MAJOR ARTICLE

A Phase III Equivalence Trial of Azithromycin versus Benzathine Penicillin for Treatment of Early Syphilis

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Background. Syphilis remains an important source of morbidity worldwide. Long-acting penicillin is the only therapy currently recommended for syphilis in much of the world. Because of hesitation to use penicillin for fear of anaphylaxis, there is a need for an effective, well-tolerated alternative to penicillin for syphilis therapy.

Methods. This multicenter, randomized clinical trial was conducted in clinics for the treatment of persons with sexually transmitted diseases. We compared serological cure rates for human immunodeficiency virus (HIV)–negative persons with early syphilis treated with azithromycin at a dosage of 2.0 g administered orally as a single dose with cure rates for those treated with benzathine penicillin G at a dosage of 2.4 million units administered intramuscularly.

Results. A total of 517 participants were enrolled in the trial. In the intention-to-treat analysis, after 6 months of follow-up, serological cure was observed in 180 (77.6%) of 232 azithromycin recipients and 186 (78.5%) of 237 penicillin recipients (1-sided lower bound 95% confidence interval, 7.2%). Nonserious adverse events were more common among azithromycin recipients than they were among penicillin recipients (61.5% vs 46.3%), and such adverse events were accounted for, in large part, by self-limited gastrointestinal complaints.

Conclusions. In this trial, the efficacy of azithromycin at a dosage of 2.0 g administered orally was equivalent to that of benzathine penicillin G for the treatment of early syphilis in persons without HIV infection.

Clinical trial registration. ClinicalTrials.gov identifier: NCT00031499.

Despite dramatic decreases since the onset of the antibiotic era, syphilis remains a relatively common disease and a major public health problem that contributes to substantial morbidity and mortality through congenital syphilis, the long-term sequelae of the disease, and biological amplification of the risk for acquisition of human immunodeficiency virus (HIV) infection [1]. For >60 years, the mainstay of syphilis treatment has been penicillin. At present, long-acting penicillin (benzathine penicillin G) is recommended as the preferred treatment for early syphilis [2] and has provided reliable therapy for patients with the disease since it was first used in the late 1940s. Penicillin therapy, however, is not without shortcomings. In developing nations, where syphilis is most common, storage of penicillin within approved temperature ranges may be challenging. In addition, ~10% of persons will report an allergy to penicillin [3], and the medication must be given via deep intramuscular injection, which causes discomfort for persons with syphilis and places health care providers at risk for needle stick injuries. There are few optimal alternatives for the treatment of early syphilis for persons who cannot receive penicillin treatment. The most widely used alternative, doxycycline, causes its own spectrum of adverse events and is not recommended for use in patients who are pregnant [2]. In addition, doxycycline must be taken twice daily for a period of 14 days for the treatment of early syphilis,

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which introduces the variable of medication adherence to efforts to cure the disease.

Azithromycin is a macrolide antimicrobial agent with broad-spectrum activity. The drug has become a mainstay of sexually transmitted diseases (STD) treatment as a recommended therapy for uncomplicated chlamydial infections and chancroid and, in doses of 2.0 g, as an alternate therapy for gonorrhea [2]. Azithromycin has also been used in a pilot study to treat early syphilis in North America, as well as in a large randomized controlled trial in Africa [4, 5]. This report describes outcomes of the first randomized controlled trial conducted under US Food and Drug Administration oversight to evaluate a new therapy for syphilis. We compared cure rates for patients with early syphilis treated with a single dose of azithromycin (2.0 g administered orally) with cure rates for those treated with benzathine penicillin G (2.4 million units administered intramuscularly).

METHODS

This open-label randomized controlled trial was conducted at 5 clinical sites in North America and 3 clinical sites in Madagascar. Participants were eligible for participation if they were 18–55 years of age, had early syphilis (primary, secondary, or early latent), had reactive rapid plasma reagin (RPR) and fluorescent treponemal antibody absorption (FTA-ABS) test results, were not pregnant, had serological test results negative for HIV infection, had not taken antibiotics effective against *Treponema pallidum* within the 30 days preceding enrollment, and had no known allergies to penicillin or macrolide antibiotics. Subjects were defined as having primary syphilis if they had genital ulceration and *T. pallidum* visualized on dark-field microscopy of lesion exudate [2, 6]. 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 were subjects with reactive RPR test results and either a nonreactive serological test result for syphilis or documented exposure to a sexual partner with primary or secondary syphilis within the preceding 12 months.

