



Published in final edited form as:

N Engl J Med. 2025 September 04; 393(9): 869–878. doi:10.1056/NEJMoa2401802.

BENZATHINE PENICILLIN G, 1 vs 3 WEEKLY DOSES, FOR EARLY SYPHILIS TREATMENT

Edward W. Hook III, MD¹, Jodie A. Dionne, MD, MSPH¹, Kimberly Workowski, MD², Candice J. McNeil, MD, MPH³, Stephanie N. Taylor, MD⁴, Teresa A. Batteiger, MD⁵, Julia C. Dombrowski, MD, MPH⁶, Kenneth H. Mayer, MD⁷, Arlene C. Seña, MD, MPH⁸, Matthew M. Hamill, MBChB, PhD, MPH, MSC⁹, Harold C. Wiesenfeld, MD¹⁰, Chunming Zhu, PhD¹¹, Charlotte Perlowski, MSPH¹², Jorge E. Mejia-Galvis, MD, MBA¹³, Lori M. Newman, MD¹³

¹Department of Medicine, University of Alabama at Birmingham, Birmingham, AL.

²Department of Medicine, Emory University, Atlanta, GA

³Department of Medicine, Wake Forest University School of Medicine, Winston-Salem, NC

⁴Department of Medicine, Louisiana State University, New Orleans LA

⁵Department of Medicine, Indiana University School of Medicine, Indianapolis IN

⁶Department of Medicine, University of Washington, Seattle, WA.

⁷Fenway Health and the Department of Medicine, Beth Israel Deaconess Medical Center/Harvard Medical School, Boston MA

⁸Department of Medicine, University of North Carolina at Chapel Hill, Chapel Hill NC

⁹Department of Medicine, Johns Hopkins University, Baltimore MD

¹⁰Department of Obstetrics and Gynecology and Reproductive Sciences and Magee-Womens Research Institute, University of Pittsburgh, Pittsburgh PA

¹¹The EMMES Corporation

¹²FHI 360, Durham, NC

¹³National Institute of Allergy and Infectious Diseases, National Institutes of Health, Rockville, MD.

Abstract

Introduction: Controversy persists on the duration of therapy of syphilis with benzathine penicillin G (BPG) for persons with early (primary, secondary, and early latent) syphilis (*Treponema pallidum* infection).

Methods. We conducted a multicenter randomized controlled non-inferiority trial (RCT) comparing a single treatment with intramuscular (IM) injections of BPG 2.4 million units (MU) to

This Author Accepted Manuscript is licensed for use under the CC-BY-NC-ND license.

Corresponding Author: Edward W. Hook III MD, 703 19th Street South, Birmingham, Alabama 35294, ehooks@uabmc.edu.

Disclosure forms provided by the authors are available with the full text of this article at [NEJM.org](https://www.nejm.org).

BPG (7.2 MU total dose) administered for three successive weeks for treatment of early syphilis in persons with and without HIV. The primary study outcome was a 4-fold (2 dilution) decline in Rapid Plasma Reagin (RPR) titer measured by 6 months.

Results. 249 persons with early syphilis were enrolled. Most participants were categorized as male sex (97%), Black race (62%), and 153 (64%) were living with HIV. The syphilis stage distribution was 19% primary, 47% secondary and 33% early latent. Serologic response at 6 months was 76% (95% Confidence Interval (CI) 0.68,0.82) in the single dose group and did not significantly differ from the three-dose group (70%, 95% CI 0.61, 0.77). No clinical relapses or treatment failures occurred. Among persons with and without HIV there was no significant difference in RPR response at 6 months: 76% in the single dose group vs. 71% in the 3-dose group (90% CI -0.05 0-0.17,0.07), respectively. Most participants (76% and 85%, respectively) experienced local injection site pain and tenderness with treatment.

Conclusions. Treatment with more than a single dose of 2.4 MU of BPG offers no benefit at 6 months post-treatment, irrespective of HIV infection status.

Syphilis is a chronic human bacterial sexually transmitted infection (STI) which has been recognized as a threat to human health for centuries. The disease remains a public health priority due to its transmissibility, the potential for neurological and cardiovascular complications, increased risk for human immunodeficiency virus (HIV) acquisition, and as a cause of adverse pregnancy outcomes. Throughout the 21st century syphilis rates have increased (1) Rates of HIV co-infection are higher among persons with syphilis. Congenital syphilis infections in the US are now at near record levels (1).

