanced regimen provides treponemicidal levels of antibiotic in cerebrospinal fluid and is suitable for administration on an outpatient basis.^{23,24}

We addressed three principal questions. First, do HIV-infected patients with early syphilis have a higher rate of treatment failure than those without HIV infection? Second, does enhanced treatment that provides treponemicidal levels of antibiotic in cerebrospinal fluid improve outcomes among patients with early syphilis? Finally, is central nervous system involvement in early syphilis clinically important?

METHODS

Study Design

This prospective, randomized, double-blind, multisite study of therapy for early syphilis included patients with and patients without HIV infection at enrollment. The treatment usually recommended by the CDC (2.4 million units of intramuscular penicillin G benzathine) was compared with an enhanced therapy consisting of the usual treatment plus 2 g of amoxicillin and 500 mg of probenecid, taken orally three times a day for 10 days.

At eight study sites, consenting patients with untreated primary, secondary, or early latent syphilis were enrolled. Patients were excluded if they were pregnant, under 18 years of age, or unable to receive penicillin; if they had received antibiotics effective against *T. pallidum* within the preceding two weeks; and if such therapy was required at enrollment in addition to treatment for syphilis. The study was approved by the boards reviewing research on human subjects at the CDC and each study site.

At enrollment, the patients were treated with benzathine penicillin and randomly assigned, by means of sequentially numbered bottles of medication, to receive either amoxicillin and probenecid or placebo capsules and tablets identical in appearance and packaging. The randomization was performed at the CDC in blocks of 10 patients stratified according to study site. At the initial visit and at 2 weeks and 1, 2, 3, 6, 9, and 12 months, the patients were interviewed and examined, and serum samples were obtained. Blood was obtained for lymphocyte analyses at the second visit. Lumbar punctures were recommended for all patients at the initial visit, and also at the six-month visit for the HIV-infected patients and for any other patient who had had abnormal cerebrospinal fluid findings at the initial visit. The patients were studied by trained clinicians using standard protocols and data-collection forms.

Laboratory Methods

The serologic tests for syphilis used in these analyses (the rapid plasma reagin card test and the microhemagglutination assay for antibodies to *T. pallidum*) were performed at the CDC with frozen serum samples.²⁵ HIV-antibody tests were performed by standard methods.²⁶

Lymphocyte analyses were performed locally for patients in Baltimore and at the CDC for patients at the other sites. The percentage of lymphocytes that were CD4-positive (the CD4 percentage) was determined by standard methods.^{27,28} A CD4 percentage of 14 percent was considered equivalent to an absolute CD4 cell count of 200 cells per cubic millimeter.²⁹

Conventional tests of cerebrospinal fluid (assays for protein and glucose; white-cell counts; and Venereal Disease Research Laboratory [VDRL] tests) were performed at each study site. The criterion for an abnormal result was the presence of a protein concentration greater than 50 mg per deciliter, a white-cell count greater than 5 per cubic millimeter, or a reactive cerebrospinal flu-

id VDRL test. Frozen specimens of cerebrospinal fluid were shipped to one laboratory to be tested for *T. pallidum* DNA by the polymerase chain reaction (PCR); specimens from 53 patients in Dallas were also analyzed by rabbit-infectivity testing. PCR and rabbit-infectivity tests were performed by previously reported methods.³⁰⁻³⁴ Rabbit-infectivity testing and PCR were performed on samples of cerebrospinal fluid obtained before treatment from 41 patients; 28 of these samples were negative on both tests, 10 were positive on both, and 3 were positive only on PCR. The PCR findings in the three specimens for which there were discrepant findings were confirmed by a second PCR targeting a different fragment of the *T. pallidum* gene.³⁴

Statistical Analysis

The target sample was 1200 patients, including 400 without HIV infection. This target was based on an anticipated failure rate of 5 percent among the patients without HIV infection, an 80 percent power to detect a treatment-related doubling or tripling of the failure rate, and an α level of 5 percent.

Kaplan-Meier product-limit survival curves were used to examine the rates of ulcer and rash resolution. The date of resolution the patient reported was used when known; otherwise, the first visit after the ulcer or rash resolved was considered the date of resolution. The Cox proportional-hazards method³⁵ was used to examine the effects of HIV infection and treatment assignment simultaneously on the resolution rates, with adjustment for potential confounders. Chi-square analysis was used to test for proportions, the Wilcoxon rank-sum test for medians, the t-test for means, and the log-rank test for survival curves.

