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Normalization of Serum Rapid Plasma Reagin Titer Predicts Normalization of Cerebrospinal Fluid and Clinical Abnormalities after Treatment of Neurosyphilis

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Abstract

Background—Success of neurosyphilis treatment is defined by normalization of cerebrospinal fluid (CSF) and clinical abnormalities. The goal of this study was to determine whether normalization of serum rapid plasma reagin (RPR) titer could accurately predict treatment success.

Methods—One hundred ten patients who were enrolled in a longitudinal study of CSF abnormalities in syphilis had asymptomatic syphilitic meningitis, symptomatic syphilitic meningitis, or syphilitic eye disease and were treated for neurosyphilis. At 4, 7, and 13 months after treatment, serum RPR titer and CSF and clinical abnormalities were analyzed for normalization. Odds ratios for normalization of each CSF and clinical abnormality when serum RPR titer had normalized and the positive predictive value of normalization of serum RPR titer for normalization of CSF and clinical abnormalities were determined.

Results—Serum RPR titer had normalized in 63 patients (57%) by 4 months after treatment, in 94 (85%) by 7 months, and in 97 (88%) by 13 months. Except for CSF protein concentration, normalization of serum RPR titer predicted normalization of other CSF and clinical abnormalities in >80% of patients at 4 months, >85% at 7 months, and >90% at 13 months. The odds of normalization of CSF and clinical abnormalities were 28–57-fold higher when serum RPR titer had normalized, compared with when it had not. Normalization of serum RPR titer was consistently less accurate in predicting treatment success in human immunodeficiency virus–infected patients who were not receiving antiretroviral therapy, compared with those who were receiving such therapy.

Conclusions—In most instances, normalization of serum RPR titer correctly predicts success of treatment of neurosyphilis, and follow-up lumbar puncture can be avoided.

Syphilis is caused by infection due to *Treponema pallidum* subspecies *pallidum*, a spirochete that cannot be visualized by light microscopy and cannot be cultured. Depending on the stage of infection, the diagnosis of syphilis is established by documentation of reactive serum nontreponemal tests (rapid plasma reagin [RPR] test or venereal disease research laboratory [VDRL] test) and treponemal tests (*T. pallidum* particle agglutination assay [TPPA] or fluorescent treponemal anti-body-absorption [FTA-ABS] test), with or without characteristic symptoms or signs of syphilis.

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Because *T. pallidum* cannot be cultured, diagnosis of neurosyphilis relies on the following indirect measures: elevated CSF WBC count or protein concentration or reactivity of the CSF VDRL test. A reactive CSF VDRL test is considered to be diagnostic of neurosyphilis, but depending on the criteria used to define neurosyphilis, this test may be nonreactive in patients with neurosyphilis [1–3]. Standard benzathine penicillin G therapy is not recommended for persons with neurosyphilis, because it yields penicillin concentrations in the CSF that are too low to kill *T. pallidum*. Instead, treatment specifically for neurosyphilis, with intravenous (IV) aqueous crystalline penicillin G or with intramuscular (IM) aqueous procaine penicillin G (APPG) plus probenecid, is recommended [4]. Alternative regimens of doxycycline or ceftriaxone are also sometimes used, but there are few data on the efficacy of these regimens [5–8].

For patients who are neurologically asymptomatic, assessment of the efficacy of neurosyphilis treatment relies solely on normalization of CSF measures. For those with symptoms or signs, resolution of clinical abnormalities is also considered when determining the efficacy of treatment. Current guidelines recommend that lumbar puncture be serially repeated after neurosyphilis therapy until all CSF measures have normalized [4]. However, patients who have received treatment of neurosyphilis may be reluctant to undergo repeated lumbar punctures to assess the effectiveness of therapy. The goal of this study was to determine whether a decrease in serum RPR titer could serve as a surrogate for normalization of CSF and clinical abnormalities after treatment of asymptomatic or symptomatic neurosyphilis.