Long-acting penicillin has been the preferred therapy for syphilis treatment since the early 1950s (2-4). While a single dose of benzathine penicillin G (BPG) has been the accepted standard for therapy of early (primary, secondary, early latent) syphilis for decades, concerns about the adequacy of single dose BPG for treatment of early syphilis for persons with HIV (PWH) are longstanding. Despite CDC recommendations for single dose BPG therapy, many clinicians treat PLWH with multiple doses of BPG (5). To address the continuing controversy regarding the optimal duration of BPG for early syphilis treatment, we conducted a multicenter randomized non-inferiority clinical trial (RCT) comparing single dose therapy with 2.4 million units (MU) of BPG to therapy with three doses of 2.4MU BPG administered at successive weekly intervals. In recent years recurring shortfalls in the availability of BPG have hampered syphilis treatment during a period of rising infection rates (6).

Methods

This open label RCT was conducted at ten U.S. sites. Participants were 18 years of age and had early syphilis (primary, secondary, or early latent) with reactive rapid plasma reagin (RPR) tests (BD Macro-Vue) confirmed by a TPPA (*Treponema pallidum* particle agglutination) test (SERODIA TPPA, Fujirebio Diagnostics). Participants with prior syphilis were required to have a 4-fold (2-dilution) rise in RPR titer compared with prior RPR titers. Participants were excluded if they were pregnant, had taken antibiotics active against *Treponema pallidum* in the preceding 30 days, had a co-existent infection requiring

therapy with drugs active against *T. pallidum*, were suspected to have neurosyphilis, or had self-reported allergies to penicillin or related antibiotics. Participants were defined as having primary syphilis if they had ano-genital ulceration at enrollment. Secondary syphilis was defined as the presence of a cutaneous rash, mucosal lesions, generalized lymphadenopathy, or other signs of secondary infection. Participants with early latent syphilis lacked examination findings of primary or secondary syphilis and had reactive RPR test results with either a prior non-reactive serological test for syphilis or, for previously infected persons, a documented 4-fold increase in RPR titer within the preceding 12 months. Full details of study conduct can be found in the protocol and SAP at [nejm.org](https://www.nejm.org).

Response to therapy was evaluated based on changes in RPR titer measured within six months of therapy. Serum specimens for determination of treatment response were collected at each follow-up visit and transferred frozen to a central laboratory at The University of Alabama at Birmingham (UAB) where they were stored until batched testing was performed. For each participant, baseline RPR and TPPA reactivity were confirmed and specimens collected during the 6-month follow-up were tested at a single time to RPR end-point using serial doubling dilutions according to the Manual of Serological Tests for Syphilis (7). In the intent-to-treat (ITT) analysis (defined below) response to therapy was defined a 4-fold (2 dilution) decrease in RPR titer or an RPR which became non-reactive by the six-month follow-up. Treatment failure in the ITT analyses was any 4-fold increase in RPR titer at any time during follow-up and serological non-response was defined as RPR titers which remained within one 2-fold dilution of the baseline RPR titer. In the evaluable participant analyses, participants with transient increases in RPR titer during the first month of follow-up which then returned to baseline or less were classified as serologically responsive or non-responsive to therapy based on RPR titers determined subsequent to the one-month follow-up visit (there were no treatment failures in the evaluable participant analyses) (8).

Treatment.

Participants were randomized to receive either a single BPG treatment or a series of three successive BPG treatments administered at weekly intervals. All participants received directly observed therapy; for each treatment participants received deep intramuscular injections of 1.2 MU of BPG in each buttock. Participants were observed for approximately 30 minutes following receipt of therapy for adverse effects. Study clinicians provided pre- and post-test counseling, recommendations for partner notification, treatment, and health department referrals per local standard of care.

Follow-up.

The primary endpoint of this trial was defined as RPR seroreversion to non-reactive or a decrease in RPR titer of 4-fold (2 dilutions) compared to the initial RPR titer within 6 months of initiation of therapy. Following initiation of treatment, participants were contacted at 24–48 hours following initial BPG treatment to evaluate post-treatment adverse effects including symptoms of possible Jarisch-Herxheimer reaction (fever, appearance or change in rash, myalgia, arthralgia). All participants were scheduled for follow-up visits at 1 week, 2 weeks, and 1, 3, 6 and 12 months. At each follow-up participants underwent a brief clinical

examination and an interval history of sexual activity, symptoms, solicited and unsolicited adverse events, and recent antibiotic use. Phlebotomy for RPR testing was carried out at each follow-up.

Statistical Analyses.

To address the specified primary outcome a non-inferiority comparison of the serological response to therapy at 6 months to test participants allocated between treatment arms in a 1:1 ratio. Differences in response rate using the Farrington-Manning test were compared without adjustment for HIV status. The pre-specified non-inferiority margin was 10%. The null hypothesis specified a response rate of 0.688 for the one-dose regimen and 0.788 for the three-dose regimen with a one-sided alpha of 0.05. Using these parameters a sample size of 420 participants (210 per treatment group) was sought. Study enrollment was profoundly slowed by the onset and course of the COVID-19 pandemic. The study was halted by the sponsor upon recommendations from the DSMB before reaching the planned sample size. Futility analyses performed at that time indicated that when response rates for the two treatment groups were similar at approximately 0.789, available data could still provide 80% power.