A decrease in the rapid plasma reagin titer by two or more dilutions (e.g., a decrease from 1:16 to 1:4) or a change to a non-reactive test was considered a satisfactory serologic response. We used logistic-regression analysis to study the effects of HIV infection and treatment assignment simultaneously on rates of serologically defined treatment failure at six months, with adjustment for potential confounders. Serologic responses were also evaluated by computing the mean difference in the rapid plasma reagin titer between the higher of the results obtained initially and at the 2-week visit and each of the titers obtained 3, 6, 9, and 12 months after enrollment. The effects of HIV status and treatment assignment on the mean decrease in the titer were examined simultaneously, with adjustment for potential confounders, with use of a mixed linear model for repeated measures.³⁶

RESULTS

Patients

The patients were enrolled between January 1991 and June 1994. Among the 541 patients, 101 (18.7 percent) were HIV-infected; 139 had primary syphilis, 253 had secondary syphilis, and 149 had early latent syphilis; and 100 (18.5 percent) had a history of syphilis. The HIV-infected patients included 59 of 265 patients receiving enhanced treatment (22.3 percent) and 42 of 276 patients receiving usual treatment (15.2 percent).

The HIV-infected patients were more likely to be men, to report having a sexual partner of the same sex, and to have a history of syphilis ($P < 0.05$) (Table 1). The HIV-infected patients had higher initial rapid plasma reagin titers ($P < 0.05$). The HIV-infected patients with primary syphilis were more likely than the other patients with primary syphilis to have multiple chancres (70 percent vs. 34 percent, $P < 0.05$), but the chancre size, the characteristics of the rash, the frequency of mucous patches

TABLE 1. CHARACTERISTICS OF THE PATIENTS AT ENROLLMENT.

CHARACTERISTIC	HIV-INFECTED (N = 101)	NOT HIV-INFECTED (N = 440)
Median age — yr	30	32
Male sex — no. of patients (%)	85 (84)	298 (68)*
Race — no. of patients (%)†		
Black	82 (81)	386 (88)
White	14 (14)	38 (9)
Other	5 (5)	15 (3)
Education — mean no. of years completed	12	12
Stage of syphilis — no. of patients (%)		
Primary	25 (25)	114 (26)
Secondary	53 (52)	200 (45)
Early latent	23 (23)	126 (29)
History of syphilis — no. of patients (%)‡	37 (38)	63 (15)*
Lumbar puncture at initial visit — no. of patients (%)	47 (47)	103 (23)*
Enhanced therapy — no. of patients (%)	59 (58)	206 (47)§
Men who had a male sexual partner in past year — no. of men (%)¶	41 (50)	28 (10)*
Median no. of sexual partners		
In past 3 months	1	2§
In past year	4	3
In lifetime	68	30*
Rapid plasma reagin — median titer	1:128	1:64§

*P<0.01 for the comparison with the HIV-infected patients.

†Data on race were missing for one patient who was not HIV-infected.

‡Data on history of syphilis were missing for three HIV-infected patients and six patients who were not HIV-infected.

§P<0.05 for the comparison with the HIV-infected patients.

¶Data on men who had a male sexual partner in the past year were missing for 3 HIV-infected patients and 11 patients who were not HIV-infected. Eighty-two HIV-infected men and 287 men without HIV infection were studied.

or condylomata lata, and the duration of the chancre or rash before enrollment did not differ significantly according to HIV status.

Among the 80 HIV-infected patients tested, the CD4 percentages at two weeks were less than 14 percent for 25 patients (31 percent). The patients in the two treatment groups were similar with regard to age, race, education, stage of syphilis, reported sexual behavior, history of syphilis, and frequency of lumbar puncture at the initial visit, but the patients assigned to enhanced therapy were more commonly infected with HIV (P=0.04).

Treatment

The rates of follow-up were 84 percent at two weeks, 61 percent at six months, and 52 percent at one year. Of the 457 patients who returned for the two-week visit, 232 (51 percent) reported taking all the medications provided. Forty patients (12 percent) followed for six months reported receiving antibiotics with antitreponemal efficacy after enrollment “incidentally” — for reasons that were unrelated to their participation in the study.

The HIV-infected patients did not differ from the uninfected patients with regard to the rate of follow-up, compliance with medication, or the receipt of antibiotics after enrollment. Jarisch–Herxheimer reactions were noted more frequently among the HIV-infected patients (22 percent, vs. 12 percent among those without HIV infection; P=0.02), as were fever (18 percent vs. 7 percent, P=0.005) and nausea or gastrointestinal upset (26 percent vs. 15 percent, P=0.02).

The patients receiving the enhanced treatment did not differ from those receiving the usual treatment with regard to the follow-up rate, compliance with medication, or the receipt of antibiotics after enrollment. Diarrhea was more common with enhanced therapy than with usual therapy (17 percent vs. 10 percent, P=0.04).

Resolution of Clinical Lesions

Chancres were noted in 177 patients, with a median reported duration before enrollment of 14 days. The time to resolution of the chancre was somewhat longer for the HIV-infected patients than for those who were not infected (median, 16.5 vs. 13 days; P=0.08). In a multivariate analysis in which HIV status and treatment assignment were considered simultaneously, the time to healing was slightly longer among the HIV-infected subjects (hazard ratio for the rate of healing, 0.70; 95 percent confidence interval, 0.45 to 1.09), but the difference was not statistically significant. The treatment assignment did not affect the time to chancre healing.

