ORIGINAL ARTICLE

One Dose versus Three Doses of Benzathine Penicillin G in Early Syphilis

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ABSTRACT

BACKGROUND

Controversy persists regarding the appropriate duration of therapy with benzathine penicillin G in persons with early (i.e., primary, secondary, or early latent) syphilis (*Treponema pallidum* infection).

METHODS

In a multicenter, randomized, controlled, noninferiority trial, we assigned persons who had early syphilis, with or without human immunodeficiency virus (HIV) infection, to receive intramuscular injections of benzathine penicillin G in a one-time dose of 2.4 million units or in doses of 2.4 million units administered at three successive weekly intervals. The primary end point was seroreversion to nonreactive status or a decrease in the rapid plasma reagin titer by two or more dilutions at 6 months, referred to here as a serologic response (noninferiority margin, 10 percentage points). A key secondary end point was a serologic response within subgroups defined according to HIV status, also assessed in a noninferiority analysis.

RESULTS

A total of 249 persons with early syphilis were enrolled. Most participants were men (97%), 62% were Black, and 153 (61%) were living with HIV infection. The distribution according to syphilis stage was 19% with primary syphilis, 47% with secondary syphilis, and 33% with early latent syphilis. The percentage of participants with a serologic response at 6 months was 76% (95% confidence interval [CI], 68 to 82) in the single-dose group and 70% (95% CI, 61 to 77) in the three-dose group (difference, −6 percentage points; 90% CI, −15 to 3, indicating noninferiority). No clinical relapse or treatment failure occurred in either group. In the one-dose group, a serologic response at 6 months was observed in 76% of participants who had HIV infection and 76% of those who did not, and in the three-dose group, a serologic response at 6 months was observed in 71% of participants who had HIV infection and 70% of those who did not. Most participants in each group had local injection-site pain and tenderness with treatment (76% with a single dose and 85% with three doses).

CONCLUSIONS

Treatment with one dose of 2.4 million units of benzathine penicillin G was noninferior to treatment with three doses with regard to serologic response 6 months after treatment. (Funded by the National Institute of Allergy and Infectious Diseases; ClinicalTrials.gov number, NCT03637660.)

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Syphilis is a chronic human bacterial (*Treponema pallidum*), sexually transmitted infection that has been recognized as a threat to human health for centuries. The disease remains a public health priority owing to its transmissibility, potential for neurologic and cardiovascular complications, association with an increased risk of human immunodeficiency virus (HIV) acquisition, and role in adverse pregnancy outcomes. Throughout the 21st century, syphilis rates have increased.[1] Rates of HIV coinfection are higher among persons with syphilis. Congenital syphilis infections in the United States are now at near-record levels.[1]

Long-acting penicillin has been the preferred therapy for syphilis treatment since the early 1950s.[2-4] Although a single dose of benzathine penicillin G has been the accepted standard for treatment of early (i.e., primary, secondary, and early latent) syphilis for decades, concerns about the adequacy of a single dose of benzathine penicillin G for treatment of early syphilis in persons with HIV infection are of long standing. Despite recommendations from the Centers for Disease Control and Prevention for single-dose benzathine penicillin G therapy, many clinicians treat persons who have HIV infection with multiple doses.[5] In recent years, recurring shortfalls in the availability of benzathine penicillin G have hampered syphilis treatment during a period of rising infection rates.[6] To address the continuing controversy regarding the appropriate duration of treatment with benzathine penicillin G for early syphilis, we conducted an open-label, multicenter, noninferiority, randomized, controlled trial comparing single-dose therapy with 2.4 million units of benzathine penicillin G to therapy with three 2.4-million-unit doses of benzathine penicillin G administered at three successive weekly intervals.