Analyses were performed for the intention to treat (ITT) cohort as well a per protocol population subset of the ITT population at the time of 6-month follow-up. The ITT population includes all participants who met eligibility criteria and were randomized. The evaluable population analyses included participants who did not have a protocol status change during follow-up are referred to as the per-protocol population. It includes all randomized participants eligible at the baseline visit, had a known HIV status determined at baseline, had positive TPPA results, received all assigned doses of BPG, (for HIV-infected participants only) HIV-uninfected status persists through month 6, had RPR test data available at baseline and at least one follow-up visit at or before Month 6 visit. Twenty-two participants with early termination were not included in the analyses because no follow-up RPR specimens were collected.

Human Subjects.

Written informed consent was obtained from all participants. The master protocol was approved by the UAB Institutional Review Board (IRB) for Human Subjects and subsequently by IRBs at each study site. During the trial National Institutes of Allergy and Infectious Diseases (NIAID) convened a Data Safety and Monitoring Board (DSMB) to review study progress and participant safety on three occasions. After the third DSMB meeting, based on the DSMB recommendation regarding slow enrollment due to the COVID-19 pandemic, the sponsor (NIAID) determined that early closure of the study was appropriate.

Results

Between 31 October 2018 and 3 March 2022, 254 persons were screened for participation at the ten study sites and 249 were enrolled in the ITT study population, leading to 199 participants who were evaluable for the primary outcome (Figure 1). Of enrolled

participants, 124 received a single treatment with BPG and 125 received 3 BPG treatments at weekly intervals. Fifty participants were excluded from the evaluable population by 6 months; reasons included loss to follow-up (n=34), 21 did not receive all scheduled BPG (all in the three weekly treatment group), 9 received antibiotics active against *T. pallidum* for reasons other than syphilis prior to having valid follow-up RPR results, and 2 developed reactive HIV tests during follow-up (some participants had multiple reasons for non-inclusion in the evaluable category).

Participants.

Most participants were male (97%) and characterized themselves as non-Hispanic (95%) and as Black (62%). Mean age was 35 (range 19–66) years (Table 1). One hundred fifty-three (61%) participants were persons with HIV (PWH), and 91 were not. Nineteen percent of participants were classified as having primary syphilis, 47% as in the secondary stage and 33% were classified as early latent syphilis (Table 2). A self-reported history of prior syphilis was present in 22 (9%). The distribution of these characteristics among the evaluable population was similar to the ITT population (Supplementary Table S1).

Among 153 PWH in the ITT population, 92% reported taking anti-retroviral therapy (ART). Among 130 PWH in the per-protocol population, 94% were taking ART. Among persons with HIV, CD4 lymphocyte concentrations at the time of treatment were >350 cells/mm³ in 110 (77%). The proportions taking ART and CD4 lymphocyte distributions did not differ meaningfully in the per protocol group.

Response to therapy.

In the ITT population, by the 6-month end-point the serological response rate was 76% (95% Wilson CI 68–82%) in the single treatment group and 70% (95% Wilson CI 61–77%) in the three treatment group (Figure 2). The Farrington-Manning test result showed the difference in the proportion of participants with serological response between the two treatment groups as -0.06 [90% CI $(-0.15, 0.03)$]. The upper confidence limit, 0.03, is less than the non-inferiority margin of 0.10, indicating that the single BPG treatment was non-inferior to three successive weekly treatments with 2.4 MU of BPG. Similarly, in the per-protocol group, single-dose treatment was again non-inferior - 77% (95% CI 66, 84%) to the three-treatment group (71% (95% CI 61%, 79%).

Among participants with at least one follow up visit 6–24 days (median 14 days) after enrollment, 72% had complete symptom resolution and the remaining 28% had improving ulcer or rash after the initial dose of BPG. Resolution rates were similar when stratified by 1 vs 3 BPG doses and by syphilis stage.

When the ITT treatment groups were further stratified by HIV status there was no significant difference in the proportion of participants with serological response (Table 3). Among participants randomized to BPG treatment on a single occasion, both 76% of PWH and persons without HIV achieved a serological response by 6 months. For participants treated for three successive weeks with BPG, 71% of PWH achieved serological responses while for persons without HIV the serological response rate was 70%. Again, results in the per protocol populations were like those found in the ITT analysis.