Skin rashes attributed to syphilis were noted in 213 patients with secondary syphilis; the median duration of rash before enrollment was 56 days. The time to the resolution of the rash did not differ according to HIV status (median in HIV-infected patients, 53 days; in uninfected patients, 49 days; P=0.34) or treatment assignment. The results were unchanged in the multivariate analysis.

Outcomes of Serologic Tests after Treatment

By our definition, 24 percent of the patients were classified as having serologically defined treatment failure at 3 months, 17 percent at 6 months, and 14 percent at 12 months. The frequency of serologically defined treatment failure was not affected by the reported degree of compliance with therapy (Table 2).

Among patients in the primary and secondary stages of syphilis, HIV-infected patients were more likely than patients without HIV infection to have serologically defined treatment failure, but the reverse was observed among patients in the early latent stage of syphilis. In the multivariate logistic-regression analysis, HIV-infected patients had a significantly higher risk of serologically defined treatment failure at six months than did uninfected patients if they were in the primary stage of syphilis;

TABLE 2. RATES OF SEROLOGICALLY DEFINED TREATMENT FAILURE AT VARIOUS INTERVALS AFTER TREATMENT FOR SYPHILIS.*

VARIABLE	TIME SINCE TREATMENT			
	3 MO	6 MO	9 MO	12 MO
	% with treatment failure (no. studied)			
Treatment assignment				
Usual therapy	23 (175)	18 (157)	18 (153)	15 (137)
Enhanced therapy	25 (185)	17 (169)	16 (148)	14 (142)
Stage of syphilis†				
Primary				
HIV-infected	17 (18)	22 (18)‡	14 (14)	14 (14)
Not HIV-infected	6 (66)	5 (59)	8 (52)	8 (53)
Secondary				
HIV-infected	36 (42)§	23 (35)‡	15 (33)	19 (32)‡
Not HIV-infected	15 (141)	10 (121)	8 (110)	6 (96)
Early latent				
HIV-infected	40 (15)	19 (16)	13 (16)	13 (15)
Not HIV-infected	49 (78)	35 (77)	37 (76)	29 (69)
Patient reported taking all amoxicillin pills				
Yes	20 (179)	18 (164)	17 (153)	13 (142)
No	29 (164)	17 (146)	17 (136)	15 (125)
Incidental antibiotic use¶				
Yes	16 (31)	8 (40)	8 (52)	2 (44)‡
No	25 (329)	19 (286)	18 (249)	17 (235)
History of syphilis				
Yes	26 (69)	26 (65)‡	23 (56)	16 (58)
No	24 (287)	16 (257)	15 (241)	14 (217)
CD4 percentage (HIV-infected patients only)				
<14%	29 (21)	24 (17)	7 (15)	20 (15)
≥14%	42 (43)	26 (42)	21 (39)	18 (38)

*Serologically defined treatment failure was considered to be present when the rapid plasma reagin titer did not decrease by two or more dilutions or the test results did not become nonreactive after treatment. The value used for comparison was that obtained at the initial visit or the two-week visit, whichever was higher.

†The interaction between HIV status and syphilis stage was significant ($P < 0.05$).

‡ $P < 0.05$ for the comparison between groups at the visit shown.

§ $P < 0.01$ for the comparison between groups at the visit shown.

¶Incidental antibiotic use (as reported by the patient) was defined as the receipt of antibiotics effective against *T. pallidum* after enrollment. The antibiotics reported were penicillin, ampicillin, amoxicillin, tetracycline, erythromycin, doxycycline, ceftriaxone, and cefadroxil.

and HIV-infected patients had a risk that was increased but not significantly so if they were in the secondary stage (Table 3). Multivariate analysis of the mean decrease in the rapid plasma reagin titer also indicated that the titer decreased more slowly among the HIV-infected patients (Table 4); this difference was statistically significant among patients in the primary stage of syphilis. Rates of serologically defined treatment failure were similar between HIV-infected patients with CD4 percentages of 14 percent or higher and those with CD4 percentages of less than 14 percent.

The frequency of serologically defined treatment failure did not differ according to treatment assign-

TABLE 3. MULTIVARIATE LOGISTIC-REGRESSION ANALYSIS OF SEROLOGICALLY DEFINED TREATMENT FAILURE AT SIX MONTHS.