METHODS

TRIAL DESIGN AND PARTICIPANTS

The trial was conducted at 10 sites in the United States. Participants were at least 18 years of age and had early syphilis, with results of reactive rapid plasma reagin (RPR) tests (BD, Macro-Vue) confirmed by a *T. pallidum* particle-agglutination (TP-PA) test (SERODIA, Fujirebio Diagnostics). Participants who had had syphilis previously were required to have an RPR titer that was at least two dilutions higher than their previous RPR titer. Participants were excluded if they were pregnant, had taken antibiotics active against *T. pallidum* in the preceding 30 days, had a coexistent infection that resulted in therapy with drugs active against *T. pallidum*, were suspected of having neurosyphilis, or had reported allergies to penicillin or related antibiotics. Participants were defined as having primary syphilis if they had anogenital ulceration at the time of 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 previous nonreactive serologic test for syphilis or, in previously infected persons, a documented increase (by a factor of four) in the RPR titer within the preceding 12 months.

All the participants provided written informed consent. The protocol was approved by the University of Alabama at Birmingham Institutional Review Board for Human Subjects and subsequently by institutional review boards at each trial site. During the trial, the sponsor (the National Institute of Allergy and Infectious Diseases) convened a data and safety monitoring board to review trial progress and participant safety on three occasions. After the third meeting, on the basis of the board's recommendation regarding slow enrollment due to the coronavirus disease 2019 (Covid-19) pandemic, the sponsor determined that early closure of the trial was appropriate.

The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. Full details of the conduct of the trial can be found in the protocol and Supplementary Appendix, available with the full text of this article at NEJM.org.

TREATMENT

Participants were randomly assigned to receive either a single benzathine penicillin G treatment or a series of three successive benzathine penicillin G treatments administered at weekly intervals. All administered therapy was directly observed; at each treatment, participants received one deep intramuscular injection of 1.2 million units of benzathine penicillin G in each buttock. Participants were observed for approximately 30

minutes after receipt of therapy to monitor for adverse effects. Trial clinicians provided counseling before and after each test as well as recommendations for partner notification, treatment, and health-department referrals in accordance with the local standard of care.

END POINTS AND ASSESSMENTS

The primary end point of this trial was seroreversion to nonreactive status or a decrease in the RPR titer by at least two dilutions from baseline at 6 months (serologic response). A key secondary end point was a serologic response at 6 months according to HIV status.

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, where they were stored until batch testing was performed. For each participant, baseline RPR and TP-PA reactivity were confirmed and specimens that were collected during the 6-month follow-up were tested at a single time for the RPR end point with the use of serial doubling dilutions according to *A Manual of Tests for Syphilis*.[7] In the intention-to-treat analysis (defined below), a response to therapy was defined as a decrease by a factor of four or more (with two dilutions) in the RPR titer or by an RPR titer that became nonreactive by the 6-month follow-up assessment. Treatment failure in the intention-to-treat analysis was defined as an increase by a factor of four or more in the RPR titer at any time during the follow-up period, and serologic nonresponse was defined as RPR titers that remained within one doubled dilution of the baseline RPR titer. Evaluable participants who had transient increases in the RPR titer during the first month of follow-up that then returned to baseline levels or lower were classified as having a serologic response or nonresponse to therapy on the basis of RPR titers performed after the 1-month follow-up visit.[8]

FOLLOW-UP

Participants were contacted 24 to 48 hours after receiving the first benzathine penicillin G injection to evaluate post-treatment adverse effects, including symptoms of possible Jarisch–Herxheimer reaction (which include fever, appearance or change in rash, myalgia, and arthralgia). All the participants were scheduled for follow-up visits at 1 week, 2 weeks, and at months 1, 3, 6, and 12. At each follow-up visit, the participants underwent a brief clinical examination and an interval history-taking of sexual activity, symptoms, solicited and unsolicited adverse events, and recent antibiotic use. Phlebotomy for RPR testing was carried out at each follow-up visit.