Among PWH in the ITT population, 110 (77%) of 142 had CD4 lymphocyte concentrations > 200 cells/mm³ and 32 (23%) had <200 cells/mm³. A 4-fold serological response to therapy by 6 months occurred in 74% of participants with >200 cells/mm³ and 69% of PLWH with <200 CD4 cells/mm³.

Several factors potentially impacting serological response to therapy were evaluated (Tables 2 and 3). In the ITT population, 0.65 (54/83) of participants classified as early latent syphilis responded serologically by the 6-month follow-up while for persons classified as primary or secondary syphilis the response rate was 0.77 (127/165). In addition, persons who experienced the Jarisch-Herxheimer reaction following initial treatment were more likely to demonstrate serological response than persons who did not (0.85 (95% CI 0.73–0.92) vs 0.69 (95% CI 0.62–0.75, Table 3). A self-reported history of prior syphilis was not significantly associated with response to therapy (Table 3).

Adverse Events.

Treatment related adverse events were common. The most common adverse events were local related to BPG injection. In the ITT population 201 (81%) of 249 participants reported local injection site pain, tenderness, or redness. In addition, 59 (24%) reported symptoms classified as a Jarisch-Herxheimer reaction. Three participants experienced serious adverse events during the study period, all judged by the site investigators to be unrelated to BPG. One participant experienced an episode of proctocolitis, and another required hospital admission for illegal drug-related psychiatric care. A third participant, developed facial paralysis following administration of the initial dose of penicillin, findings thought to reflect the natural history of that participant's syphilis which would have occurred irrespective of the administration of therapy. The facial paralysis resolved following therapy for neurosyphilis.

Participants in the two arms demonstrated significant differences in terms of the frequency and the self-reported severity of events. Pain was the most common adverse event (76% in the 1-dose vs. 85% in the 3-dose group). Among solicited systemic symptoms, the same pattern was recognized where more cases occurred in the 3-dose arm compared to the one dose arm (32 events vs 27 events) and reported events were moderately more severe.

For investigator assessed related unsolicited adverse events, 10 participants had related adverse events, five in each arm, with no differences in severity.

Discussion

The therapy of syphilis has been a scientific and public health priority for over 100 years. Since the mid-1940s, *Treponema pallidum* as a relatively slowly dividing, exclusively human pathogen has remained sensitive to relatively low doses of penicillin G (2, 3,9). In the 1950s the introduction of BPG allowed the infection to be treated with single injections (3). Since then, BPG has remained the foundation of syphilis therapy (4). Nonetheless, periodically investigators have questioned whether the outcomes of syphilis therapy might be improved with longer durations or higher doses of therapy, particularly for persons whose response to therapy might be compromised by coexistent immunosuppression such as that

due to HIV infection (5). This trial provides data that for patients with uncomplicated early syphilis (i.e. excluding clinical neurosyphilis including ocular and otic syphilis), a single treatment of 2.4 MU of BPG is non-inferior to three BPG treatments administered a week apart. These data complement the study by Rolfs et al which showed that higher doses of penicillin do not improve response to therapy (10).

Treatment on a single occasion with BPG for early syphilis is appealing for several reasons including antimicrobial stewardship and patient comfort. During the trial, as on several occasions over the past several decades, BPG was in short supply in the US. This led public health authorities to need to prioritize which patients receive BPG and which should be treated with alternate therapies. (6) Global BPG stockouts are also common, undermining syphilis control efforts in many countries (11). Further, injections of BPG are uncomfortable for patients and represent a disincentive to follow-up. In this trial, the most common adverse event reported by participants was injections site pain and tenderness. As noted, injection pain was reported more commonly in the participant group randomized to a series of three weekly injections, possibly related to cumulative discomfort of serial injections. Of 125 participants randomized to receive three weekly treatments with BPG, 21 (17%) did not receive all planned BPG injections. In this group, while the reasons for not receiving all doses were not consistently recorded, the discomfort of further injections may have been a contributor. In addition, anecdotally, among persons pre-screened for study participation, several who had prior syphilis cited the possibility of receiving multiple BPG injections as their reasons for choosing to not participate. With no observable benefit to multiple treatments, a single treatment using 2.4 MU should be, in our opinion, the preferred treatment for early syphilis.

Our study had several limitations. The number of women in the trial was low. The data are insufficient to evaluate response to therapy in women and there are no data on outcomes of therapy for pregnant persons. In addition, many persons diagnosed with syphilis present with latent syphilis of unknown duration, a group who were excluded from this trial. Evaluation of therapy for pregnant persons as well as those with late syphilis, latent syphilis of unknown duration, and clinical neurosyphilis remain research priorities. For the up to 20% of persons who report possible allergy to penicillin, alternatives to penicillin are needed as well (12, 13). A further limitation of the study is our continued reliance upon serological response to therapy as an indicator of therapeutic effect (10, 14). Serologic response is an imperfect measure as it may take months to occur and even after as long as six months following the initiation of therapy, about 20% of persons treated for early syphilis have no significant change in RPR titers (10, 14). While the sense is that these patients are unlikely to have failed treatment, development of improved methods to diagnose active syphilis and to assess response to therapy are needed.