VARIABLE	TREATMENT FAILURE no. of failures/ no. of patients (%)	ADJUSTED ODDS RATIO (95% CI)*
Treatment assignment		
Usual therapy	28/157 (18)	1.1 (0.6–2.2)
Enhanced therapy	29/169 (17)	1.0
Stage of syphilis		
Primary		
HIV-infected	4/18 (22)	7.6 (1.3–44.2)
Not HIV-infected	3/59 (5)	1.0
Secondary		
HIV-infected	8/35 (23)	2.9 (0.9–8.9)
Not HIV-infected	12/121 (10)	1.0
Early latent		
HIV-infected	3/16 (19)	0.4 (0.1–2.2)
Not HIV-infected	27/77 (35)	1.0
History of syphilis		
Yes	17/65 (26)	2.0 (0.9–4.5)
No	40/257 (16)	1.0
Incidental antibiotic use†		
Yes	3/40 (8)	0.4 (0.1–1.4)
No	54/286 (19)	1.0

*Odds ratios are adjusted by logistic-regression analysis for age, sex, stage of syphilis, history of syphilis, HIV status, treatment assignment, initial rapid plasma reagin titer, study site, degree of compliance with medication, and incidental use of antibiotics. CI denotes confidence interval.

†Incidental antibiotic use (as reported by the patient) was defined as the receipt of antibiotics effective against *T. pallidum* after enrollment. The antibiotics reported were penicillin, ampicillin, amoxicillin, tetracycline, erythromycin, doxycycline, ceftriaxone, and cefadroxil.

ment (Tables 2 and 3). The mean decrease in the rapid plasma reagin titer was slightly greater with enhanced treatment, but the difference between treatment groups was significant only at nine months (Table 4). Serologically defined treatment failure was less likely, and the mean decrease in the rapid plasma reagin titer greater, among patients who incidentally received antibiotics effective against *T. pallidum* after enrollment (Tables 2 and 4).

Cerebrospinal Fluid Findings

On the cerebrospinal fluid examination at the initial visit, HIV-infected patients were significantly more likely than those without HIV infection to have more than 5 white cells per cubic millimeter and somewhat more likely to have reactive VDRL tests of cerebrospinal fluid and elevated protein levels (Table 5).

Among 131 patients in whom PCR, rabbit-infectivity testing, or both were performed before treatment, *T. pallidum* was detected by one or both tests in 32 patients (24 percent); the rate of detection of *T. pallidum* did not differ according to HIV status or treatment assignment. *T. pallidum* was identified in pretreatment samples of cerebrospinal fluid from 8 of 20 patients with primary syphilis (40 percent),

TABLE 4. ADJUSTED DIFFERENCE BETWEEN GROUPS IN THE MEAN DECLINE OF THE RAPID PLASMA REAGIN TITER AFTER TREATMENT.*

VARIABLE	ADJUSTED DIFFERENCE, MEAN DECREASE IN TITERT	STANDARD ERROR	P VALUE‡
Enhanced vs. usual treatment			
6 mo	0.32	0.183	0.08
9 mo	0.37	0.188	0.05
12 mo	0.27	0.192	0.16
HIV-infected vs. non-HIV-infected patients			
6 mo	-0.81	0.247	<0.01
9 mo	-0.42	0.250	0.09
12 mo	-0.58	0.253	0.02
Primary syphilis	-1.53	0.352	<0.001
Secondary syphilis	-0.35	0.234	0.14
Early latent syphilis	0.09	0.336	0.79
Incidental antibiotic use vs. no such use§	0.36	0.128	<0.01
History of syphilis vs. no such history	-0.41	0.174	0.02

*This analysis used a mixed linear model for repeated measures that included interaction terms between treatment assignment and the time since treatment, HIV status and time since treatment, and HIV status and stage of syphilis. The model also adjusted for age, sex, initial rapid plasma reagin titer, reported degree of compliance, history of syphilis, incidental receipt of antibiotics, and study site. Essentially identical results were obtained by the method of generalized estimating equations.³⁷

†The mean difference between the two groups in the rapid plasma reagin titer, expressed as the decrease in the number of dilutions, is shown, after adjustment for the other variables in the model. Positive values indicate that the titer decreased more in the group listed first, and negative values that the titer decreased more in the group listed second. There were significant interactions between treatment assignment and the time since treatment, HIV status and time since treatment, and HIV status and stage of syphilis; these results are presented according to the stratum of the interacting variable. For example, at six months, the mean titer in the enhanced-treatment group had decreased 0.32 dilution more than that in the usual-treatment group.

‡P values are based on the t-statistic for the regression coefficient, β_j .

§Incidental antibiotic use (as reported by the patient) was defined as the receipt of antibiotics effective against *T. pallidum* after enrollment. The antibiotics reported were penicillin, ampicillin, amoxicillin, tetracycline, erythromycin, doxycycline, ceftriaxone, and cefadroxil.

15 of 66 patients with secondary syphilis (23 percent), and 9 of 45 patients with early latent syphilis (20 percent, $P=0.20$). *T. pallidum* was identified somewhat more commonly (40 percent vs. 24 percent, $P=0.09$) when the white-cell count in cerebrospinal fluid was elevated, but the identification of *T. pallidum* was not related to cerebrospinal fluid VDRL reactivity or protein elevation. Serologically defined treatment failure was no more likely to occur among patients who had *T. pallidum* detected in pretreatment samples of cerebrospinal fluid than among those who did not.

