**Optimal Dose of Benzathine Penicillin G for the Treatment of Early Syphilis in HIV-Infected Patients in the Era of Combination Antiretroviral Therapy**

To the Editor—we read with interest the article by Ganesan et al [1] that addresses a key question in syphilis management regarding the optimal dose of benzathine penicillin G (BPG) for the treatment of early syphilis in human immunodeficiency virus (HIV)-infected patients [2]. In this retrospective cohort study of 350 Department of Defense beneficiaries with 393 episodes of early syphilis between 1986 and 2013, the authors found that treatment with 1 dose and 2 or more doses of BPG resulted in a similar rate of a ≥4-fold decline of nontreponemal antibody titers in 141 and 252 cases of early syphilis, respectively, at 13 months of follow-up (92% vs 92%). The study spanned >20 years, during which time the sexually transmitted diseases treatment guidelines have evolved [3] and combination antiretroviral therapy has been introduced. One-fourth of the patients in this study contributed >1 episode of early syphilis, for which different treatment regimens or doses of BPG might be administered for the subsequent episodes. Comparisons of the baseline characteristics of the 2 treatment groups are not shown in the article, which precludes assessment of any confounding factors or bias involved. Furthermore, whether the patients who might have received oral antibiotics for reasons other than syphilis during the follow-up were excluded is not described. Furthermore, limited by the case number, the study was not powered to draw a conclusion that the serological response rates to the 2 different doses of BPG were similar in HIV-infected patients with early syphilis.

The serological response rate in the study by Ganesan et al [1] is significantly higher than that reported in our recently published multicenter prospective cohort study that included 573 HIV-infected patients with early syphilis, in which 198 of 295 patients (67.1%) received 1 dose and 208 of 278 (74.8%) received 3 weekly doses of BPG [4]. In our study, the 2 treatment groups were similar in the clinical characteristics that have been reported to be associated with treatment response, and the sample size was of sufficient power to demonstrate the noninferiority of 1 dose to 3 weekly doses of BPG. At 12 months of treatment, however, we failed to demonstrate that 1 dose was noninferior to 3 doses of BPG given the finding that the 1-sided 95% confidence interval of the difference (15.1%) exceeded the predefined noninferiority margin (10%) [4]. The discrepancy of treatment responses between the study by Ganesan et al and ours may be related to the study design, subjects included for analysis, and definition for treatment failure. In our study, 94% of the patients were men who have sex with men, a population that has been identified as a high-risk group for treatment failure from reinfection [5]. Indeed, we included in the definition of treatment failure those who had an increase of rapid plasma reagin (RPR) titer after ever achieving a ≥4-fold decline within 12 months of treatment with 1 or 3 doses of BPG because it was difficult to differentiate relapse from reinfection solely based on the changes of RPR titers in this observational study. However, a substantial proportion of patients presented with primary and/or secondary syphilis in either treatment group during follow-up, suggestive of reinfection [4]. Therefore, we might have underestimated the effectiveness of the 2 treatment regimens. When the data were analyzed using the proportion of the patients who could achieve a ≥4-fold decline of RPR titers following treatment, the response rate was 88.1% and 86.0% for the 1-dose and 3-dose groups, respectively.

Both the study by Ganesan et al [1] and our study [4] are observational in design and subject to bias [6]. Although the optimal dose of BPG for early syphilis among HIV-infected patients remains unclear until randomized controlled clinical trials that use improved diagnostic modalities to reflect disease activity of syphilis are available to inform clinical decisions, we already have observed that the proportion of HIV-infected patients given 3 doses of BPG in our study has decreased from 60.2% (133/221) in 2007–2009 to 39.3% (53/135) in 2011 and 25.0% (12/80) in 2012 after the sexually transmitted diseases treatment guidelines recommended a single dose of BPG for the treatment of early syphilis in HIV-infected patients in 2010 [3]; besides, no cases of neurological complications suggesting neurosyphilis have been detected after follow-up for ≥3 years [4]. We believe that, until randomized clinical trials are available to address this key question, more observational studies among different risk groups will be beneficial in providing more insight into this dilemma [7].

**Note**

**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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Clinical Infectious Diseases* 2015;60(9):1443–4
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DOI: 10.1093/cid/civ029