High-Dose Oral Amoxicillin Plus Probenecid Is Highly Effective for Syphilis in Patients With HIV Infection

Ryutaro Tanizaki,1 Takeshi Nishijima,1 Takahiro Aoki,1 Katsuji Teruya,1 Yoshimi Kikuchi,1 Shinichi Oka,1,2 and Hiroyuki Gatanaga1,2

1AIDS Clinical Center, National Center for Global Health and Medicine, Tokyo, and 2Center for AIDS Research, Kumamoto University, Japan

Background. Intramuscular benzathine penicillin G (BPG) is widely used for the treatment of syphilis. However, BPG is not available in some countries. This study examined the effectiveness and safety of high-dose oral amoxicillin plus probenecid for the treatment of syphilis in patients with human immunodeficiency virus type 1 (HIV-1).

Methods. This retrospective observational study included 286 HIV-infected male patients with syphilis (median age, 36 years; median CD4 count, 389 cells/µL) who were treated with oral amoxicillin 3 g plus probenecid. Syphilis was diagnosed by both serum rapid plasma reagin (RPR) titers ≥8 and positive Treponema pallidum hemagglutination test. Patients with neurosyphilis diagnosed by cerebrospinal fluid examination were excluded. Successful treatment was defined as a at least 4-fold decrement in RPR titer.

Results. The overall treatment efficacy was 95.5% (95% confidence interval [CI], 92.4%–97.7%; 273/286 patients), and efficacy for primary, secondary, early latent, late latent, and unknown duration syphilis was 93.8% (95% CI, 68.1%–99.8%; 15/16), 97.3% (95% CI, 92.9%–99.2%; 142/146), 100% (95% CI, 90.5%–100%; 37/37), 85.7% (95% CI, 58.6%–96.4%; 18/21), and 92.4% (95% CI, 81.9%–97.3%; 61/66), respectively. Treatment duration was mostly 14–16 days (49.7%) or 28–30 days (34.3%), with efficacy of 94.4% (134/142) and 95.9% (94/98), respectively; 96.3% of successfully treated patients achieved a ≥4-fold decrement in RPR titer within 12 months. Adverse events were noted in 28 (9.8%) patients, and 25 of these (89.3%) were successfully treated. Only 6% of patients underwent lumbar puncture.

Conclusions. The combination of oral amoxicillin 3 g plus probenecid was highly effective and tolerable for the treatment of syphilis in patients with HIV-1 infection.

Keywords. syphilis; amoxicillin; HIV; MSM; treatment.

Syphilis is a common sexually transmitted infection caused by Treponema pallidum, and in recent years, an increase in the number of cases with syphilis has been reported among men who have sex with men (MSM), particularly among those with human immunodeficiency virus type 1 (HIV-1) infection in resource-rich settings [1, 2]. A recent study of syphilis in HIV-1–infected men, comprised mostly of MSM, showed that syphilis is associated with an increase in HIV-1 RNA load and with a small decrement in CD4 cell count, suggesting that syphilis may increase a risk of HIV-1 transmission. Furthermore, progression to neurosyphilis may be faster in HIV-1–infected patients than patients without HIV-1 infection [4–6], and HIV-1 infection may exacerbate the clinical symptoms of neurosyphilis [7]. For the above-mentioned reasons, early diagnosis and treatment of syphilis are important in HIV-infected patients.

One-shot intramuscular benzathine penicillin G (BPG) injection is widely used for the treatment of primary, secondary, and early latent syphilis based on its high efficacy and convenience [8–10]; however, intramuscular injection is painful and, for the treatment of

Received 9 January 2015; accepted 21 March 2015; electronically published 31 March 2015.
Correspondence: Takeshi Nishijima, MD, AIDS Clinical Center, National Center for Global Health and Medicine, 1-21-1, Toyama, Shinjuku, Tokyo 162-0052, Japan (tnishiji@acc.nogm.go.jp).

Clinical Infectious Diseases® 2015;61(2):177–83
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DOI: 10.1093/cid/civ270
late latent syphilis and syphilis of unknown duration, 3 injec-
tions at 1-week intervals (3 hospital visits in total) is required. BPG is not available in some countries, including Japan [11,12], and oral amoxicillin plus probenecid has been used as an alter-
native for BPG in the treatment of syphilis.