Our study has limited data on persons with advanced or untreated HIV. Nearly all participants with HIV in our trial were taking ART and 77% had CD4 concentrations greater than 350 cells/mm³. No significant difference was observed when PWH were subset by those with low CD4 counts (<200 CD4 /mm³). We suspect that a single treatment with BPG would be effective for untreated PWH or those with profound immunosuppression however our data are insufficient to fully address these questions.

In summary, this trial provides data to indicate that a single treatment of persons with early syphilis, including PWH, can be effectively treated on a single occasion with 2.4MU of BPG. The elimination of unnecessary doses of BPG reduces the cost of treatment, aligns with the principles of antimicrobial stewardship, and is more convenient for patients by decreasing the numbers of painful intramuscular injections and clinic visits.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

UAB. Paula Dixon,

EMORY: Gary Friend

Wake Forest: Andrea Lewis, Cynthia Dalton, Dexter Jenkins, Rica Abbott

Indiana University: Lora Fortenberry

University of Washington Angela LeClair, Dwyn Dithmer

Fenway: L Marcy Gelman, Julian Dormitzer, Jessica Kraft

University of North Carolina: Chris Sellers, Chris Evans

Johns Hopkins: Jonathan Zenilman MD, Curtisha Charles

University of Pittsburgh: Ingrid Macio, Danielle Litzinger

Family Health International: Linda McNeil, Shilysha Davis-Dublin, Latrisha Farley, Katlyn Hurst, Bailey Knight, Ginger Pittman, Marcy Steigerwald, Lara Stone

NIAID: Carolyn Deal, Peter Wolff

Funding

This work was funded by the National Institute of Allergy and Infectious Diseases (Sexually Transmitted Infections Clinical Trials Group) Contract HHSN2722013000121.

References

1. CDC. STI Surveillance Report. 2023. 2024. Available at <https://www.cdc.gov/sti-statistics/annual/index.html>
2. Kampmeier RH. The introduction of penicillin for the treatment of syphilis. *Sex Trans Dis* 1981; 8: 260–265.
3. Schroeter AL, Lucas JB, Price EV et al. Treatment for Early Syphilis and Reactivity of Serological Tests. *JAMA* 1972; 221; 471–476. [PubMed: 4556863]
4. Workowski KA, Bachmann LH, Chan PA, Johnston CM, Muzny CA, Park I, Reno H, Zenilman JM, Bolan GA. Sexually Transmitted Infections Treatment Guidelines, 2021. *MMWR Recomm Rep* Jul 23 2021;70(4):1–187. doi:10.15585/mmwr.rr7004a1
5. Dowell D, Polgreen PM, Beekman SE, Workowski KA, Berman SM, Peterman TA. Dilemmas in the Management of Syphilis: A Survey of Infectious Disease Experts. *Clin Infect Dis* 2009; 49; 1526–9. Doi; 10.1086/644737. [PubMed: 19845476]
6. Bachmann LH, Mena L. Clinical Reminders during Bicillin L-A® Shortage. CDC Dear Colleague Letter July 20, 2023.

7. Larsen SA, Pope V, Johnson RE, Kennedy EJ. A manual of tests for syphilis. 9th ed. Washington DC. American Public Health Association 1998: 3–6.
8. Holman KM, Wolff M, Sena AC, Martin DH, Behets F, Van Damme K, Leone P, McNeil L, Gehrig ML, Hook EW III. Rapid plasma reagin titer variation in the 2 weeks after syphilis therapy. *Sex Transm Dis* 2012;39:645–647. [PubMed: 22801348]
9. Moore JE, Mahoney JF, Schwartz W, Sternberg T, Wood WB. The treatment of early syphilis with penicillin. A preliminary report of 1,418 cases. *JAMA* 1944;26: 67–73.
10. Rolfs RT, Joesoef MR, Hendershot EF, Rompalo AM, Augenbraun MH, Chiu M, Bolan G, Johnson SC, French P, Steen E, Radolf JD, Larsen S., A randomized trial of enhanced therapy for early syphilis in patients with and without human immunodeficiency virus infection. The Syphilis and HIV Study Group. *N Engl J Med*, 1997. 337(5): p. 307–14. doi: 10.1056/NEJM199707313370504.
11. Taylor Melanie M.; Wi Teodora; Gerbase Antonio; Thwin Soe Soe; Gottlieb Sami; Babovic Maria Theresa; Low-Beer Daniel; Alonso Monica; Mello Maeve B.; Ishikawa Naoko; Brink Anne; Hermez Joumana; Sabry Ahmed; Sanni Saliyou; Ouedraogo Leopold; Rewari Bharat; Sharma Mukta; Seguy Nicole; Vovc Elena; Askew IA. Assessment of country implementation of the WHO global health sector strategy on sexually transmitted infections (2016–2021). *PLoS ONE*, 2022: 17 (5); p1–13.
12. Blumenthal KG, Peter JG, Trubiano JG, Phillips EG. Antibiotic Allergy. *Lancet* 2019: 393 (10167); 183–198. [PubMed: 30558872]
13. Shenoy ES, Macy E, Rowe T, Blumenthal RG. Evaluation and management of penicillin allergy: A review *JAMA* 2019: 321 (2) ; 188–199. [PubMed: 30644987]
14. Sena AC, Wolff M, Martin DH, Behets F, Van Damme K, Leone P, McNeil L, Hook EW III. Predictors of serological cure and the serofast state after treatment in HIV-negative persons with early syphilis. *Clin Infect Dis* 2011;53:10–92-1099.