METHODS

Procedures

Patients were enrolled in a study of CSF abnormalities in syphilis in Seattle, Washington [1]. Enrollment criteria included clinical or serological evidence of syphilis with neurological or ocular symptoms or signs, a serum RPR titer ≥1:32, or concomitant HIV infection. The study protocol was reviewed and approved by the University of Washington Institutional Review Board, and human experimentation guidelines were observed in the conduct of this research. After written informed consent was obtained, patients underwent a standardized interview and a standardized neurological examination and had blood and CSF samples obtained. On the basis of the results of CSF analysis, the patients' medical providers decided whether the patient should be treated for neurosyphilis and chose the treatment regimen. Treatment was not randomized and was not provided by the study. Twenty-eight patients were treated with IV penicillin G (14.4–24 million U per day for ≥10 days), and 70 patients received IM APPG (2.4 million U for ≥10 days) plus oral probenecid (500 mg 4 times per day for ≥10 days). Four patients received oral doxycycline (200 mg twice per day for 21 days), and 8 patients received ceftriaxone (2 g IM or IV per day for ≥10 days). Patients returned for follow-up visits at 3, 6, and 12 months after treatment. All patients underwent lumbar puncture at the 3-month visit, but the lumbar puncture was repeated at 6 and 12 months only if the previous CSF profile was abnormal. Blood samples were obtained at all follow-up visits.

Clinical definitions

Syphilitic meningitis was defined as new onset of ≥ 1 of: at least moderate headache, at least moderate subjective hearing loss, decreased hearing to finger friction test on neurological examination. Syphilitic eye disease was defined as new onset of subjective visual loss and/or visual acuity in either eye that was ≥20/200, as measured using a hand-held screener or a wall-mounted Snellen chart.

Laboratory measures

Local Clinical Laboratory Improvement Amendments–certified clinical laboratories assessed CSF WBC count, protein concentration, CSF VDRL titer, serum TPPA or FTA-ABS test findings, peripheral blood $CD4^+$ T cell count, and plasma HIV RNA level. $CD4^+$ T cell counts and plasma HIV RNA levels determined within 90 days before or after the diagnosis of neurosyphilis were used. Serum RPR titers were measured at a single research laboratory.

Statistical methods

Patients were included in the analysis if they had ≥ 1 CSF or clinical abnormality and had not had neurosyphilis in the past. Normalization of serum RPR or CSF VDRL test was defined as a 4-fold decrease in titer or reversion of the test to nonreactive. Normalization of CSF WBC count was defined as a decrease from >20 cells/μL to =≤20 cells/μL, and normalization of CSF protein concentration was defined as a decrease from >50 mg/dL to ≤50 mg/dL. Resolution of meningitis or syphilitic eye disease was defined as absence of all components of their respective definitions.

The χ^2 test was used to compare dichotomous variables, and the Mann-Whitney *U* test was used to compare continuous variables. We assessed normalization of CSF and clinical abnormalities and serum RPR titer by 4, 7, and 13 months after treatment. The extra month was added to the standard follow-up times to account for delayed follow-up visits. The proportion of patients with normalization of each measure by each time was used to calculate the positive predictive value of previous normalization of serum RPR titer. Time-dependent Cox proportional hazard models were used to calculate ORs for normalization of each CSF and clinical abnormality P<.05 was considered to be statistically significant.

RESULTS

Patients

One hundred ten patients were included in the analysis. Their characteristics are shown in table 1. Most were HIV-infected men, reflecting the demographic characteristics of syphilis in Seattle and other metropolitan areas [9]. Duration of follow-up did not differ significantly between patients who did and patients who did not experience normalization of CSF or clinical abnormalities. Duration of follow-up, HIV status, proportion of HIV-infected patients receiving antiretroviral therapy (ART), $CD4^+$ T cell count, proportion of patients with meningitis or eye disease, and pretreatment CSF measures did not significantly differ between patients who received treatment with IV aqueous penicillin G and those who received IM APPG plus oral probenecid. The median log plasma HIV RNA level was significantly higher in patients who received treatment with IM APPG plus probenecid than it was in those who received treatment with IV aqueous penicillin G (median log plasma HIV RNA level, 4.67 [interquartile range, 3.53–5.24] vs. 4.04 [interquartile range, 2.77–4.52]; $P = .02$).

Normalization of serum RPR titer

Serum RPR titer had normalized in 63 (57%) of 110 patients by 4 months after neurosyphilis treatment, 94 (85%) of 110 patients by 7 months, and 97 (88%) of 110 patients by 13 months.

Normalization of CSF WBC count

Normalization of serum RPR titer predicted normalization of CSF WBC count in >90% of patients (table 2). The odds of normalizing CSF WBC count at any time after treatment were ~40 times greater when the serum RPR titer had normalized than when the serum RPR titer had not normalized (table 3).