However, there is no evidence available on the efficacy and safety of oral amoxicillin plus probenecid for the treatment of syphilis; the only available evidence is from pharmacokinetic studies published in the 1970s–1980s [13, 14].

We investigated the efficacy and safety of high-dose oral amoxicillin (3 g) plus probenecid for the treatment of syphilis (excluding neurosyphilis) in patients with HIV-1 infection in an observational setting.

**METHODS**

**Patients and Study Design**

We conducted a retrospective cohort study of HIV-1–infected pa-
tients with syphilis to investigate the efficacy and safety of oral amoxicillin plus probenecid for the treatment of syphilis at the AIDS Clinical Center, National Center for Global Health and Medicine (NCGM), Tokyo, Japan. The enrollment criteria were HIV-1–infected patients who were diagnosed with syphilis and started treatment with 3 g oral amoxicillin plus probenecid at our center between January 2000 and June 2014. We included all patients treated with the combination of 3 g amoxicillin and probenecid, irrespective of the dose of the latter. The diagnosis of syphilis was based on both serum rapid plasma regain (RPR) titers ≥8 and positive T. pallidum hemagglutination (TPHA) result [15]. The following exclusion criteria were applied: (1) lack of follow-up tests, (2) patients with neurosyphilis diagnosed based on the findings of cerebrospinal fluid (CSF) [16], or ocular or auditory syph-
ilis, (3) patients who started treatment with antibiotics other than 3 g amoxicillin plus probenecid, (4) patients with clinical symp-
toms compatible with primary or secondary syphilis but RPR titers <8, (5) patients suspected of reinfection after initiation of syphilis treatment (≥4-fold rise in RPR titer after 4-fold decre-
ment with or without symptoms) [15, 17].

**Data Collection**

Data on the following parameters were collected at the time of treatment of syphilis: stage of syphilis infection, age, sex, race, route of HIV-1 infection, antiretroviral therapy (ART) use, history of syphilis treatment, status of hepatitis B and C infection, RPR titer, CD4 count, and HIV-1 RNA load. The stage of syphilis was classified into early syphilis (including primary, secondary, and early latent syphilis) and late syphilis (including late latent syphilis and syphilis of unknown duration) [8, 9]. Early latent syphilis was defined as asymptomatic syphilis that was confirmed to be infected within a year from the day of diagnosis, and late latent syphilis was defined as asymptomatic syphilis confirmed to be infected more than a year before diagnosis [8, 9]. Syphilis with unknown duration was defined as asymptomatic syphilis that could not be classified into either early latent or late latent syphilis [8, 9]. The methods of amoxicillin and probenecid adminis-
tration, treatment duration, treatment efficacy, adverse events during treatment, and changes to doxycycline from amoxicillin were also collected from the medical records. Among the adverse events, the presence of fever and/or acute exacerbation of macu-
lopupular skin rash within 24 hours of administration of amoxi-
cillin was defined as Jarisch-Herxheimer reaction for syphilis and was not regarded as drug-related adverse events [18].

Successful treatment of syphilis was defined as at least 4-fold decre-
ment in RPR titer within 24 months after initiation of treat-
ment. Follow-up serum RPR titer was examined at the discretion of the attending physician. Because at our clinic, written in-
formed consent was obtained from each patient to store serum samples at the first and subsequent visits [19], the RPR data based on stored samples were also used to supplement the RPR data from daily clinical practice order to determine treatment re-
sponse and the syphilis staging. RPR Test “Sankoh” (EIDIA Co, Ltd, Tokyo, Japan) was used for the measurement of RPR titer both in clinical practice and with stored samples.