Response to therapy was evaluated on the basis of changes in RPR titer. Serum samples for determination of response to therapy were transferred frozen to a central laboratory where they were stored until testing. For each participant, all RPR tests through the 6-month follow-up visit were performed simultaneously at the central laboratory at the University of Alabama at Birmingham by trained technicians according to package inserts and *The Manual of Serological Tests for Syphilis* [7]. Study participants' initial RPR titer was defined as the highest RPR titer value measured on day 0 (enrollment), 7, or 14 of study participation.

Treatment. All subjects received directly observed therapy. Subjects randomized to receive azithromycin received four 500-mg tablets of azithromycin orally and were observed for a period of 30 min after medication ingestion. Subjects who received benzathine penicillin received 2 deep intramuscular injections of 1.2 million units of benzathine penicillin and were similarly observed.

The primary end point of this trial was serological cure of infection, which was defined as a decrease in RPR titer at the time of the 6-month follow-up visit of $\geq$2 dilutions (4-fold) when compared with the initial RPR titer.

When a subject had a protocol status change, the patient was recommended to be retreated with the penicillin therapy. Reasons for a change of protocol status included participants who did not tolerate treatment (eg, 3 azithromycin treatment group participants who vomited within 30 min of medication ingestion), subjects who did not complete at least 6 months of follow-up, subjects who took intercurrent antibiotics active against *T. pallidum*, women who became pregnant, subjects deemed to be reinfected with syphilis, and subjects who were found to have HIV infection while participating in the trial.

Follow-up. Following enrollment, subjects were scheduled for follow-up at 7 days, 14 days, 30 days, 3 months, and 6 months. At each follow-up visit, subjects underwent a brief clinical examination, and an interval history of sexual activity, symptoms, and recent antibiotic ingestion was obtained. At each follow-up visit, an additional serum sample was obtained for serological testing for syphilis. HIV testing was performed at the time of enrollment and at the 6-month follow-up visit. Participants who were found to be HIV infected at the time of enrollment or during study follow-up were treated with benzathine penicillin G, their protocol status was changed, and they continued in the study only for safety follow-up.

Statistical analysis. Analyses were performed for the intent-to-treat cohort, as well as a subset of the intent-to-treat cohort, referred as the per protocol cohort. The intent-to-treat analysis includes all subjects who met the eligibility criteria of the study as mentioned earlier. The per protocol analysis includes all subjects who did not have protocol status change during the period (6 months post treatment) when the primary endpoint data were collected (Table 1).

The study objective was to use the cure rates to determine whether azithromycin treatment is noninferior to penicillin treatment. An equivalence margin was predefined as an observed azithromycin cure rate $\leq$12% below the observed penicillin cure rate (ie, this is a 1-sided test to determine whether the lower bound of the 95% confidence interval [CI] for the difference in cure rate between the azithromycin and penicillin groups was at least -0.12). A normal approximation was used in calculating the confidence interval. The primary objective was to test noninferiority. The per protocol analysis is more likely to exhibit wider confidence intervals and, therefore, provides a less conservative primary end point based on data at 6 months among the per protocol cohort.

Table 1. Exclusion Criteria for the Per Protocol and Intent-to-Treat Groups

Group	Exclusion criteria
Per protocol	Subjects who did not tolerate treatment (reason 04 on Change in Protocol Status Form: vomiting within 2 h of azithromycin treatment) Subjects who did not complete at least 6 months of follow-up (Study Completion/Early Term form completed prior to visit 06 or prior to 6 months) Subjects who were deemed to be reinfected with syphilis (reason 10 on Change in Protocol Status Form: possible reinfection with syphilis) Subjects who became HIV infected while participating in the trial (reason 06 on Change in Protocol Status Form: intercurrent HIV infection) Subjects who became pregnant prior to visit 06 (reason 08 on Change in Protocol Status Form: pregnancy) Subjects who had a nonreactive or 1+ FTA-Abs test result with corresponding nonreactive or 1+ TPPA test results for visits 01–03 from the central laboratory Subject received intercurrent therapy or illness prior to visit 01 (conmed or reason 09 or 99 for subjects 08005, 10031 on Change in Protocol Status Form) Any subject that had a Change in Protocol Status form prior to visit 06 Missing data
Intent-to-treat	Subjects found to be ineligible on the basis of study inclusion and exclusion criteria (reason 01, 03 on Change in Protocol Status Form) Subjects who had a nonreactive or 1+ FTA-Abs test result with corresponding nonreactive or 1+ TPPA for visits 01–03 from the central laboratory Missing data