After taking into account the strong predictive value of normalization of serum RPR titer for normalization of CSF WBC count, several other CSF and clinical abnormalities had a statistically significant impact on the odds of normalization of CSF WBC count (table 4). The odds of normalization of CSF WBC count were ~70% less among HIV-infected patients than among HIV-uninfected patients, ~60% less among patients who received treatment with IM APPG plus probenecid than among those who received treatment with IV aqueous penicillin G, and ~50% less when the pretreatment serum RPR titer was ≥1:32 than when it was <1:32. On the other hand, the odds of normalization of CSF WBC count were almost 4-fold higher among patients receiving ART than among those who were not receiving ART and were ~2.5 times higher when the pretreatment CSF WBC count was high. It is important to note that, in these multivariable analyses in which other factors significantly affected odds of normalization of CSF WBC count, normalization of serum RPR titer still conferred an estimated 32–75-fold increase in the odds of normalization of CSF WBC count—at least an order of magnitude greater than the other laboratory and clinical measures.

Normalization of CSF protein concentration

Normalization of serum RPR titer was less accurate for predicting normalization of CSF protein concentration, compared with normalization of CSF WBC count (table 2), and predicted CSF protein normalization in 46%–75% of patients. Nonetheless, the odds of normalization of CSF protein concentration at any time after treatment were still ~28 times greater when the serum RPR titer had normalized than when it had not (table 3). Taking into account the strong effect of normalization of serum RPR titer, 2 other variables also significantly affected the odds of normalization of CSF protein concentration (table 4). The odds of normalization of CSF protein concentration were ~60% less among patients with early syphilis than among patients with late syphilis and were >4-fold higher among patients receiving ART than among those who were not. In these multivariate analyses, normalization of serum RPR titer conferred an estimated 26–92-fold increase in the odds of normalization of CSF protein concentration.

Because it is possible that elevated CSF WBC count and elevated CSF protein concentration could be a result of HIV infection rather than (or in addition to) neurosyphilis, we repeated our analyses with increased precision of the diagnosis of neurosyphilis. Specifically, we restricted the analysis to patients who had a reactive CSF VDRL in addition to elevated CSF WBC count or elevated CSF protein concentration. We found that the odds of normalization of CSF WBC count when serum RPR titer had normalized were again significantly higher among patients who were receiving ART than among those who were not receiving ART (OR, 7.7; 95% CI, 1.4–42.2; $P = .02$). The odds of normalization of CSF protein concentration when serum RPR titer had normalized remained higher among patients receiving ART than among those not receiving ART, but the statistical significance was reduced to a trend (OR, 3.1; 95% CI, 0.9–11.1; $P = .08$), possibly reflecting the reduced number of patients available for analysis.

Normalization of CSF VDRL titer

Normalization of serum RPR titer predicted normalization of CSF VDRL titer in 90%–94% of patients (table 2). The odds of normalization of the CSF VDRL titer at any time after treatment were almost 60 times higher when the serum RPR titer had normalized than when it had not (table 3). Taking into account normalization of serum RPR titer, the only other measure that significantly affected the odds of normalization of CSF VDRL titer was pretreatment serum RPR titer. The odds of normalization of CSF VDRL titer were 90% lower among patients whose pretreatment serum RPR titer was ≥1:32 than among patients whose pretreatment serum RPR titer was <1:32 (table 4). In this multivariate analysis, normalization of serum RPR titer was estimated to confer 98-fold increased odds of normalization of CSF VDRL titer.

Normalization of clinical abnormalities

Normalization of serum RPR titer predicted resolution of meningitis in 80%– 91% of patients (table 2). The odds of resolution of meningitis were ~28-fold greater when the serum RPR titer had normalized than when it had not. After controlling for normalization of serum RPR titer, the odds of resolution of meningitis were ~13-fold higher among patients receiving ART than among patients who were not receiving ART (table 4). In this multivariate analysis, normalization of serum RPR titer conferred an estimated 45-fold increase in the odds of resolution of meningitis. Normalization of serum RPR titer predicted resolution of eye disease in 86%–95% of patients (table 2). However, the small number of patients with available data prevented further assessment of this relationship.

Misclassification of normalization of CSF and clinical measures

We defined misclassification as a situation in which the serum RPR titer had normalized but the CSF or clinical abnormalities had not. Thirty-six (37%) of 98 patients did not experience normalization of at least CSF or clinical abnormality when serum RPR titer had normalized. In 24 (67%) of the 36 patients, the only measurement that did not normalize was CSF protein concentration. Misclassification of any CSF or clinical abnormality was more common among patients who were not receiving ART than among those who were receiving ART (21 [50%] of 42 patients vs. 1 [8%] of 13 patients; $P = .007$); however, misclassification was not significantly associated with pretreatment serum RPR titer, syphilis stage, HIV status, or $CD4^+$ T cell count or log plasma HIV RNA level.