Patients visited our clinic at least once every 3 months for monitoring and prescription, as the prescription period under the Japanese healthcare system is limited to 3 months [20]. The study was approved by the Human Research Ethics Commit-
tee of NCGM, and was conducted according to the princi-

**Statistical Analysis**

The study patients were classified according to the results of the combination treatment into the success group (patients with successful treatment of syphilis) and failure group (failure of treatment). The baseline characteristics were compared between the 2 groups using the Student t test or χ² test (Fisher exact test when appropriate) for continuous or categorical variables, re-

**RESULTS**

During the study period, 403 HIV-1–infected patients were di-
agnosed with syphilis. One hundred seventeen patients were ex-
cluded from the study based on the inclusion and exclusion criteria set for this study (Figure 1), and data of the remaining
286 patients were analyzed. All study patients were men with a median age of 36 years (interquartile range [IQR], 30–42 years). They were mostly Asians who were infected with HIV-1 through homosexual contact. The median CD4 count was 389 cells/µL (IQR, 276–538 cells/µL), ART had been started in 156 (54.5%) patients, and 170 patients (59.4%) had a history of syphilis treatment. Primary syphilis, secondary syphilis, early latent syphilis, late latent syphilis, and syphilis with unknown duration were diagnosed in 16 (5.6%), 146 (51.0%), 37 (12.9%), 21 (7.3%), and 66 (23.1%) patients, respectively. Furthermore, 199 (69.6%) patients were categorized with early syphilis, which included primary, secondary, and early latent syphilis, and 87 (30.4%) with late syphilis, which included late latent syphilis and syphilis of unknown duration.

Treatment with 3 g oral amoxicillin and probenecid decreased RPR titer by 4-fold and was thus regarded successful in 273 (95.5% [95% CI, 92.4%–97.7%]) patients (success

Figure 1. Patient enrollment process. Abbreviations: HIV-1, human immunodeficiency virus type 1; RPR, rapid plasma reagin.

Table 1. Baseline Characteristics of the Study Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (N = 286)</th>
<th>Patients With Successful Treatment (n = 273)</th>
<th>Patients With Treatment Failure (n = 13)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y⁰</td>
<td>36 (30–42)</td>
<td>36 (30–42)</td>
<td>30 (24–37)</td>
<td>.003</td>
</tr>
<tr>
<td>Male sex</td>
<td>286 (100)</td>
<td>273 (100)</td>
<td>13 (100)</td>
<td></td>
</tr>
<tr>
<td>Asian race</td>
<td>281 (98.3)</td>
<td>268 (96.2)</td>
<td>13 (100)</td>
<td></td>
</tr>
<tr>
<td>Route of HIV-1 transmission</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homosexual</td>
<td>274 (95.8)</td>
<td>262 (96.0)</td>
<td>11 (84.6)</td>
<td></td>
</tr>
<tr>
<td>Heterosexual</td>
<td>7 (2.4)</td>
<td>6 (2.2)</td>
<td>1 (7.7)</td>
<td></td>
</tr>
<tr>
<td>Injection drug user</td>
<td>3 (1.0)</td>
<td>2 (0.7)</td>
<td>1 (7.7)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (0.7)</td>
<td>2 (0.7)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>ART use</td>
<td>156 (54.5)</td>
<td>150 (54.9)</td>
<td>6 (46.2)</td>
<td>.579</td>
</tr>
<tr>
<td>History of syphilis treatment</td>
<td>170 (59.4)</td>
<td>163 (59.7)</td>
<td>7 (53.8)</td>
<td>.775</td>
</tr>
<tr>
<td>Stage of syphilis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early syphilis</td>
<td>199 (69.6)</td>
<td>194 (71.1)</td>
<td>5 (38.5)</td>
<td>.025⁰</td>
</tr>
<tr>
<td>Primary</td>
<td>16 (5.6)</td>
<td>15 (5.5)</td>
<td>1 (7.7)</td>
<td></td>
</tr>
<tr>
<td>Secondary</td>
<td>146 (51.0)</td>
<td>142 (52.0)</td>
<td>4 (30.8)</td>
<td></td>
</tr>
<tr>
<td>Early latent</td>
<td>37 (12.9)</td>
<td>37 (13.6)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Late syphilis</td>
<td>87 (30.4)</td>
<td>79 (28.9)</td>
<td>8 (61.5)</td>
<td></td>
</tr>
<tr>
<td>Late latent</td>
<td>21 (7.3)</td>
<td>18 (6.6)</td>
<td>3 (23.1)</td>
<td></td>
</tr>
<tr>
<td>Unknown duration</td>
<td>66 (23.1)</td>
<td>61 (22.3)</td>
<td>5 (38.5)</td>
<td></td>
</tr>
<tr>
<td>Baseline RPR titer⁰</td>
<td>96 (32–128)</td>
<td>128 (32–128)</td>
<td>64 (32–128)</td>
<td>.510</td>
</tr>
<tr>
<td>CD4 count, cells/µL⁰</td>
<td>389 (276–538)</td>
<td>393 (285–542)</td>
<td>286 (180–369)</td>
<td>.003</td>
</tr>
<tr>
<td>HIV-1 load, log₁₀ copies/mL⁰</td>
<td>2.06 (1.70–4.49)</td>
<td>1.91 (1.70–4.45)</td>
<td>4.26 (3.04–4.70)</td>
<td>.048</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>35 (12.2)</td>
<td>35 (12.8)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Positive HBsAg</td>
<td>30 (10.5)</td>
<td>30 (11.0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Positive HCV antibody</td>
<td>5 (1.7)</td>
<td>5 (1.8)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Lumbar puncture performed</td>
<td>17 (5.9)</td>
<td>12 (4.4)</td>
<td>5 (38.5)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Data are presented as No. (%) unless otherwise specified.
Abbreviations: ART, antiretroviral therapy; HBsAg, hepatitis B surface antigen; HCV, hepatitis C; HIV-1, human immunodeficiency virus type 1; RPR, rapid plasma reagin.