NOTE. FTA-Abs, fluorescent treponemal antibody absorption; HIV, human immunodeficiency virus; TPPA, *Treponema pallidum* particle agglutination.

Statistical tests were also performed to compare baseline characteristics and adverse events between the 2 treatment groups. Two-sided tests were used at the significance level of 5%, and all were performed using SAS, version 9.1 (SAS). In general, χ^2 tests or, if necessary, Fisher's exact tests were used for categorical outcomes, such as sex, race, and adverse event rate. Student's *t* tests were used for numerical outcomes, such as age.

Human subjects. Written informed consent was obtained from participants. The master protocol was reviewed and approved by the University of Alabama at Birmingham Institutional Review Board for Human Subjects and subsequently by Institutional Review Boards serving each of the study sites. During the trial, study progress and participant safety were evaluated on 2 occasions by a Data Safety Monitoring Board convened by the National Institutes of Allergy and Infectious Diseases.

RESULTS

Study population. From 1 June 2000 through 31 March 2007, 7112 subjects were screened and 517 participants were enrolled into the intent-to-treat study population; of these participants, 255 received azithromycin and 262 received penicillin G (Figure 1). Table 2 summarizes the baseline characteristics of the 2 groups. Across both study groups, the mean age of study participants was 27 years. One hundred and thirty-nine (55%) of the azithromycin recipients and 174 (66.4%) of the penicillin recipients were male ($P = .006$, by χ^2 test). The distribution of racial groups between the 2 treatment groups is similar. Specifically, ~16% of participants were African American; 2% were white; 82% were Malagasy, and <1% were other race or ethnicity (Table 2). Of the study participants, 26% were in the primary stage of infection, 46% were in the secondary stage of infection, and 28% had early latent syphilis. There was no statistically significant differences in the distribution of the syphilis clinical stages between the 2 treatment groups ($P = .35$, by Fisher's exact test). The distribution of the demographic and baseline characteristic data for the per protocol cohort were similar to those for the intent-to-treat cohort (data not shown). There were no statistically significant differences found between the 2 treatment groups for any of the categories. The sex difference observed in the intent-to-treat cohort was not statistically significant in the per protocol cohort ($P = .10$, by χ^2 test).

Adverse events. By the sixth month of follow-up, 8 (2.8%) of the azithromycin recipients and 10 (3.5%) of the penicillin recipients had experienced serious adverse events, including 6 deaths (3 in each group). No serious adverse events were related to the study drug.

Nonserious adverse events were ascertained for ~1 month (through visit 4) after syphilis treatment (Table 3). Overall, 174 (61.5%) of the study participants in the azithromycin group and 132 (46.3%) of the study participants in the penicillin group experienced nonserious adverse events ($P < .001$, by Fisher's exact test). This difference is attributable in large part to the fact that significantly more gastrointestinal adverse events occurred among azithromycin recipients than occurred among penicillin recipients. Among subjects with nonserious adverse events, gastrointestinal adverse events (including nausea, gastrointestinal discomfort, and diarrhea) occurred in a larger per-