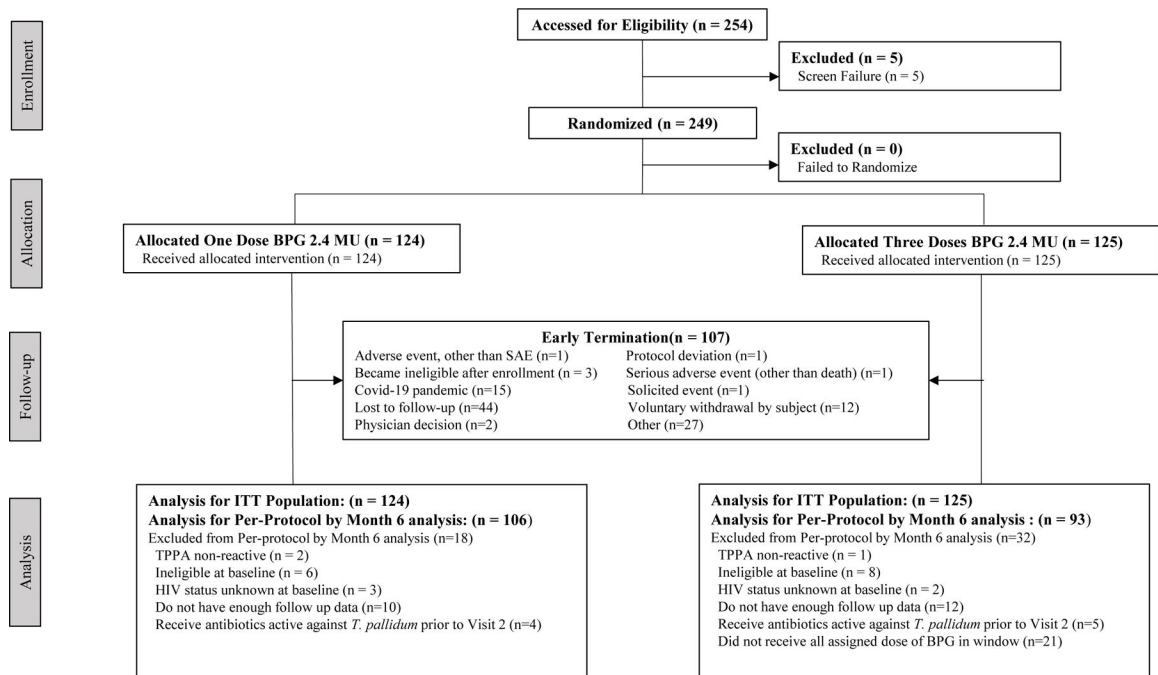


Figure 1.
Disposition of Study Subjects Flow Chart (CONSORT Diagram), Benzathine Penicillin, 1 vs 3 Doses for Early Syphilis Treatment.