STATISTICAL ANALYSIS

The prespecified primary end-point analysis was a noninferiority comparison of the serologic response to therapy at 6 months. Participants were randomly assigned to the treatment groups in a 1:1 ratio. Between-group differences in response, as shown with the use of the Farrington–Manning test, were compared without adjustment for HIV infection status. The prespecified noninferiority margin was 10 percentage points. The null hypothesis specified that a response would occur in 68.8% of the participants who received the one-dose regimen and 78.8% of the participants who received the three-dose regimen, with a one-sided alpha level of 0.05. We estimated that a sample size of 420 participants (210 per treatment group) was needed to provide the trial with 80% power to show noninferiority; however, enrollment was profoundly slowed by the onset and course of the Covid-19 pandemic. Futility analyses performed at the time the trial was halted showed that when approximately 78.9% of the participants in each group had a response, available data could still provide the trial with 80% power to show noninferiority.

Analyses were performed for the intention-to-treat population as well a per-protocol population at the time of the 6-month follow-up. The intention-to-treat population included all the participants who met eligibility criteria and underwent randomization. The evaluable population of participants who did not have a protocol-specified status change during follow-up were referred to as the per-protocol population. The evaluable population includes all the participants who were eligible at the baseline visit, had a known HIV infection status that was determined at baseline, had positive TP-PA results, received all assigned doses of benzathine penicillin G, had RPR test data available at baseline, and had at least one follow-up visit at or before the 6-month visit; participants who did not have HIV infection were included in the evaluable population if they met the eligibility criteria and if their HIV-uninfected status persisted through month 6.

RESULTS

PARTICIPANTS

Between October 31, 2018, and March 3, 2022, a total of 254 persons were screened for participation at the 10 trial sites, and 249 were enrolled in the intention-to-treat trial population, leading to 199 participants who were evaluable for the primary end point (Fig. 1). Of the enrolled participants, 124 received a single treatment with benzathine penicillin G and 125 received three benzathine penicillin G treatments at weekly intervals. As of 6 months after they received the first dose (or the only dose, in the one-dose group), 50 participants were excluded from the evaluable population; among the reasons for exclusion were

