

## Single Dose Versus 3 Doses of Intramuscular Benzathine Penicillin for Early Syphilis in HIV: A Randomized Clinical Trial

### BACKGROUND:

- Some observational studies show conflicting results, suggesting that 2.4 million units of BPG compared to those treated with 7.2 million units of BPG may lead to higher rates of treatment failure in coinfecting patients.
- There have been no randomized controlled trials comparing the efficacy of a single dose of BPG with that of 3 doses of BPG administered at 1-week intervals for early syphilis in HIV-infected patients.

### OBJECTIVE

- To compare the efficacy of 3-dose vs single-dose regimens of intramuscular BPG for the treatment of early syphilis in HIV-infected patients.

### METHODS

- **Study design:** Prospective, randomized, open-label study
- **Study duration:** Treatment then follow-up visit at 3, 6, 9, and 12 months
- **Inclusion criteria:** Patients  $\geq 18$  years, HIV infection diagnosed by enzyme-linked immunosorbent assay and Western blot testing, and untreated early syphilis.
- **Exclusion criteria:** History of penicillin allergy, diagnosis of late latent syphilis, and antibiotic use with significant activity against *Treponema pallidum* (i.e. macrolides, tetracyclines, and cephalosporins) within the preceding 2 weeks.
- **# of patients enrolled:** 108 subjects were assessed for study participation. 64 subjects underwent randomization.
- **Drug regimens/dosages used:** 35 were assigned to receive 2.4 million units of BPG x 1. 29 were assigned to receive 2.4 million units of BPG x 3.
- **Primary outcome measure:** Decrease in RPR titer of  $\geq 2$  dilutions (4-fold) from the initial RPR titer during the 12-month follow-up period
- **Secondary outcome measures:** CD4 T-cell count at baseline ( $\leq 350$  and  $> 350$  cells/uL), RPR titer at baseline ( $< 32$  and  $\leq 32$ ), virologic suppression (defined as HIV RNA load  $\leq 50$  copies/mL), and syphilis stage (primary, secondary, or early latent).
- **Power:** Set at 80% and required sample size in each group was 59 subjects (total 118 subjects).
- **Data handling method:** Both intention-to-treat and per-protocol analyses were performed

### RESULTS

- **All patients completed the study:**
  - **ITT Analysis:** 35 in the 2.4 million units BPG x 1 and 29 in the 2.4 million units of BPG x 3 (64 total)
  - **Per-Protocol Analysis:** 29 in the 2.4 million units BPG x 1 and 27 in the 2.4 million units of BPG x 3 (56 total)
- **Primary outcome measure:**
  - **ITT Analysis:** treatment success rates by 12 months of follow-up were 80% (28 of 35 subjects) in the standard therapy group and 93% (27 of 29 subjects) in the enhanced therapy group (absolute difference, 13% [95% CI, -5% to 30%];  $P = .17$ ).
  - **Per-Protocol Analysis:** treatment success rates were 93% (27 of 29) and 100% (27 of 27) in the standard and enhanced groups, respectively (absolute difference, 7% [95% CI, -7% to 22%];  $P = .49$ ).

- **Secondary outcome measures:** No significant changes were seen when treatment effect was evaluated in subgroup analyses (Table 2) by CD4 count at baseline ( $\leq 350$  and  $>350$  cells/ $\mu$ L), HIV RNA load, use of antiretroviral therapy at enrollment, RPR titer at enrollment ( $<32$  and  $\geq 32$ ), or syphilis stage (primary, secondary, or early latent). Of those patients with undetectable HIV RNA viral load, only 1 of 20 (5%) did not achieve treatment success with a single dose of intramuscular BPG.
- **Author's conclusion:** The study's findings suggest that a 3-dose regimen of BPG does not improve outcome in HIV-infected patients with early syphilis compared with a single-dose regimen.

#### STRENGTHS

- Proper randomization achieved
- No dropouts
- Per-protocol was used
- Inclusion and exclusion criteria allows for extrapolation towards population of interest

#### LIMITATIONS

- Smaller sample size than expected
- Unblinded
- Selection bias towards male and MSM (men who have sex with men)
- HAART (highly active antiretroviral therapy) may affect results since only 64% were on it
- No data provided to account for adherence

#### CONCLUSION

- The study's findings suggest that a 3-dose regimen of BPG does not improve outcomes in HIV-infected patients with early syphilis compared with a single-dose regimen.
  - There were no statistically significant difference in any of the baseline characteristics between the two different therapy groups. Thus, single dose or 3-doses of BPG for treatment would be an appropriate first line therapy for treatment of early syphilis in HIV-infected patients.
  - Patients that should best receive this therapy: male and MSM.
  - Single dose would have better compliance rates and be more cost-friendly compared to the 3-dose regimen.
- Future research:
  - Larger sample size in multicenter sites to better represent the population of patients with early syphilis in HIV.
  - A sample size with a more diverse group of patients in regards to gender and sexual orientation would be beneficial. Thus, the study will increase external validity for both male and female regardless of sexual orientation.

**Reference:** Andrade R, Rodriguez-Barradas MC, Yasukawa K et al. Single dose versus 3 doses of intramuscular benzathine penicillin for early syphilis in HIV: a randomized clinical trial. Clin Infect Dis. 2017;64(6):759-64.