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group). Among 13 patients with treatment failure (failure group), none showed any evidence of clinical failure. The baseline HIV-1 load was lower in the success group than the failure group, whereas the baseline CD4 count was higher in the success group. Lumbar puncture for the examination of CSF was performed before treatment initiation in only 17 (5.9%) patients, including 13 patients with late syphilis, and neurosyphilis was ruled out in all 17 patients based on negative TPHA in the CSF [16]. The treatment efficacy of primary, secondary, early latent, late latent, and unknown duration syphilis was 93.8% (95% CI, 68.1%–99.8%; 15/16 patients), 97.3% (95% CI, 92.9%–99.2%; 142/146), 100% (95% CI, 90.5%–100%; 37/37), 85.7% (95% CI, 58.6%–96.4%; 18/21), and 92.4% (95% CI, 81.9%–97.3%; 61/66), respectively (Table 1). Also, the treatment efficacy for early syphilis (including primary, secondary, and early latent syphilis) and late syphilis (including late latent syphilis and syphilis of unknown duration) was 97.5% (95% CI, 94.1%–99.2%) and 90.8% (95% CI, 82.6%–96.4%), respectively. Treatment duration was mostly 14–16 days (49.7%) or 28–30 days (34.3%), with 94.4% (134/137) and 95.9% (94/98) efficacy, respectively. Among patients with early syphilis, treatment efficacy did not differ between the 2-week treatment and 4-week treatment (105 of 107 [98.1%] vs 109 of 113 [96.5%]; P = .49 by Fisher exact test). However, among patients with late syphilis, treatment efficacy tended to be lower among patients treated for 2 weeks than those treated for 4 weeks, although the difference was not statistically significant (29 of 35 [82.9%] vs 34 of 36 [94.4%]; P = .15). The frequency of oral amoxicillin administration was mainly 3 times a day (80.8%) with 96.1% (222/231) efficacy. The dosage of probenecid was 0.75 g/day in the majority of patients (60.1%), 1.0 g/day (23.4%), and 1.5 g/day (13.3%), with success rate of 96.5% (166/172), 92.5% (62/67), and 94.7% (36/38), respectively (Table 2). For patients with successful treatment, the median time for the documentation of ≥4-fold decrement in RPR titer after treatment was 4 months (IQR, 3–6 months), and 96.3% of the success group achieved the ≥4-fold decrease in RPR titers within 12 months (Figure 2). The median number of follow-up RPRs for the success group and the failure group was 1 (IQR, 1–2) and 4 (IQR, 2–6), respectively, and follow-up RPRs were more frequently measured for the failure group than for the success group (P < .001).