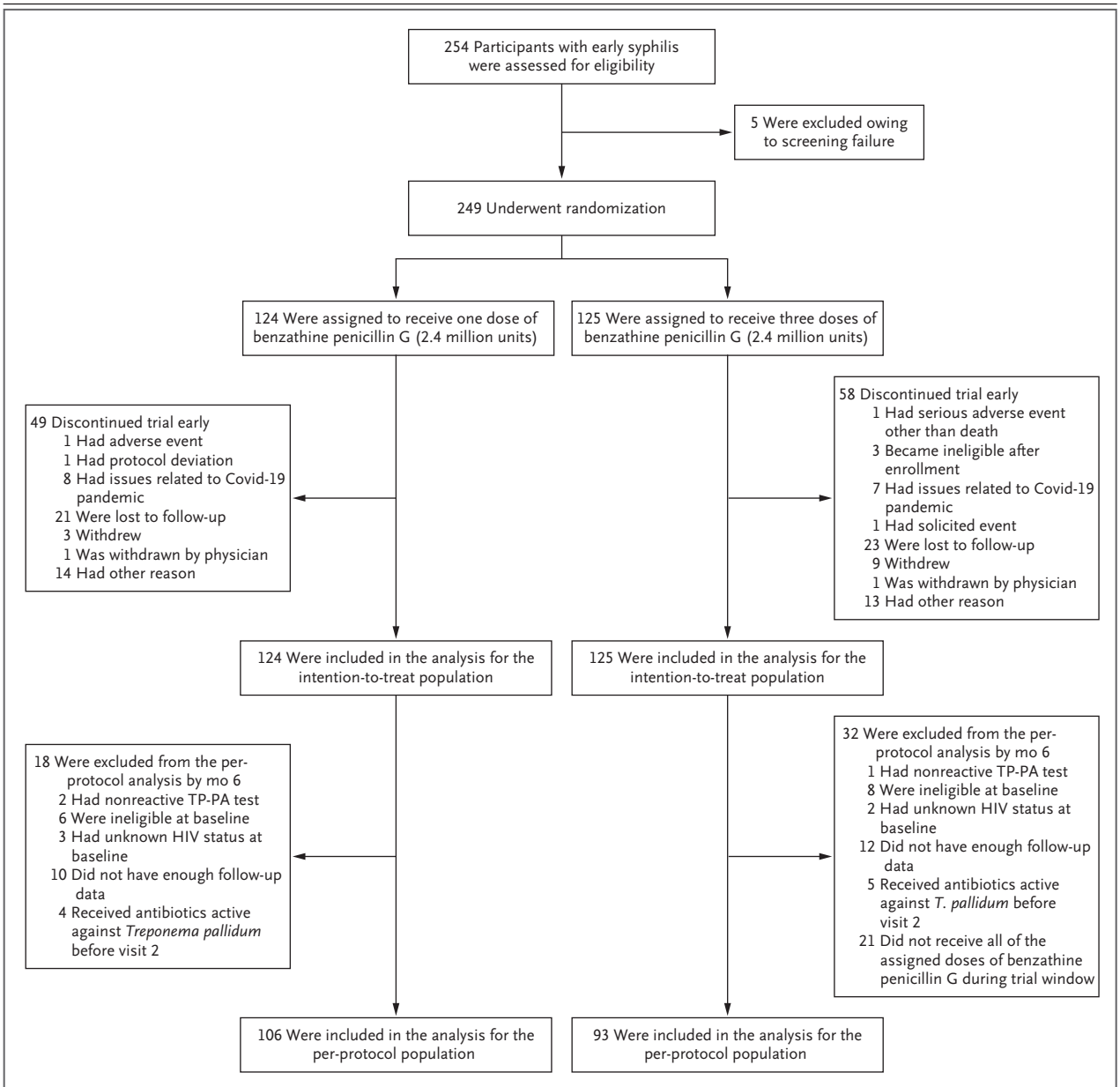

Figure 1. Screening and Randomization.

Participants could be excluded from the per-protocol analysis for more than one reason. Covid-19 denotes coronavirus disease 2019, HIV human immunodeficiency virus, and TP-PA *Treponema pallidum* particle agglutination.

loss to follow-up (34 participants), failure to receive all scheduled benzathine penicillin G doses (21 participants, all of whom were in the three-dose treatment group), receipt of antibiotics active against *T. pallidum* for reasons other than syphilis before having valid follow-up RPR results (9 participants), and a reactive HIV test result during follow-up (2 participants). Some participants had multiple reasons for not being included in the evaluable category. A total of 22 participants who discontinued participation in the trial early were not included in the analyses because no follow-up RPR specimens were collected.

Most of the participants were male (97%) and characterized themselves as non-Hispanic (95%) and Black (62%). The mean age was 35 years (range, 19 to 66) (Table 1). A total of 153 participants (61%) had HIV infection and 91 did not. With regard to syphilis status, 19% of the participants were classified as having primary syphilis, 47% as having secondary syphilis, and 33% as having early latent syphilis (Table 2). A total of 22 participants (9%) reported having had syphilis previously. The distribution of these characteristics among the evaluable population was similar to that in the intention-to-treat population (Table S1 in the Supplementary Appendix).

Among 153 participants with HIV infection in the intention-to-treat population, 92% reported taking antiretroviral therapy (ART). Among the 130 participants with HIV infection in the per-protocol population, 94% were taking ART. A total of 110 participants with HIV infection (77%) had CD4 lymphocyte concentrations at the time of treatment that were higher than 350 cells per cubic millimeter. The distribution of participants who were taking ART and had CD4 lymphocyte concentrations higher than 350 cells per cubic millimeter did not differ meaningfully between the two groups.