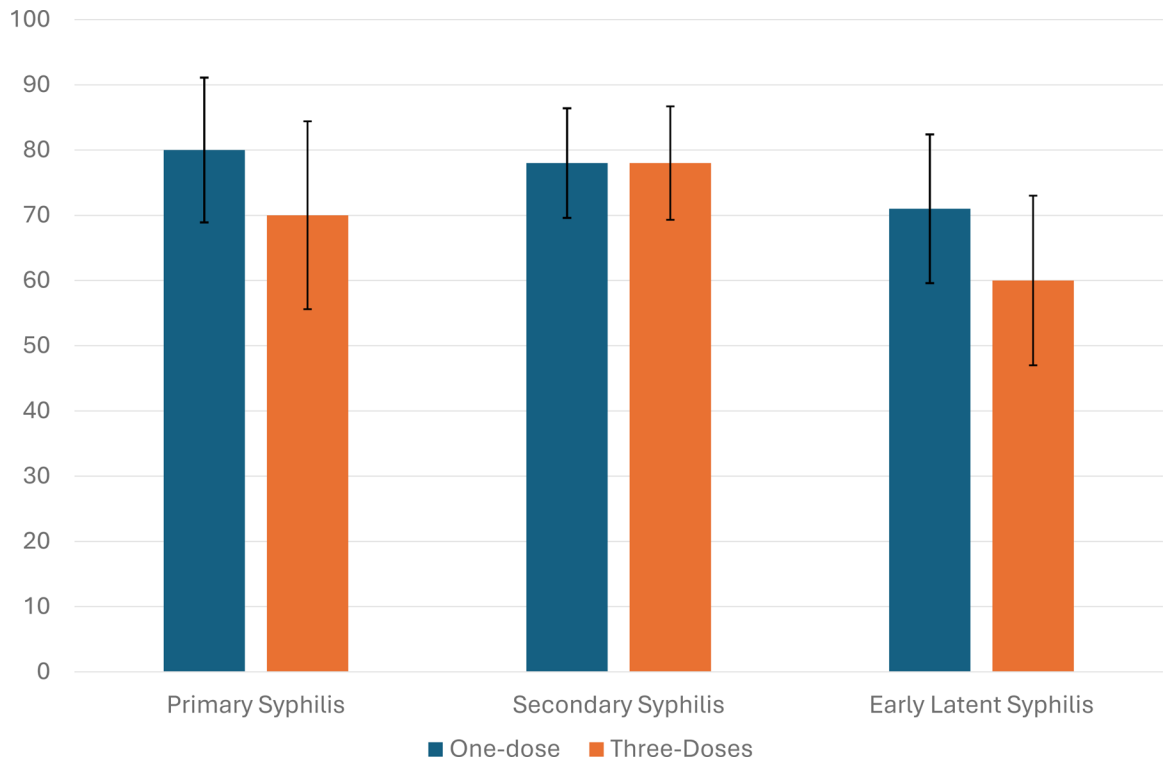


Figure 2. Serological Response to Benzathine Penicillin (95% CI) Therapy Stratified by Stage and Treatment Group.

Table 1 –
Baseline Characteristics of Early Syphilis Study Participants by Treatment Randomization Group (n=249)

Characteristic	Three-dose BPG (n=125)	One-dose BPG (n=124)	Total (n=249)
Median Age in Years (IQR)	31 (26,41)	33 (27,43)	32 (27,42)
Race			
Black	80 (64%)	74 (60%)	154 (62%)
White	28 (22%)	35 (28%)	63 (25%)
Asian/Other	17 (14%)	15 (12%)	32 (13%)
Hispanic Ethnicity			
	4 (3%)	8 (6%)	12 (5%)
Sex at Birth			
Male	123 (98%)	119 (96%)	242 (97%)
Female	2 (2%)	5 (4%)	7 (3%)
HIV Status			
Positive (PWH)	83 (66%)	70 (56%)	153 (61%)
Negative	40 (32%)	51 (41%)	91 (37%)
Prescribed ART (among PLWH)			
	73/83	68/70	141/153
Study Site Location			
Atlanta, GA	38 (30%)	37 (30%)	75 (30%)
Baltimore, MD	2 (2%)	2 (2%)	4 (2)
Baton Rouge, Louisiana	16 (13%)	16 (13%)	32 (13%)
Birmingham, AL	20 (16%)	21 (17%)	41 (16%)
Boston, MA	6 (5%)	6 (5%)	12 (5%)
Chapel Hill, NC	2 (2%)	3 (2%)	5 (2%)
Indianapolis, Indiana	10 (8%)	11 (9%)	21 (8%)
Pittsburgh, PA	2 (2%)	1 (1%)	3 (1%)
Seattle, WA	8 (6%)	7 (6%)	15 (6%)
Wake Forest, NC	21 (17%)	20 (16%)	41 (17%)
History of Syphilis (self-report)			
	13 (10%)	9 (7%)	22 (9%)
Sex Partners			
MSM	99 (79%)	91 (73%)	190 (76%)
MSW	12 (10%)	15 (12%)	27 (11%)
MSMW	12 (10%)	16 (13%)	28 (11%)
Number of Sex Partners in past 6 months			
	2 (1,4)	2 (1,4)	2 (1,4)
RPR Titer			
1:1	1(1%)		
1:1	2 (2%)	1 (1%)	2 (1%)
1:2	6 (5%)	0 (0%)	2 (1%)
1:4	9 (7%)	5 (4%)	11 (4%)
1:8	4 (3%)	7 (6%)	16 (6%)