Adverse events related to treatment of syphilis were recorded in 28 (9.8%) patients, with skin rash being the most common symptom (n = 21), followed by fever (n = 9), diarrhea (n = 2),...
and elevated liver enzymes (n = 1). Furthermore, 5 patients presented with both rash and fever. Analysis of the medical records showed that treatment with amoxicillin was changed to doxycycline in 21 (75%) patients due to the side effects. Despite the adverse events, treatment was considered successful in 25 of the 28 (89.3%) patients. Among the 7 patients who showed adverse events but did not change amoxicillin to doxycycline, treatment was successful in 6, although amoxicillin was administered for the median of only 10 days (IQR, 10–18 days). None of the patients discontinued amoxicillin due to Jarisch-Herxheimer reaction.

Logistic regression analysis was performed to identify the risk factors associated with treatment failure. Univariate analysis demonstrated that late syphilis (OR, 3.9 [95% CI, 1.25–12.4]; P = .019) and high HIV-1 load (per 1 log_{10} copies/mL: OR, 1.5 [95% CI, 1.03–2.26]; P = .033) before treatment were associated with treatment failure (Table 3). On the other hand, older age was associated with successful treatment (per 1 year: OR, 0.9 [95% CI, .84–.99]; P = .025), and higher CD4 count was also marginally associated (per 1 cell/µL: OR, 1.0 [95% CI, .99–1.00]; P = .053).

**DISCUSSION**

The present study investigated the treatment efficacy of 3 g oral amoxicillin plus probenecid for early and late syphilis among HIV-1–infected patients in an observational setting. The results showed that 95.5% of the study patients were successfully treated based on 4-fold decrement in RPR titer. Treatment efficacy was 97.5% in patients with early syphilis (including primary, secondary, and early latent syphilis) and 90.8% in patients with late syphilis (including late latent syphilis and syphilis with unknown duration). This high treatment efficacy is surprising considering that our study population could have included asymptomatic neurosyphilis, because neurosyphilis in HIV-infected patients could occur even in early syphilis without clinical symptoms [5, 6], and most study patients (94.1%) did not undergo lumbar puncture for CSF examination. Furthermore, because increased rate of treatment failure has been reported in HIV-1–infected patients compared with noninfected patients [21, 22], the treatment efficacy shown in this study can be generalized to or could be even better among patients without HIV-1 infection. The regimen of 3 g oral amoxicillin plus probenecid was highly tolerable as well; only 28 (9.8%) patients experienced adverse events, and amoxicillin was switched to doxycycline in only 21 (7.3%) patients. It is also noteworthy that treatment of syphilis was successful in 89.3% of the patients who developed adverse events. Thus, high-dose oral amoxicillin (3 g) plus probenecid can be considered the treatment of choice for early syphilis, late latent syphilis, and syphilis of unknown duration where intramuscular BPG is not available or 3 injections of intramuscular BPG at 1-week intervals is not feasible or is inconvenient to patients with late syphilis.

In the present study, the treatment duration for most patients was either for 14–16 days (49.7%) or 28–30 days (34.3%). Comparison of treatment efficacy between early and late syphilis according to treatment duration showed that treatment efficacy was similar for both 2-week and 4-week treatment in early syphilis, whereas it tended to be lower for 2-week than 4-week treatment in late syphilis, albeit statistically insignificant (P = .15). Based on these results and considering that the majority of the study patients used 750 mg of probenecid, we recommend 2 weeks of treatment with 3 g oral amoxicillin plus 750 mg

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**Table 3. Results of Univariate Analysis to Estimate Risk Factors for Treatment Failure With Oral Amoxicillin Plus Probenecid for Syphilis**

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 1 y)</td>
<td>0.9 (.84–.99)</td>
<td>.025</td>
</tr>
<tr>
<td>Late syphilis vs early syphilis</td>
<td>3.9 (1.25–12.4)</td>
<td>.019</td>
</tr>
<tr>
<td>HIV-1 load (per 1 log_{10} copies/mL)</td>
<td>1.5 (1.03–.226)</td>
<td>.033</td>
</tr>
<tr>
<td>CD4 count (per 1 cell/µL)</td>
<td>1.0 (.99–1.00)</td>
<td>.053</td>
</tr>
<tr>
<td>ART use</td>
<td>0.7 (.23–2.15)</td>
<td>.536</td>
</tr>
<tr>
<td>History of syphilis treatment</td>
<td>0.8 (.26–2.41)</td>
<td>.675</td>
</tr>
<tr>
<td>Adverse events</td>
<td>3.0 (.77–11.5)</td>
<td>.114</td>
</tr>
</tbody>
</table>

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV-1, human immunodeficiency virus type 1; OR, odds ratio.
probencid for patients with early syphilis and 4 weeks of treatment using the same doses for patients with late latent syphilis and syphilis of unknown duration.