END POINTS

In the intention-to-treat population at 6 months after the first dose (or the only dose, in the single-dose group), the percentage of participants with a serologic response was 76% (95% Wilson confidence interval [CI], 68 to 82) in the single-dose group and 70% (95% Wilson CI, 61 to 77) in the three-dose group (Fig. 2). Use of the Farrington–Manning test showed the between-group difference in the percentage of participants with a serologic response was −6 percentage points (90% CI, −15 to 3). The upper confidence limit of 3 percentage points is less than the noninferiority margin of 10 percentage points, which indicates that the single benzathine penicillin G treatment was noninferior to three successive weekly treatments with 2.4 million units of benzathine penicillin G. Similarly, in the per-protocol group, the single-dose treatment was again shown to be noninferior to the three-dose treatment (serologic response, 77% [95% CI, 66 to 84] and 71% [95% CI, 61 to 79], respectively). There were no treatment failures shown in the analyses that included evaluable participants.

Among participants with at least one follow-up visit 6 to 24 days (median 14 days) after enrollment, 72% had complete symptom resolution and the remaining 28% had a reduction in ulcers or rash after the initial dose of benzathine penicillin G. Resolution of symptoms was similar when stratified according to the number of doses of benzathine penicillin G and according to syphilis stage.

When the treatment groups in the intention-to-treat population were further stratified according to HIV infection status, there was no apparent difference in the percentage of participants with a serologic response (Table 3). Among participants assigned to the one-dose group, a serologic response was observed at 6 months in 76% of participants with HIV infection and 76% of participants who did not have HIV infection. Of the participants who received the three-dose treatment, a serologic response at 6 months was observed in 71% of participants who had HIV infection and 70% of those who did not. Results in the per-protocol population were similar to those in the intention-to-treat population.

Of the 142 participants with HIV infection in the intention-to-treat population, 110 (77%) had CD4 lymphocyte concentrations of 200 cells per cubic millimeter or higher, and 32 (23%) had CD4 lymphocyte concentrations lower than 200 cells per cubic millimeter. A serologic response to therapy at 6 months occurred in 74% of the participants with 200 CD4 cells per cubic millimeter or more and 69% of participants with HIV infection and less than 200 CD4 cells per cubic millimeter.

Several factors potentially affecting serologic response to therapy were evaluated (Tables 2 and 3). In the intention-to-treat population, 65% of the participants (54 of 83) with early latent syphilis

Table 1. Characteristics of the Participants at Baseline.*

Characteristic	One Dose (N=124)	Three Doses (N=125)	Total (N=249)
Median age (IQR) — yr	33 (27–43)	31 (26–41)	32 (27–42)
Race and ethnic group — no. (%)†			
Black	74 (60)	80 (64)	154 (62)
White	35 (28)	28 (22)	63 (25)
Asian or other	15 (12)	17 (14)	32 (13)
Hispanic	8 (6)	4 (3)	12 (5)
Sex at birth — no. (%)			
Male	119 (96)	123 (98)	242 (97)
Female	5 (4)	2 (2)	7 (3)
HIV infection status — no. (%)			
Positive	70 (56)	83 (66)	153 (61)
Negative	51 (41)	40 (32)	91 (37)
Positive and prescribed ART — no./total no.	68/70 (97)	73/83 (88)	141/153 (92)
Trial site — no. (%)			
Atlanta	37 (30)	38 (30)	75 (30)
Baltimore	2 (2)	2 (2)	4 (2)
Baton Rouge, LA	16 (13)	16 (13)	32 (13)
Birmingham, AL	21 (17)	20 (16)	41 (16)
Boston	6 (5)	6 (5)	12 (5)
Chapel Hill, NC	3 (2)	2 (2)	5 (2)
Indianapolis	11 (9)	10 (8)	21 (8)
Pittsburgh	1 (1)	2 (2)	3 (1)
Seattle	7 (6)	8 (6)	15 (6)
Wake Forest, NC	20 (16)	21 (17)	41 (16)
History of syphilis — no. (%)‡	9 (7)	13 (10)	22 (9)
Sex partners — no. (%)			
Same sex	91 (73)	99 (79)	190 (76)
Opposite sex	15 (12)	12 (10)	27 (11)
Both sexes	16 (13)	12 (10)	28 (11)
Sex partners in past 6 mo — no. (range)	2 (1–4)	2 (1–4)	2 (1–4)
RPR titer results — no. (%)			
1:1	1 (1)	1 (1)	2 (1)
1:2	0 (0)	2 (2)	2 (1)
1:4	5 (4)	6 (5)	11 (4)
1:8	7 (6)	9 (7)	16 (6)
1:16	11 (9)	4 (3)	16 (6)
1:32	20 (16)	21 (17)	41 (16)
1:64	28 (23)	31 (25)	59 (24)
1:128	25 (20)	28 (22)	53 (21)
1:256	16 (13)	12 (10)	28 (11)