In 23 patients who were HIV-infected and 12 patients who were not HIV-infected but had abnormal cerebrospinal fluid findings at the initial visit, specimens of cerebrospinal fluid were studied for *T. pallidum* both before and after treatment. Six of 13

TABLE 5. RESULTS OF CEREBROSPINAL FLUID EXAMINATION OF THE PATIENTS WHO UNDERWENT LUMBAR PUNCTURE AT THEIR INITIAL VISIT, ACCORDING TO HIV STATUS AT ENROLLMENT.

LABORATORY TEST*	HIV-INFECTED	NOT HIV-INFECTED
	no. testing positive/ no. studied (%)	
White cells	20/46 (43)	22/99 (22)†
Reactive VDRL test	7/45 (16)	7/99 (7)
Protein	17/47 (36)	25/102 (25)
Any of the above	28/46 (61)	39/97 (40)‡
<i>T. pallidum</i> §	11/43 (26)	21/88 (24)

*The criteria for a positive test are given in the Methods section.

† $P<0.01$ for the comparison between groups.

‡ $P<0.05$ for the comparison between groups.

§PCR, the rabbit-infectivity test, or both were used to detect *T. pallidum* in cerebrospinal fluid.

patients in whom *T. pallidum* was detected before treatment remained positive after treatment; 2 patients subsequently tested negative without additional treatment. One of the 22 patients with initially negative cerebrospinal fluid findings was positive after treatment. That patient, who was not HIV-infected, had 20 white cells per cubic millimeter, 48 mg of protein per deciliter, and a reactive VDRL test at the initial cerebrospinal fluid examination; this patient was tested by PCR only. The cerebrospinal fluid examination after treatment, at which the PCR was positive for *T. pallidum*, showed no white cells, 41 mg of protein per deciliter, and a nonreactive VDRL test. Detection of *T. pallidum* in cerebrospinal fluid after treatment was no more common in HIV-infected patients or those who received standard therapy with penicillin alone. None of the seven patients in whom *T. pallidum* was detected in cerebrospinal fluid after treatment had signs or symptoms of neurosyphilis at that time.

Clinical Outcomes

A single clinically defined treatment failure was detected, as evidenced by a new palmoplantar rash, accompanied by an increase in the rapid plasma reagin titer from 1:32 at 12 weeks to 1:256 at 26 weeks. That patient was infected with HIV and received usual therapy. One other patient (not HIV-infected) had an atypical palmar rash accompanied by an increase in the rapid plasma reagin titer from 1:32 at 4 weeks to 1:128 at 39 weeks; the patient was considered reinfected on the basis of his sexual history. Symptomatic neurosyphilis did not develop in any patient during follow-up.

DISCUSSION

Only case reports and small or retrospective studies have addressed the first question we sought to answer: whether outcomes of treatment for syphilis in HIV-infected patients and those without HIV infection differ.³⁸⁻⁴¹ In this controlled study of 541 patients with syphilis, we observed few clinical differences according to HIV status either at enrollment or after treatment for syphilis. Notably, serious central nervous system and eye complications were not observed after treatment. However, serologic responses were poorer among the HIV-infected patients with primary syphilis and, to a lesser extent, those with secondary syphilis. The same finding was observed in earlier retrospective studies.^{40,41}

How do we interpret this difference in serologic responses when there was no concomitant difference in clinical outcomes? The rarity and delayed occurrence of sequelae have prompted a dependence on serologic criteria in the judgment of therapeutic efficacy in previous studies and clinical practice.⁴²⁻⁴⁴ The clinical importance of different patterns of serologic response and the criteria that should predict treatment failure remain unknown, however. This difference in serologic responses may indicate an increased rate of treatment failure among HIV-infected patients, but it could also result from differences in immune response that are unrelated to treatment outcomes.⁴⁵ The absence of serious, clinically evident sequelae is reassuring, but the reassurance must be tempered by the fact that the sample was smaller than desired, because of the declining incidence of syphilis and the fact that there were fewer HIV-infected patients than expected. The 95 percent confidence interval indicates that our finding of no serious clinical sequelae is statistically compatible with a true rate of sequelae as high as 1.3 percent in the overall study and one as high as 6 percent among the HIV-infected patients.⁴⁶ Thus, we cannot rule out the infrequent occurrence of serious adverse clinical outcomes in HIV-infected patients after treatment for syphilis. A second concern is the suboptimal rate of follow-up, which may have allowed some serious sequelae to go undetected. We do not believe that this is likely. At each study site, investigators actively solicited the cooperation of the clinicians involved in the care of HIV-infected patients, and at most sites the investigators were themselves clinically active at institutions where these patients would have been most likely to receive care in the event of serious sequelae. A reasonable interpretation of our findings is that some HIV-infected patients respond differently from uninfected patients to therapy for early syphilis but that in most cases the difference is not clinically important.