DISCUSSION

When patients have symptomatic neurosyphilis, success of therapy is assessed by normalization of CSF abnormalities, including pleocytosis, elevated protein concentration, or a reactive CSF VDRL test, and by resolution of symptoms and signs. If neurosyphilis is asymptomatic, normalization of CSF measures is the only means of assessing treatment success. Current guidelines recommend that CSF be examined 6 months after completion of neurosyphilis treatment and that examinations be repeated until the CSF profile is normal [4]. No large study has examined the frequency of neurosyphilis treatment failure, but case reports and small series have reported treatment failure, particularly among HIV-infected patients [10,11].

In this cohort of patients treated specifically for neurosyphilis, we determined the positive predictive value of normalization of serum RPR titer for normalization of CSF WBC count, CSF protein concentration, and CSF VDRL titer and resolution of meningitis and ocular disease by 4, 7, and 13 months after treatment of neurosyphilis. Normalization of serum RPR titer predicted normalization of all measures except CSF protein concentration with a high degree of certainty The odds of resolution of eye disease could not be determined because of insufficient data, but the odds of normalization of the remaining measures were significantly higher when serum RPR titer had normalized than they were when serum RPR titer had not normalized (~28-fold higher for CSF protein concentration and meningitis, ~42-fold higher for CSF WBC count, and ~57-fold higher for CSF VDRL titer).

We examined whether additional laboratory or clinical abnormalities affected the odds of normalization of CSF abnormalities or resolution of meningitis after taking into account the effect of normalization of serum RPR titer. Compared with patients who were receiving ART, patients who were not receiving ART had decreased odds of normalization of CSF WBC count and CSF protein concentration and of resolution of meningitis. The odds of normalization of CSF WBC count and CSF VDRL titer were significantly lower when the pretreatment serum RPR titer was ≥1:32. Some associations were seen only with normalization of a single CSF

measure and, thus, may be of less importance; high pretreatment CSF WBC count increased and treatment with IM APPG plus probenecid significantly decreased only the odds of normalization of CSF WBC count. The odds of normalization of CSF protein concentration were lower among patients with early syphilis than among patients with late syphilis; this was the only variable that differed between these groups. In these multivariate analyses, normalization of serum RPR titer conveyed an order of magnitude greater effect on the odds of normalization of CSF abnormalities and resolution of meningitis, compared with all other variables investigated.

Overall, our data reveal that normalization of serum RPR titer is a good predictor of normalization of CSF measures after treatment of neurosyphilis. However, its accuracy is lower among HIV-infected patients with neurosyphilis who are not receiving ART than among HIV-infected patients who are receiving ART. This finding cannot be explained by falsely attributing elevated CSF WBC count and protein concentration to neurosyphilis when they are actually a result of HIV infection. We repeated our analysis, restricting it to patients with both a reactive CSF VDRL and elevated CSF WBC count or elevated CSF protein concentration. The association between normalization of CSF WBC count and use of ART remained statistically significant, and the association of CSF protein concentration and use of ART trended toward statistical significance. In a previous study, we showed that, after neurosyphilis treatment, CSF protein concentration remained elevated despite normalization of other CSF measures [12]. This finding was independent of HIV status. In the current study, we also found that CSF protein concentration was often the only measure that did not normalize. Taken together, these data suggest that the definition of elevated protein concentration may be too conservative or that the time to normalization of CSF protein concentration after successful neurosyphilis treatment may be longer than the time to normalization of other CSF and clinical measures.

Our study has limitations. Eighty percent of our patients were infected with HIV, and two-thirds had early syphilis. However, the odds of resolution of CSF and clinical abnormalities when serum RPR titer had normalized were high, even when we took into account HIV status or stage. Regardless of whether serum RPR titer had normalized, the odds of normalization of CSF WBC count among patients who received IM APPG plus probenecid were 60% lower than such odds among patients who received IV aqueous penicillin G. These associations were not seen for normalization of other CSF and clinical abnormalities and are of uncertain significance. Neurosyphilis treatment allocation was not random but was determined by the referring provider. Thus, our finding regarding the influence of IV versus IM therapy should be interpreted cautiously and does not warrant modification of recommended therapy regimens at this time.

We emphasize that our data regarding the predictive value of normalization of serum RPR titer for normalization of CSF and clinical measures are relevant only to patients treated specifically with recommended neurosyphilis regimens. Our data cannot be extrapolated to suggest that normalization of serum RPR titer after standard nonneurosyphilis therapy (for example, with benzathine penicillin G) ensures that neurosyphilis will not occur or that unrecognized asymptomatic neurosyphilis has been adequately treated. In fact, in a recent report involving 49 patients with symptomatic neurosyphilis, 12 had previously received treatment of syphilis, and stage-appropriate treatment was documented for 9. Normalization of serum RPR titer occurred in 6 of these 9 patients, despite development of neurosyphilis [13].

Our study has practical implications for clinicians caring for patients with neurosyphilis. In most instances, normalization of serum RPR titer correctly predicts normalization of CSF and clinical measures after neurosyphilis treatment, and follow-up lumbar puncture can be avoided. However, using the serum RPR criterion, 12%–37% of individuals will be misclassified as experiencing treatment success. Among HIV-infected individuals, misclassification is most

common in those not receiving ART. Ideally, our data should be replicated in a randomized, blinded treatment trial or in a larger observational study of CSF and clinical outcomes in patients treated for neurosyphilis who receive follow-up serological testing. Because of cost and logistical issues, neither of these studies is likely to be performed. Clinicians will need to weigh the applicability of our data to their patients on a case-by-case basis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of the study patients.

Characteristic	Patients (*n* = 110)
Male sex	106/110 (96)
Age, median years (IQR)	37 (31–42)
Duration of follow-up, median months (IQR)	12.4 (7.9–13.5)
HIV infection	86/110 (78)
Peripheral blood $CD4^+$ T cell count,[a] median cells/cells/μL (IQR)	401 (256–519)
Log_{10} plasma HIV RNA level,[a] median copies/mL (IQR)	4.44 (3.09–5.15)
Currently receiving antiretroviral therapy	14/62 (23)
CSF WBC count	
>20 cells/μL	74/110 (67)
Median cells/μL (IQR)	45 (31–80)
Normalized by final follow-up visit	67/74 (90)
CSF protein concentration	
>50 mg/dL	68/109 (62)
Median mg/dL (IQR)	69 (59–89)
Normalized by final follow-up visit	33/68 (48)
Reactive CSF VDRL	60/110 (54)
Median CSF VDRL titer (IQR)	2 (1–4)
CSF VDRL titer normalized by final follow-up visit	56/60 (93)
Median serum RPR titer (IQR)	128 (16–256)
Serum RPR titer normalized by final follow-up visit	98/110 (89)
Stage of syphilis	
Early	68/98 (69)
Late[b]	30/98 (31)
Syphilitic meningitis[c]	37/109 (34)
Meningitis resolved by final follow-up visit	34/37 (92)
Syphilitic eye disease[d]	23/107 (21)
Syphilitic eye disease resolved by final follow-up visit	20/23 (87)

NOTE. Data are no. (%) of patients, unless otherwise indicated. IQR, interquartile range; RPR, rapid plasma reagin; VDRL, venereal disease research laboratory.

[a] Data are for 85 patients.

[b] Includes syphilis of unknown duration.

[c] Syphilitic meningitis was defined as new onset of ≥1 of: at least moderate headache, at least moderate subjective hearing loss, decreased hearing to finger friction test on neurological examination.

[d] Syphilitic eye disease was defined as new onset of subjective visual loss and/or visual acuity in either eye that was ≥20/200, as measured using a hand-held screener or a wall-mounted Snellen chart.

Table 2

Normalization of CSF measures in patients whose serum rapid plasma reagin (RPR) titer had normalized by the time of each visit.

	Time after neurosyphilis treatment, months					
	4		7		13	
Variable	PPV	NPV	PPV	NPV	PPV	NPV
CSF WBC count	39/43 (91)	23/28 (82)	56/61 (92)	5/8 (62)	60/62 (97)	1/3 (33)
CSF protein concentration	18/39 (46)	21/25 (84)	27/52 (52)	4/7 (57)	30/40 (75)	2/3 (67)
CSF VDRL titer	30/32 (94)	21/26 (81)	46/51 (90)	3/5 (60)	50/53 (94)	1/1 (100)
Meningitis[a]	20/25 (80)	10/12 (83)	29/33 (88)	2/3 (67)	30/33 (91)	0/1 (0)
Eye disease[b]	12/14 (86)	6/9 (67)	17/20 (85)	2/3 (67)	20/21 (95)	NA