Table 1. (Continued.)

Characteristic	One Dose (N=124)	Three Doses (N=125)	Total (N=249)
1:512	4 (3)	1 (1)	5 (2)
>1:512	2 (2)	4 (3)	3 (>1)
Geometric mean RPR titer (95% CI)	60.0 (47.5–75.9)	57.1 (44.2–73.5)	58.5 (49.3–69.5)

* Percentages may not total 100 owing to rounding. Each dose was 2.4 million units of benzathine penicillin G. ART denotes antiretroviral therapy, CI confidence interval, HIV human immunodeficiency virus, IQR interquartile ratio, and RPR rapid plasma reagin.
† Race and ethnic group were reported by the participant.
‡ History of syphilis was reported by the participant.

had a serologic response by the 6-month follow-up; the percentage of participants with a response among those with primary or secondary syphilis was 77% (12 of 165 participants). In addition, participants who had a Jarisch–Herxheimer reaction after receiving their initial treatment were more likely to have a serologic response than those who did not (85% [95% CI, 73 to 92] and 69% [95% CI, 62 to 75], respectively) (Table 3). A participant-reported history of syphilis was not strongly associated with a response to therapy (Table 3).

ADVERSE EVENTS

Treatment-related adverse events were common. The most common adverse events were localized and related to the benzathine penicillin G injection. In the intention-to-treat population, 201 participants (81%) reported local injection-site pain, tenderness, or redness. In addition, 59 participants (24%) reported symptoms that were classified as a Jarisch–Herxheimer reaction.

Serious adverse events — all of which were judged by the site investigators to be unrelated to benzathine penicillin G — were reported by three participants. One participant had an episode of proctocolitis, and one was hospitalized for psychiatric care related to illegal drug use. The third serious adverse event was facial paralysis that developed in one participant after administration of the initial dose of penicillin, an effect that investigators deemed to be a result of the natural history of syphilis in that participant and an event that would have occurred irrespective of the administration of therapy. The facial paralysis resolved after the participant was treated for neurosyphilis.

There were clinically important between-group differences in the frequency and participant-reported severity of adverse events. Pain was the most common adverse event (reported by 76% of the participants in the one-dose group and 85% in the three-dose group). Among solicited systemic symptoms, the same pattern was recognized, with more events occurring in the three-dose group than in the one-dose group (32 events vs. 27 events), and the reported events were moderately more severe in the three-dose group than in the one-dose group. Investigator-assessed, treatment-related, unsolicited adverse events were reported in 10 participants — 5 in each group — with no material differences in severity.