To our knowledge, this is the first study to report the treatment efficacy of high-dose oral amoxicillin plus probenecid for syphilis, regardless of HIV-1 infection status. Although the treatment of oral amoxicillin plus probenecid is described as an alternative syphilis treatment in the UK national guidelines on the management of syphilis [10], previous studies were either only pharmacokinetic studies that examined amoxicillin level in the CSF, or anecdotal, and all of these studies were published in the 1970s and 1980s [13, 14, 23, 24]. It is also noteworthy that amoxicillin, similar to aqueous penicillin, crosses the blood-brain barrier to reach the causative bacteria in the CSF [13, 25], whereas BPG, the preferred choice for early and late syphilis, does not [26]. This might be particularly important for patients with HIV-1 infection because these patients likely present with asymptomatic neurosyphilis, and progression to neurosyphilis is faster in HIV-1–infected patients than in noninfected patients [4–6]. Doxycycline and azithromycin are alternative choices for oral treatment of syphilis for patients with penicillin allergy listed in the guidelines [10]; however, evidence for treatment efficacy of these regimens is limited, particularly among patients with HIV-1 infection [27], and unfortunately, emerging resistance of azithromycin for T. pallidum has been reported [28, 29].

Despite several strengths of our study, such as novelty and large number of patients treated with the same regimen of oral amoxicillin plus probenecid, we acknowledge several limitations. First, cases of early latent syphilis might have been included among those with syphilis of unknown duration, because blood samples 1 year before the diagnosis of syphilis were not necessarily available for all patients. Thus, the treatment efficacy for syphilis of unknown duration might be overestimated. However, because only 5.9% of the study patients underwent lumbar puncture, neurosyphilis might be included in this group as well, suggesting that the treatment efficacy might be underestimated. Second, this study defined successful treatment as a ≥4-fold decrement in RPR titer by 24 months after starting treatment. This criterion was chosen because the serologic response after treatment in HIV–infected patients is slower than that in noninfected patients [21, 30]. Although the long observation period might increase the risk of unexpected antibiotic exposure and might contribute to overestimated treatment efficacy, in this study, 96.3% of patients with successful treatment against syphilis achieved a ≥4-fold decrement in RPR titer within 12 months after treatment (Figure 2). Third, the retrospective nature of the study could have introduced some selection and information biases. In fact, although all study patients were treated with 3 g amoxicillin plus probenecid, the duration of treatment, frequency of drug administration, and probenecid dose were not identical among the study patients. However, as described above, most patients were treated for either 2 weeks or 4 weeks, and the treatment efficacy was equally high (the efficacy of 2 weeks’ treatment tended to be lower than that of 4 weeks among patients with late syphilis, though not statistically significant). Similarly, most (80.8%) patients were treated with amoxicillin 3 times a day, and 60.1% were treated with probenecid 750 mg/day. These are the reasons for recommending 2 weeks of 3 g oral amoxicillin plus 750 mg probenecid for patients with early syphilis and 4 weeks of treatment for patients with late syphilis.

In conclusion, the efficacy of 3 g oral amoxicillin plus 750 mg probenecid daily was very high in HIV–1–infected patients with early and late syphilis. This regimen was also highly tolerable and required only a single hospital visit. Two weeks of this regimen for patients with primary, secondary, and early latent syphilis, and 4 weeks of treatment for late latent syphilis and syphilis of unknown duration are suggested. Three grams of amoxicillin plus probenecid may be an acceptable replacement for intramuscular BPG. Additional prospective studies are warranted.

Notes

Acknowledgments. The authors thank Akiko Nakano, the study coordinator, and all other clinical staff at the AIDS Clinical Center for their help in completion of this study.

Financial support. This work was supported by Grants-in Aid for AIDS research from the Japanese Ministry of Health, Labour, and Welfare (grant numbers H23-AIDS-001 and H24-AIDS-003).

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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