Our study design was well suited to answer our second question — whether enhanced therapy im-

proves treatment outcomes. The enhanced treatment was well tolerated, but it did not affect the rate of serologically defined treatment failure or reduce that rate among HIV-infected patients. The unequal assignment of the HIV-infected patients to the treatment groups caused concern about the process of randomization.⁴⁷ An examination of the relevant procedures and records, however, produced no evidence that the randomization protocol had been modified or the treatment assignments unblinded at any site. We believe the unequal assignment was a chance occurrence that our analysis has controlled for and one that should not affect the results of the study.

Given that we found no benefit from the enhanced regimen, should other regimens be evaluated? Neurosyphilis has been reported in HIV-infected patients after multiple doses of benzathine penicillin, the most likely alternative regimen, as well as after a single dose.^{4,5} A daily regimen of parenteral penicillin or ceftriaxone would be impractical in most clinical settings, and other studies have suggested that high-dose parenteral penicillin and ceftriaxone cannot prevent or cure neurosyphilis in some HIV-infected patients.^{48,49} The better serologic responses among the patients who received antibiotics incidentally after enrollment suggest that this question has not been definitively answered, however. Given the severe consequences of unsuccessful treatment for neurosyphilis in some HIV-infected patients, some clinicians will reasonably decide to provide more aggressive initial treatment to all such patients. Nevertheless, neither this study nor other available evidence indicates how the recommended treatment might be changed to improve outcomes.

The third question we studied concerns the importance of central nervous system involvement, especially as a mechanism for the failure of syphilis treatment in HIV-infected patients. The frequency at which *T. pallidum* was detected in samples of cerebrospinal fluid obtained before treatment was similar to that in previous studies⁸ and indicates that invasion of the central nervous system is common in early syphilis. However, we found no evidence during one year of follow-up that such invasion is clinically important. The detection of *T. pallidum* was not more common among the HIV-infected patients than among patients not infected with HIV, was not associated with symptomatic neurosyphilis, and did not predict treatment failure. These findings suggest that the testing of cerebrospinal fluid before treatment, including testing for *T. pallidum*, is not useful in current clinical decision making. *T. pallidum* was also detected in cerebrospinal fluid after treatment in HIV-infected patients and in uninfected patients who had cerebrospinal fluid abnormalities before treatment. Determining the importance of finding *T. pallidum* in cerebrospinal fluid after

treatment for early syphilis will require a longer follow-up of more patients.

The CDC and others have recommended that patients whose rapid plasma reagin titers do not decrease by two or more dilutions by three months after treatment for primary or secondary syphilis should be evaluated for treatment failure and that lumbar puncture should be performed if the patient is HIV-infected.^{18,43,50,51} Our findings and those of the retrospective study by Romanowski et al.⁵² suggest that when that standard is used, a substantial proportion of patients will be candidates for cerebrospinal fluid studies and retreatment. The rarity of clinically defined treatment failure in our study suggests that the CDC recommendation is inappropriate for patients who are not HIV-infected. The severe sequelae seen after treatment failure in a few HIV-infected patients described elsewhere suggest the importance of close follow-up, but it may be reasonable to delay the application of this serologic criterion until at least six months after treatment.

In conclusion, our findings suggest that most patients with early syphilis respond adequately to the currently recommended therapy with benzathine penicillin, whether they are HIV-infected or not, and that little benefit can be expected from enhancing the usual therapy so that higher levels of antibiotic are provided in the cerebrospinal fluid. This conclusion is stronger in the case of patients who are not HIV-infected, because of the larger number of such patients in the study.

We are indebted to Merck Sharp & Dohme Research Laboratories for supplying probenecid and probenecid placebo tablets, and to SmithKline Beecham Pharmaceuticals for supplying amoxicillin and amoxicillin placebo capsules.

APPENDIX

The following members of the Syphilis and HIV Study Group participated in this study: M. Gold, D. Hildebrandt, J. O'Donnell, and M. Urban, Philadelphia Department of Public Health and Medical College of Pennsylvania-Hahnemann University, Philadelphia; E. Hook, III, C. Reichart, and J. Zenilman, Baltimore Health Department and Johns Hopkins University Medical Center, Baltimore; W. McCormack and B. Smith, State University of New York Health Sciences Center at Brooklyn, Brooklyn; M. Goldberg and D. Turner, University of Texas Southwestern Medical Center, Dallas; L. Bayne, J. Engleman, J. Flood, and S. Schwarcz, San Francisco Department of Public Health, San Francisco; C. Hicks, Walter Reed Army Medical Center, Washington, D.C.; M. Htoo and R. Vitkevich, New York City Department of Public Health, New York; H. Stark, National Naval Medical Center, Bethesda, Md.; V. Pope, Division of STD Laboratory Research, National Center for Infectious Diseases, Centers for Disease Control and Prevention (CDC), Atlanta; S. Goforth and R. Johnson, Division of STD and HIV Prevention, National Center for Prevention Services, CDC; and W. Alexander, S. Lukehart, and L. Magder, Data Safety Monitoring Committee.