DISCUSSION

The treatment of syphilis has been a scientific and public health priority for more than 100 years. Since the mid-1940s, *T. pallidum*, 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 benzathine penicillin G allowed the infection to be treated with a single injection.[3] Since then, benzathine penicillin G has remained the foundation of syphilis therapy.[4] Nonetheless, investigators periodically have questioned whether the outcomes of syphilis therapy might be improved with longer durations or higher doses of treatment, particularly in persons whose response to treatment might be compromised by coexistent immunosuppression, such as that caused by HIV infection.[5] This trial provides data showing that in participants with uncomplicated early syphilis (i.e., excluding clinical neurosyphilis and ocular and otic syphilis), a single treatment with benzathine penicillin G at a dose of 2.4 million units was noninferior to three treatments with benzathine penicillin G administered a week apart (for

Table 2. Serologic Response to Treatment with Benzathine Penicillin G at Month 6, According to Syphilis Stage.

Syphilis Stage	Intention-to-Treat Analysis			Per-Protocol Analysis		
	One Dose*	Three Doses	Total	One Dose†	Three Doses	Total
	number/total number (percent)					
Primary	20/25 (80)	16/23 (70)	36/48 (75)	19/21 (90)	14/20 (70)	33/41 (80)
Secondary	45/58 (78)	46/59 (78)	91/117 (78)	40/52 (77)	32/45 (71)	72/97 (74)
Primary and secondary	65/83 (78)	62/82 (76)	127/165 (77)	59/73 (81)	46/65 (71)	105/138 (76)
Early latent	29/41 (71)	25/42 (60)	54/83 (65)	23/33 (70)	20/28 (71)	43/61 (70)

* Treatment failure occurred in one participant with secondary syphilis and three participants with early latent syphilis.
† Treatment failure occurred in one participant with primary syphilis, one participant with secondary syphilis, and three participants with early latent syphilis.

a total of 7.2 million units). These data complement the findings by Rolfs et al., which showed that higher doses of penicillin did not improve the response to therapy.[10]

A single treatment with benzathine penicillin G for early syphilis is appealing for several reasons, including antimicrobial stewardship and patient comfort. During our trial, as on several occasions over the past several decades, benzathine penicillin G was in short supply in the United States. This shortage led public health authorities to prioritize which patients receive benzathine penicillin G and which should be treated with alternative therapies.[6] Global shortages of benzathine penicillin G are also common and undermine syphilis-control efforts in many countries.[11] In addition, injections of benzathine penicillin G are uncomfortable for patients and create a disincentive to follow-up treatment. In this trial, the most common adverse event reported by participants was injection-site pain and tenderness. As noted, injection pain was reported more commonly in the group assigned to receive three doses, a factor possibly related to cumulative discomfort caused by serial injections. Of the 125 participants assigned to the three-dose group, 21 participants (17%) did not receive all three planned treatments. Although the participants' reasons for not receiving all doses were not consistently recorded, the potential for discomfort from the additional injections may have been a contributor. Anecdotally, among the persons prescreened for trial participation, several who had had syphilis previously cited the possibility of receiving multiple benzathine penicillin G injections as among their reasons for choosing to not participate. With no observable benefit to multiple treatments, a single treatment at a dose of 2.4 million units should be, in our opinion, the preferred treatment for early syphilis.

Our trial has several limitations. The number of women in the trial was low. The data are insufficient to evaluate the response to therapy among women, and there are no data on outcomes of therapy for pregnant persons. In addition, many persons with a diagnosis of 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 persons with late syphilis, latent syphilis of unknown duration, and clinical neurosyphilis remain research priorities. Alternatives to penicillin are needed for the treatment of persons who report an allergy to penicillin (up to 20% of the population).[12,13] A further limitation of the trial is our continued reliance on serologic response to therapy as an indicator of therapeutic effect.[10,14] Serologic response is an imperfect measure because it may take months to occur, and even after as long as 6 months after the initiation of therapy, approximately 20% of persons treated for early syphilis have no clinically important change in RPR titers.[10,14] Although it is widely considered to be unlikely that treatment failed in these participants, improved methods to diagnose active syphilis and to assess response to therapy are needed.