Characteristic	Three-dose BPG (n=125)	One-dose BPG (n=124)	Total (n=249)
1:16	21 (17%)	11 (9%)	16 (6%)
1:32	31 (25%)	20 (16%)	41 (16%)
1:64	28 (22%)	28 (23%)	59 (24%)
1:128	12 (10%)	25 (20%)	53 (21%)
1:256	1 (1%)	16 (13%)	28 (11%)
1:512	4 (3%)	4 (3%)	5 (2%)
>1:512		2 (2%)	3 (2%)
Geometric Mean RPR Titer (95% CI)	57.1 (44.2, 73.5)	60.0 (47.5, 75.9)	58.5 (49.3, 69.5)

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 2A –
Serological Response to Therapy by Month 6 by Syphilis Stage and Treatment Group: Intention to Treat (ITT)

	One-dose BPG 2.4 MU n (%)	Three-doses BPG 2.4 MU n (%)	Total n (%)
Primary	20/25 (80)	16/23 (70)	36/48 (75)
Secondary	45/58 (78)	46/59 (78)	91/117 (78)
Primary + Secondary	65/83 (78)	62/82 (76)	127/165 (77)
Early Latent	29/41 (71)	25/42 (60)	54/83 (65)

*treatment failure occurred in the one-dose arm in 1 participant with secondary syphilis and 3 participants with early latent syphilis

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 2B –
Serological Response to Therapy by Month 6 by Treatment Group: Per-Protocol Analysis

	One-dose BPG 2.4 MU n (%)	Three-doses BPG 2.4 MU n (%)	Total n (%)
Primary	19/21 (90)	14/20 (70)	33/41 (80)
Secondary	40/52 (77)	32/45 (71)	72/97 (74)
Primary + Secondary	59/73 (81)	46/65 (71)	105/138 (76)
Early Latent	23/33 (70)	20/28 (71)	43/61 (70)

*treatment failure occurred in the one-dose arm in 1 participant with primary syphilis, 1 participant with secondary syphilis and 3 participants with early latent syphilis

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 3A –
Serological Response to Therapy by Month 6 and Treatment Group by Other Factors: Intention to Treat (ITT)

		One-dose BPG 2.4 MU n [proportion, 95%CI]	Three-doses BPG 2.4 MU n [proportion, 95%CI]	Total n [proportion, 95%CI]
Person Living with HIV (PWH)	Yes	53 [0.76 (0.65, 0.84)]	59 [0.71 (0.61, 0.80)]	112 [0.73 (0.66, 0.80)]
	No	39 [0.76 (0.63, 0.86)]	28 [0.70 (0.55, 0.82)]	67 [0.74 (0.64, 0.82)]
Prior Syphilis History (self-report)	Yes	4 [0.44(0.19,0.73)]	9 [0.69(0.42, 0.87)]	13 [0.59(0.39, 0.77)]
	No	90 [0.78(0.70, 0.85)]	78 [0.70(0.61, 0.77)]	168 [0.74(0.68, 0.79)]
JH reaction after BPG dose	Yes	23 [0.85(0.68, 0.94)]	27 [0.84(0.68, 0.93)]	50 [0.85(0.73, 0.92)]
	No	71 [0.73,(0.64, 0.81)]	60 [0.65(0.54, 0.73)]	131 [0.69(0.62, 0.75)]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 3B –
Serological Response to Therapy by Month 6 and Treatment Group by Other Factors: Per-Protocol analysis

		One-dose BPG 2.4 MU n [proportion, 95%CI]	Three-doses BPG 2.4 MU n [proportion, 95%CI]	Total n [proportion, 95%CI]
Person with HIV (PWH)	Yes	46 [0.72 (0.60, 0.81)]	45 [0.68 (0.56, 0.78)]	91 [0.70 (0.62, 0.77)]
	No	36 [0.86 (0.72, 0.93)]	21 [0.78 (0.59, 0.89)]	57 [0.83 (0.72, 0.90)]
Prior Syphilis History (self-report)	Yes	3 [0.50(0.18, 0.81)]	6 [0.50(0.25, 0.75)]	9 [0.50(0.29, 0.71)]
	No	79 [0.79(0.70, 0.86)]	60 [0.74(0.64, 0.83)]	139 [0.77(0.70, 0.82)]
JH reaction after BPG dose	Yes	21 [0.84(0.65, 0.94)]	18 [0.82(0.61,0.93)]	39 [0.83(0.70, 0.91)]
	No	61 [0.75(0.65, 0.83)]	48 [0.68(0.56, 0.77)]	109 [0.72(0.64, 0.78)]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript