Syphilis Treatment and Outcomes in HIV-Positive Patients: Does a Lumbar Puncture Make a Difference?
Sharon Weissman, MD, Paul Anthony, MD, Merilda Blanco Guzman, MD, and Brent A. Moore, PhD

Abstract

- **Objective:** To determine if lumbar puncture (LP) improves clinical outcomes for HIV+ patients with syphilis who meet Centers for Disease Control and Prevention (CDC) criteria for LP.
- **Methods:** A retrospective review of HIV+ patients with syphilis was conducted. The primary endpoint was treatment failure, defined as serological failure, clinical neurosyphilis, or syphilis retreatment. We compared success versus failure based on whether an LP was done as well as syphilis and HIV demographic characteristics.
- **Results:** 28 cases were included. LP was performed on 10 cases (35.7%). Treatment success was 80% and 82.4% for the LP and no LP groups, respectively. Five patients failed therapy. No patient characteristic predicted failure. All failures were serologic failures. No patient had clinical failure during a mean follow up of 38.2 months.
- **Conclusion:** Our data suggest that LP in HIV patients without clinical symptoms of neurosyphilis did not affect treatment success. Future studies on HIV and syphilis should focus on clinical outcomes.

In order to rule out asymptomatic neurosyphilis, the 2006 CDC guidelines recommend performing an LP for HIV-positive patients with syphilis meeting the following criteria: (a) late latent syphilis, defined as syphilis for more than 1 year, or (b) syphilis of unknown duration [8]. Nevertheless, considerable controversy remains regarding which patients with HIV and syphilis should have an LP performed [9–13]. Some studies suggest that HIV-positive patients with syphilis whose rapid plasma reagin (RPR) titer is ≥ 1:32 or whose CD4 count is ≤ 350 cells/mm³ are at greater risk of having asymptomatic neurosyphilis [9–13]. In these studies, the diagnosis of neurosyphilis is based on surrogate markers such as CSF pleocytosis, elevated CSF protein, and CSF venereal disease research laboratory (VDRL) test [9–13]. Yet HIV alone can alter CSF findings, and thus may lead to an over diagnosis of asymptomatic neurosyphilis [14]. Despite the controversy, based on these studies, the CDC also suggests considering an LP for HIV-positive patients with syphilis who have a CD4 count ≤ 350 cells/mm³ or a serum nontreponemal test titer ≥ 1:32. Some experts even recommend lumbar punctures for all HIV-infected individuals [8].

In practice many patients meeting CDC guidelines for an LP do not have an LP performed. Numerous reasons for not performing an LP have been cited, including logistic, economic, and time constraints or patient refusal [9,15]. Furthermore, controversy exists regarding the significance of LP results in asymptomatic HIV-positive patients with syphilis [9,11,14]. The goal of this study is to review our experience in the evaluation and treatment of patients with HIV and syphilis meeting criteria for LP and compare long-term outcomes between those who did and did not have the procedure done.

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**Methods**

This study was conducted with the approval of the institutional review board, Hospital of Saint Raphael. Outpatient charts were reviewed for all HIV-infected patients seen between 1 Jan 1997 and 31 Dec 2008 who had positive nontreponemal test (RPR or VDRL) and a positive confirmatory fluorescence treponemal antibody absorption test. Only patients whose initial nontreponemal titer was 1:4 or greater were included in the analysis. Patients with nontreponemal titers less than 1:4 were excluded as it would be difficult to determine if the patient had successful serological response to therapy. The following data were extracted: demographics (age, race, HIV risk factor), CD4 count at the time of syphilis diagnosis, CD4 cell count nadir, HIV viral load at the time of syphilis diagnosis, current use and history of antiretroviral therapy (ART), nontreponemal titers, syphilis stage (defined according to CDC guidelines [8]), LP result (if performed), and syphilis treatment and response.

Patients were categorized as meeting strict LP criteria based on CDC criteria (late latent or syphilis of unknown duration) or suggested LP criteria (CD4 ≤ 350 cells/mm³ or a serum nontreponemal test titer ≥ 1:32). Asymptomatic neurosyphilis was defined as CSF pleocytosis (white blood cell count > 10 cells/μL), positive CSF VDRL, and/or CSF protein > 50 mg/d in patients without symptoms of neurologic involvement.

Patients meeting LP criteria who had an LP done were compared with those who did not have an LP done. The primary endpoint was treatment failure at 12 months. Treatment failure was defined as (1) evidence of serological failure (defined as failure of nontreponemal titers to decrease fourfold within 12 months of therapy, or a fourfold increase in nontreponemal test titers at any time), (2) evidence of clinical neurosyphilis based on clinical notes, or (3) need for syphilis retreatment or further testing (LP after initial treatment). Charts were also reviewed to determine long-term treatment success, defined as lack of treatment failure at last follow-up or end of study period. Lastly, baseline characteristics between treatment failure patients (failure at 12 months) were compared with treatment success patients to determine if any characteristic was predictive of treatment failure.

**Data Analyses**

Primary analyses were descriptive. Comparisons of patients with an LP to those without an LP and treatment failure versus treatment success at 12 months were performed on all demographic and endpoint measures using the t test for continuous measures and the chi-square test for categorical measures. Distributional properties of all variables were evaluated prior to inferential statistics. Comparisons were made for patients meeting strict LP criteria and suggestive LP criteria. Multivariate analyses were planned but not conducted due to the small sample size.

**Results**

Fifty-four patients with HIV infection and evidence of syphilis based on positive nontreponemal and treponemal syphilis test were identified. Eighteen patients were excluded because the initial nontreponemal titer was less than 1:4. Of the remaining 36 patients, 9 more were excluded from the analysis because syphilis infection occurred prior to HIV diagnosis (4), initial nontreponemal titer was not available (2), or treatment outcome was unable to be assessed (3). Analysis is based on 27 patients, 28 cases. One patient had 2 distinct episodes of syphilis infection. His initial episode of syphilis was treated with 3 doses of 2.4 million IU of intramuscular benzathine penicillin. After treatment his RPR titer went from 1:64 to nonreactive and remained nonreactive for 5 years. He then had another documented exposure to syphilis from a known source. His RPR titer rose to 1:128 and he had a clinical syndrome consistent with secondary syphilis. He again had successful response to treatment. For the analysis, we counted these 2 episodes as separate cases.

Baseline characteristics of the study population are shown in the Table. Most cases occurred in men (86%), particularly men reporting MSM as their HIV risk factor (82%).

**Table. Baseline Demographics**

<table>
<thead>
<tr>
<th>Sex, %</th>
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<tbody>
<tr>
<td>Male</td>
<td>85.7</td>
</tr>
<tr>
<td>Female</td>
<td>14.3</td>
</tr>
<tr>
<td>Mean age, yr</td>
<td>38.4 ± 9.1</td>
</tr>
<tr>
<td>Race, %</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>35.7</td>
</tr>
<tr>
<td>African American</td>
<td>50.0</td>
</tr>
<tr>
<td>Hispanic</td>
<td>14.3</td>
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<tr>
<td>HIV risk factor, %</td>
<td></td>
</tr>
<tr>
<td>MSM</td>
<td>82.1</td>
</tr>
<tr>
<td>Heterosexual</td>
<td>17.9</td>
</tr>
<tr>
<td>Viral load at syphilis diagnosis, undetectable, %</td>
<td>21.4</td>
</tr>
<tr>
<td>CD4 at syphilis diagnosis, %</td>
<td></td>
</tr>
<tr>
<td>&lt; 350 cells/mm³</td>
<td>46.4</td>
</tr>
<tr>
<td>&gt; 350 cells/mm³</td>
<td>53.6</td>
</tr>
<tr>
<td>CD4 nadir prior to syphilis, cells/mm³</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>160.6 ± 145.6</td>
</tr>
<tr>
<td>Median</td>
<td>122.5</td>
</tr>
<tr>
<td>HAART, %</td>
<td>42.9</td>
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</table>

HAART = highly active antiretroviral therapy; MSM = men who have sex with men.
Less than half the patients (43%) were on ART at the time of the syphilis diagnosis. Only 22% had an undetectable viral load at the time of syphilis diagnosis and 46% had CD4 count ≤ 350 cells/mm$^3$. There was no difference in baseline characteristics between those who had an LP and those who did not (all $P$ values > 0.10).

Figure 1 compares treatment outcomes between the LP and no LP groups and gives a breakdown by LP criteria. All cases met either strict or suggested LP criteria. The majority of cases met more than 1 LP criteria. Seventeen cases met strict CDC LP criteria, presenting with late latent syphilis or syphilis of unknown duration. Syphilis stage at presentation for the remaining cases was secondary syphilis (10) and primary syphilis (1). Treatment success was 80% and 82.4% for the LP and no LP groups, respectively. Three of 17 (17.6%) patients meeting strict LP criteria and 4 of 25 (16%) patients meeting suggested LP criteria failed therapy at 12 months. There was no difference in treatment failure versus success based on any of the LP criteria. All treatment failures were based on lack of serological response. There were no clinical failures.

Ten patients had an LP performed (Figure 1). There was evidence of asymptomatic neurosyphilis in 4 cases (based on CSF pleocytosis and elevated CSF protein). None of the patients had a reactive CSF VDRL. One patient with asymptomatic neurosyphilis was treated with oral doxycycline. He had a history of severe penicillin allergy. He was initially treated with a combination of oral doxycycline and intravenous ceftriaxone. He failed to achieve a serological response and thus was successfully retreated with intravenous penicillin after desensitization. The other failure in the LP group was initially treated with a standard intravenous penicillin course. He failed to achieve a serological response and thus was retreated. He had a late serological relapse at 45 months and required retreatment (Figure 2). At 98 months he remains both a serological and clinical success. The other 6 patients in the LP group, none of whom had asymptomatic neurosyphilis, were all successfully treated with intramuscular penicillin. Eighteen patients did not have an LP. In the no LP group, 3 patients met the primary endpoint (failing initial syphilis treatment). Failure was based on a lack of serological response at 12 months. One of these failures was treated with doxycycline. He was retreated twice but never achieved serological success. The other two failures were treated with intramuscular penicillin. Despite retreatment none ever achieved a successful serological response during a mean follow-up of 45 months. For the other 15 patients in the no LP group, one was treated with doxycycline. The others received intramuscular penicillin. Fourteen of these 15 patients had successful serological response at 12 months. One patient had a successful response at 6 months (RPR went from 1:256 to 1:2) but did not have further nontreponemal testing.

There was no difference in treatment failure between the LP and no LP groups. In addition, there was no difference in treatment failure according to baseline CD4 count, non-treponemal titer, or syphilis stage. Although 5 patients had evidence of treatment failure based on a lack of serological
response, none of the patients developed evidence of clinical symptoms to suggest neurosyphilis or treatment failure during a mean follow-up of 38.2 months.

**Discussion**

Controversy exists regarding the use of LP in HIV-infected patients with syphilis and no symptoms of neurosyphilis [9–13]. Although the CDC recommends a LP for the HIV infected patient with late latent or syphilis of unknown duration many experts recommend considering an LP for any HIV infected patient with syphilis and a CD4 ≤ to 350 cells/mm³ or a serum nontreponemal test titer ≥ 1:32, regardless of syphilis stage or symptoms [8,9,11,12]. Such an approach would add considerably to the number of LPs needed. LPs require additional resources, time, and expense and potentially lead to additional more aggressive therapies. Diagnosis of asymptomatic neurosyphilis in HIV-infected patients using CSF pleocytosis and/or elevated protein is problematic. HIV can alter CSF findings leading to overdiagnosis of asymptomatic neurosyphilis. The prognostic significance of CSF pleocytosis or elevated protein in HIV-infected patients is unknown [10,13,14]. In a recent survey of infectious disease experts, there was variability in performing LP for syphilis in HIV-infected patients. Providers with more HIV experience were less likely to perform an LP [15].

In our series, LP did not impact treatment failure. LP performance in HIV patients without symptoms of neurosyphilis did not affect clinical outcomes at 12 months of follow-up. This observation was independent of the criteria used as indications for LP, syphilis stage, nontreponemal titer, and certain characteristics related to HIV, including CD4 counts and viral load. Importantly there were no clinical failures at 12 months or during long-term monitoring of the patients.

Using CDC's criteria for LP (late latent syphilis or syphilis of unknown duration), 17 patients would have required an LP. If the suggested criteria of CD4 ≤ 350 cells/mm³ or a serum nontreponemal test titer ≥ 1:32 were also included, an additional 11 LPs would have been required. If only the suggested LP criteria were applied, then 25 of the 28 cases would have required an LP. This would have led to additional expenses, patient discomfort and potentially more aggressive therapies with complications and expenses. Our data do not suggest that a more aggressive diagnostic and treatment approach would have led to better clinical outcomes.

Early in the HIV epidemic, there were many reported cases of HIV-infected individuals with early symptomatic neurosyphilis or late relapses of clinical neurosyphilis despite adequate syphilis therapy. It is postulated that the depressed cellular immunity associated with HIV leads to slower clearance of the syphilis treponemes [4,7]. We did not find any cases of early or relapsed symptomatic neurosyphilis. One explanation for the difference may be the use of ART leading to immune restoration. Although the majority of our cases were not on ART at the time of their syphilis diagnosis, these patients were eventually started on ART and showed

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**Figure 2.** Long-term follow-up: serologic failures. LP = lumbar puncture.
improvements in CD4 counts. HIV-infected patients with higher CD4 counts or treatment with ART have improved serological syphilis response [16,17]. It may be that with the widespread use of ART symptomatic neurosyphilis in HIV-infected patients will become rare.

Our study has several limitations. The retrospective nature and small sample size precludes strong correlations. There were few LPs performed in our series and only 4 cases of asymptomatic neurosyphilis diagnosed. None of our cases had a positive CSF VDRL, which may be a stronger indicator of asymptomatic neurosyphilis [12,13]. Many cases were excluded from the analysis because of a low initial nontreponemal titer. We used 12-month serological response rather than 24 months (as suggested by CDC for latent syphilis) to determine failure. This may overestimate failure. Despite these limitations, our data reflect true-life clinical practice in which LPs are often not done despite CDC and other recommendations. Patients are often reluctant to have LP, and clinic time, clinician training, and space limits the ability to perform LP. In addition, uncertainty of the significance of LP findings in patients with HIV and syphilis leads to confusion regarding the need to perform an LP. Our data is reassuring in that, despite the low number of LPs done, we saw no evidence of clinical neurosyphilis develop during long-term follow-up of our HIV infected patients with syphilis. We recommend that future studies of syphilis and HIV focus on clinical outcomes in addition to surrogate markers of asymptomatic neurosyphilis.

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References