Our trial produced limited data on persons with advanced or untreated HIV infection. Nearly all the participants with HIV infection in our trial were receiving ART, and 77% had CD4 concentrations greater than 350 cells per cubic millimeter; no apparent difference in response was observed when data from persons with HIV infection and low CD4 counts (<200 cells per cubic millimeter) were analyzed. We suspect that a single treatment with benzathine penicillin G would be effective in persons with untreated HIV infection or in persons with profound immunosuppression; however, our data are insufficient to fully address these knowledge gaps.

This trial provides data that indicate that persons with early syphilis, including persons with HIV infection, can be effectively treated on

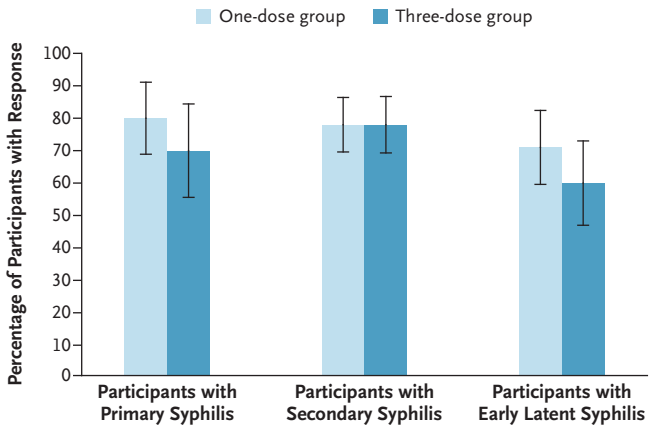

Figure 2. Serologic Response to Treatment with Benzathine Penicillin G.

Table 3. Serologic Response to Treatment with Benzathine Penicillin G at Month 6, According to Other Factors.

Factor and Analysis	One-Dose Group		Three-Dose Group		Total	
	no. with response/ total no.	*percent (95% CI)*	*no. with response/ total no.*	*percent (95% CI)*	*no. with response/ total no.*	*percent (95% CI)*
HIV status						
Intention-to-treat analysis						
Positive	53/70	76 (65–84)	59/83	71 (61–80)	112/153	73 (66–80)
Negative	39/51	76 (63–86)	28/40	70 (55–82)	67/91	74 (64–82)
Per-protocol analysis						
Positive	46/64	72 (60–81)	45/66	68 (56–78)	91/130	70 (62–77)
Negative	36/42	86 (72–93)	21/27	78 (59–89)	57/69	83 (72–90)
History of syphilis*						
Intention-to-treat analysis						
Present	4/9	44 (19–73)	9/13	69 (42–87)	13/22	59 (39–77)
Absent	90/115	78 (70–85)	78/112	70 (61–77)	168/227	74 (68–79)
Per-protocol analysis						
Present	3/6	50 (18–81)	6/12	50 (25–75)	9/18	50 (29–71)
Absent	79/100	79 (70–86)	60/81	74 (64–83)	139/181	77 (70–82)
Jarisch–Herxheimer reaction to benzathine penicillin G						
Intention-to-treat analysis						
Present	23/27	85 (68–94)	27/32	84 (68–93)	50/59	85 (73–92)
Absent	71/97	73 (64–81)	60/93	65 (54–73)	131/190	69 (62–75)
Per-protocol analysis						
Present	21/25	84 (65–94)	18/22	82 (61–93)	39/47	83 (70–91)
Absent	61/81	75 (65–83)	48/71	68 (56–77)	109/152	72 (64–78)

* History of syphilis was reported by the participant.

a single occasion with benzathine penicillin G administered in a single dose of 2.4 million units. The elimination of unnecessary doses of benzathine penicillin G reduces the cost of treatment, aligns with the principles of antimicrobial stewardship, and is more convenient for patients in that the numbers of clinic visits and painful intramuscular injections are decreased.

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