REFERENCES

1. Johns DR, Tierney M, Felsenstein D. Alteration in the natural history of neurosyphilis by concurrent infection with the human immunodeficiency virus. *N Engl J Med* 1987;316:1569-72.
2. Berry CD, Hooton TM, Collier AC, Lukehart SA. Neurologic relapse after benzathine penicillin therapy for secondary syphilis in a patient with HIV infection. *N Engl J Med* 1987;316:1587-9.
3. Musher DM, Hamill RJ, Baughn RE. Effect of human immunodeficiency virus (HIV) infection on the course of syphilis and on the response to treatment. *Ann Intern Med* 1990;113:872-81.
4. Lanska MJ, Lanska DJ, Schmidley JW. Syphilitic polyradiculopathy in an HIV-positive man. *Neurology* 1988;38:1297-301.
5. Kase CS, Levitz SM, Wolinsky JS, Sulis CA. Pontine pure motor hemiparesis due to meningovascular syphilis in human immunodeficiency virus-positive patients. *Arch Neurol* 1988;45:832.
6. Feraru ER, Aronow HA, Lipton RB. Neurosyphilis in AIDS patients: initial CSF VDRL may be negative. *Neurology* 1990;40:541-3.
7. Graman PS, Trupei MA, Reichman RC. Evaluation of cerebrospinal fluid in asymptomatic late syphilis. *Sex Transm Dis* 1987;14:205-8.
8. Lukehart SA, Hook EW III, Baker-Zander SA, Collier AC, Critchlow CW, Handsfield HH. Invasion of the central nervous system by *Treponema pallidum*: implications for diagnosis and treatment. *Ann Intern Med* 1988;109:855-62.
9. Musher DM. How much penicillin cures early syphilis? *Ann Intern Med* 1988;109:849-51.
10. Tramont EC. Syphilis in the AIDS era. *N Engl J Med* 1987;316:1600-1.
11. Recommendations for diagnosing and treating syphilis in HIV-infected patients. *MMWR Morb Mortal Wkly Rep* 1988;37:600-2, 607-8.
12. Fiumara NJ. Treatment of seropositive primary syphilis: an evaluation of 196 patients. *Sex Transm Dis* 1977;4:92-5.
13. Byrne TN, Bose A, Sze G, Waxman SG. Syphilitic meningitis causing paraparesis in an HIV-negative woman. *J Neurol Sci* 1991;103:48-50.
14. Chemouilli P, Amarencio P, Roulet E, Marteau R. Neurosyphilis tardive: maladie d'actualité. *Rev Med Interne* 1989;10:503-8.
15. Tramont EC. Persistence of *Treponema pallidum* following penicillin G therapy: report of two cases. *JAMA* 1976;236:2206-7.
16. Hira SK, Patel JS, Bhat SG, Chilikima K, Mooney N. Clinical manifestations of secondary syphilis. *Int J Dermatol* 1987;26:103-7.
17. Hook EW III. Management of syphilis in human immunodeficiency virus-infected patients. *Am J Med* 1992;93:477-9.
18. Zenker PN, Rolfs RT. Treatment of syphilis, 1989. *Rev Infect Dis* 1990;12:Suppl 6:S590-S609.
19. Yoder FW. Penicillin treatment of neurosyphilis: are recommended dosages sufficient? *JAMA* 1975;232:270-1.
20. Ducas J, Robson HG. Cerebrospinal fluid penicillin levels during therapy for latent syphilis. *JAMA* 1981;246:2583-4.
21. Mohr JA, Griffiths W, Jackson R, Saadah H, Bird P, Riddle J. Neurosyphilis and penicillin levels in cerebrospinal fluid. *JAMA* 1976;236:2208-9.
22. Polnikorn N, Witoonpanich R, Vorachit M, Vejajiva S, Vejajiva A. Penicillin concentrations in cerebrospinal fluid after different treatment regimens for syphilis. *Br J Vener Dis* 1980;56:363-7.
23. Morrison RE, Harrison SM, Tramont EC. Oral amoxicillin, an alternate treatment for neurosyphilis. *Genitourin Med* 1985;61:359-62.
24. Faber WR, Bos JD, Rietra PJGM, Fass H, Van Eijk RVW. Treponemoidal levels of amoxicillin in cerebrospinal fluid after oral administration. *Sex Transm Dis* 1983;10:148-50.
25. Larsen SA, Hunter EF, Kraus SJ, eds. A manual of tests for syphilis. 8th ed. Washington, D.C.: American Public Health Association, 1990.
26. Update: serologic testing for antibody to human immunodeficiency virus. *MMWR Morb Mortal Wkly Rep* 1988;36:833-40, 845.
27. Kidd PG, Vogt RF Jr. Report of the workshop on the evaluation of T-cell subsets during HIV infection and AIDS. *Clin Immunol Immunopathol* 1989;52:3-9.
28. Landay AL, Muirhead KA. Procedural guidelines for performing immunophenotyping by flow cytometry. *Clin Immunol Immunopathol* 1989;52:48-60.
29. 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR Morb Mortal Wkly Rep* 1992;41(RR-17):1-19.
30. Sánchez PJ, Wendel GD Jr, Grimpel E, et al. Evaluation of molecular methodologies and rabbit infectivity testing for the diagnosis of congenital syphilis and neonatal central nervous system invasion by *Treponema pallidum*. *J Infect Dis* 1993;167:148-57.
31. Radolf JD. PCR detection of *Treponema pallidum*. In: Persing DH, Smith TF, Tenover FC, White TJ, eds. *Diagnostic molecular microbiology: principles and applications*. Washington, D.C.: American Society for Microbiology, 1993:224-9.
32. Weigel LM, Brandt ME, Norgard MV. Analysis of the N-terminal region of the 47-kilodalton integral membrane lipoprotein of *Treponema pallidum*. *Infect Immun* 1992;60:1568-76.
33. Hsu P-L, Chamberlain NR, Orth K, et al. Sequence analysis of the 47-kilodalton major integral membrane immunogen of *Treponema pallidum*. *Infect Immun* 1989;57:196-203.
34. Akins DR, Purcell BK, Mitra MM, Norgard MV, Radolf JD. Lipid