NOTE. Positive predictive value (PPV) was calculated as the number of patients in whom both CSF or clinical abnormalities and serum RPR titer normalized divided by the sum of these patients and the number of patients in whom CSF or clinical abnormalities did not normalize but serum RPR titer did normalize. The PPV is the percentage of patients in whom normalization of serum RPR titer predicts normalization of the CSF or clinical measure. Negative predictive value (NPV) was calculated as the number of patients in whom both CSF or clinical abnormalities and serum RPR titer did not normalize divided by the sum of these patients and the number of patients in whom CSF or clinical abnormalities normalized but serum RPR titer did not. The NPV is the percentage of patients in whom nonnormalization of serum RPR titer predicts nonnormalization of CSF or clinical measures. NA, serum RPR titer normalized in all patients. VRDL, venereal disease research laboratory.

[a] Syphilitic meningitis was defined as new onset of ≥1 of: at least moderate headache, at least moderate subjective hearing loss, decreased hearing to finger friction test on neurological examination.

[b] Syphilitic eye disease was defined as new onset of subjective visual loss and/or visual acuity in either eye that was >20/200, as measured using a hand-held screener or a wall-mounted Snellen chart.

Table 3

Odds of normalization of CSF and clinical abnormalities when serum rapid plasma reagin (RPR) titer had normalized.

Variable	OR (95% CI)	*P*
CSF WBC count	41.5 (19.8–86.8)	<001
CSF protein concentration	28.1 (9.8–80.4)	<001
CSF VDRL titer	57.3 (25.6–128.5)	<001
Meningitis[a]	27.7 (9.6–79.7)	<001

NOTE. VDRL, venereal disease research laboratory.

[a] Syphilitic meningitis was defined as new onset of ≥1 of: at least moderate headache, at least moderate subjective hearing loss, decreased hearing to finger friction test on neurological examination.

Table 4

Odds of normalization of CSF and clinical abnormalities when serum rapid plasma reagin (RPR) titer had normalized, taking into account other measures.

Variable taken into account in addition to normalization of serum RPR titer	OR of normalization (95% C I)			
	CSF WBC count (*n* = 74)	CSF protein concentration (*n* = 68)	CSF VDRL titer[a] (*n* = 59)	Meningitis[b] (*n* = 37)
Pretreatment serum RPR titer ≥1 :32	0.46 (0.22–0.95)[c]	1.1 (0.47–2.6)	0.12 (0.03–0.43)[d]	0.93 (0.45–1.9)
HIV infection	0.28 (0.13–0.57)[e]	0.44(0.19–1.1)	0.86 (0.45–1.6)	0.40 (0.15–1.1)
Use of antiretrovirals to treat HIV infection[f]	3.8 (1.5–9.3)[e]	4.4 (1.3–15.3)[c]	0.76 (0.30–1.9)	13.1 (1.4–118)[c]
High pretreatment value	2.6 (1.4–5.0)[d]	0.50 (0.19–1.31)	0.59 (0.31–1.1)	NA
Intramuscular treatment[g]	0.44 (0.23–0.81)[d]	0.83 (0.38–1.82)	1.3 (0.63–2. 5)	1.7 (0.77–3.9)
Early stage[h]	0.74 (0.43–1.3)	0.41 (0.18–0.93)[c]	1.8 (0.87–3.8)	1.1 (0.43–2.8)

NOTE. NA, not applicable; VDRL, venereal disease research laboratory.

[a] One case of a reactive VDRL test was censored before the earliest event in the stratum.

[b] Syphilitic meningitis was defined as new onset of ≥1 of: at least moderate headache, at least moderate subjective hearing loss, decreased hearing to finger friction test on neurological examination.

[c] $P < .05$.

[d] $P < .01$.

[e] $P < .001$.

[f] Information on use of antiretroviral therapy was available for 62 patients. Data on CSF WBC count were available for 46 patients, data on CSF protein concentration were available for 38, data on CSF VRDL findings were available for 36, and data on meningitis were available for 22.

[g] Data on CSF WBC count were available for 65 patients, data on CSF protein concentration were available for 61, data on CSF VRDL findings were available for 52, and data on meningitis were available for 32.

[h] Information on syphilis stage was available for 98 patients. Data on CSF WBC count were available for 69 patients, data on CSF protein concentration were available for 64, data on CSF VRDL findings were available for 51, and data on meningitis were available for 31. Late stage includes syphilis of unknown duration.