- modification of the 17-kilodalton membrane immunogen of *Treponema pallidum* determines macrophage activation as well as amphiphilicity. Infect Immun 1993;61:1202-10.
35. Altman DG. Practical statistics for medical research. London: Chapman & Hall, 1991.
36. Littell RC, Milliken GA, Stroup WW, Wolfinger RD. SAS system for mixed model. Cary, N.C.: SAS Institute, 1996:87-134.
37. Zeger SL, Liang K-Y. Longitudinal data analysis for discrete and continuous outcomes. Biometrics 1986;42:121-30.
38. Hutchinson CM, Hook EW III, Shepherd M, Verley J, Rompalo AM. Altered clinical presentation of early syphilis in patients with human immunodeficiency virus infection. Ann Intern Med 1994;121:94-100.
39. Gourevitch MN, Selwyn PA, Davenny K, et al. Effects of HIV infection on the serologic manifestations and response to treatment of syphilis in intravenous drug users. Ann Intern Med 1993;118:350-5.
40. Telzak EE, Greenberg MS, Harrison J, Stoneburner RL, Schultz S. Syphilis treatment response in HIV-infected individuals. AIDS 1991;5:591-5.
41. Yinnon AM, Coury-Doniger P, Polito R, Reichman RC. Serologic response to treatment of syphilis in patients with HIV infection. Arch Intern Med 1996;156:321-5.
42. Brown ST, Zaidi A, Larsen SA, Reynolds GH. Serological response to syphilis treatment: a new analysis of old data. JAMA 1985;253:1296-9.
43. Guinan ME. Treatment of primary and secondary syphilis: defining failure at three- and six-month follow-up. JAMA 1987;257:359-60.
44. Schroeter AL, Lucas JB, Price EV, Falcone VH. Treatment for early syphilis and reactivity of serologic tests. JAMA 1972;221:471-6.
45. Lane HC, Masur H, Edgar LC, Whalen G, Rook AH, Fauci AS. Abnormalities of B-cell activation and immunoregulation in patients with the acquired immunodeficiency syndrome. N Engl J Med 1983;309:453-8.
46. Goodman SN, Berlin JA. The use of predicted confidence intervals when planning experiments and the misuse of power when interpreting results. Ann Intern Med 1994;121:200-6. [Erratum, Ann Intern Med 1995;122:4781.]
47. Schulz KF. Subverting randomization in controlled trials. JAMA 1995;274:1456-8.
48. Dowell ME, Ross PG, Musher DM, Cate TR, Baughn RE. Response of latent syphilis or neurosyphilis to ceftriaxone therapy in persons infected with human immunodeficiency virus. Am J Med 1992;93:481-8.
49. Gordon SM, Eaton ME, George R, et al. The response of symptomatic neurosyphilis to high-dose intravenous penicillin G in patients with human immunodeficiency virus infection. N Engl J Med 1994;331:1469-73.
50. Rolfs RT. Treatment of syphilis, 1993. Clin Infect Dis 1995;20:Suppl 1:S23-S38.
51. 1993 Sexually transmitted diseases treatment guidelines. MMWR Morb Mortal Wkly Rep 1993;42(RR-14).
52. Romanowski B, Sutherland R, Fick GH, Mooney D, Love EJ. Serologic response to treatment of infectious syphilis. Ann Intern Med 1991;114:1005-9.