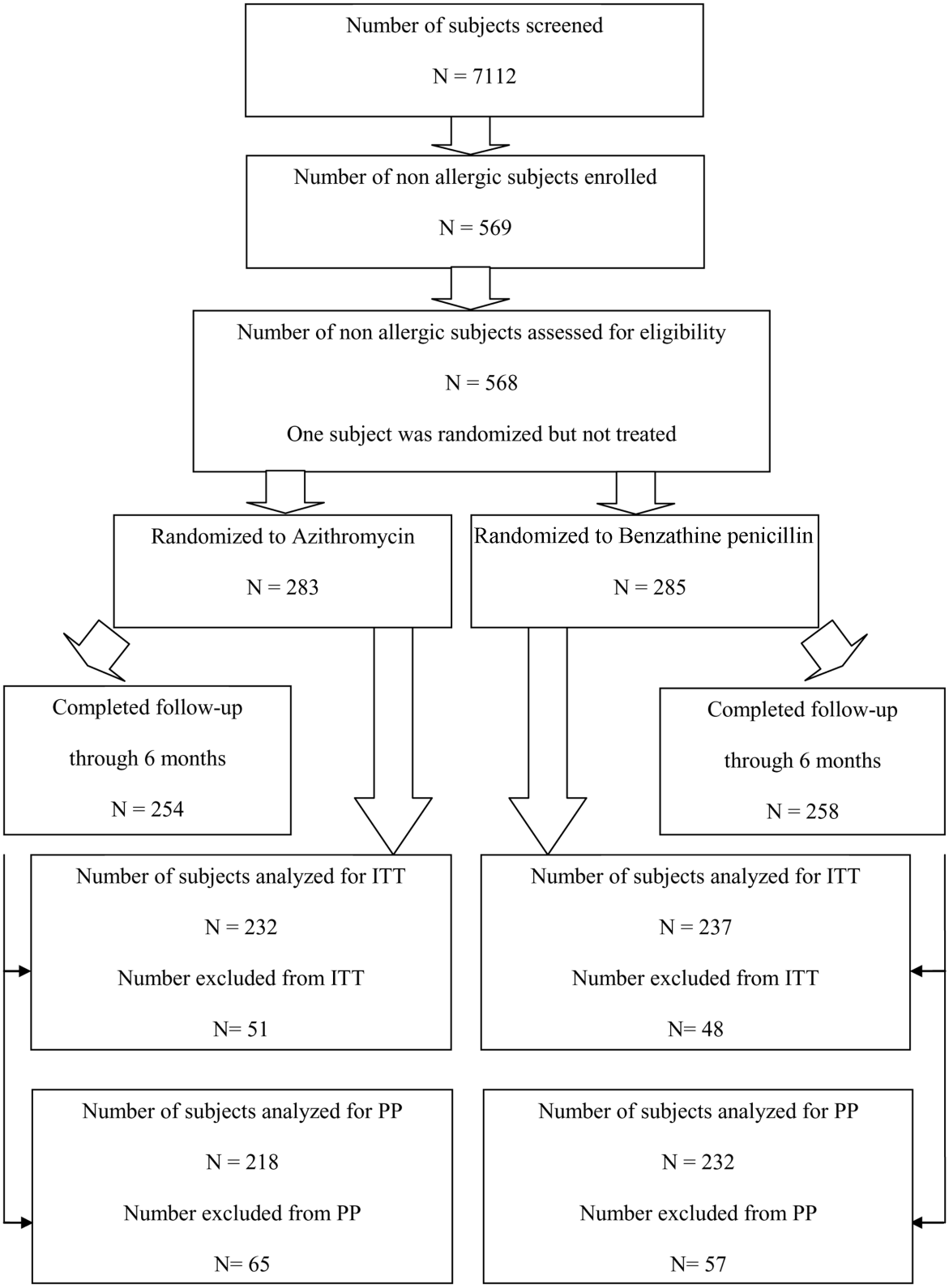

Figure 1. Flow of patients through the study. ITT, intent-to-treat; PP, per protocol.

Table 2. Phase III Equivalence Trial of Azithromycin vs Benzathine Penicillin for Early Syphilis (DMID99005), Intent-to-Treat Population

Variable	Azithromycin group (n = 255)	Penicillin group (n = 262)
Male sex	139 (55)	174 (66)
Race/ethnicity		
African American	40 (16)	43 (16)
White	5 (2)	6 (2)
Malagasy	209 (82)	212 (81)
Other	1	1
Age, mean years	27	27
Syphilis stage		
Primary	63 (25)	73 (28)
Secondary	117 (46)	120 (46)
Early latent	74 (29)	69 (26)

NOTE. Data are no. (%) of subjects, unless otherwise indicated.

centage of recipients who received azithromycin, compared with those who received penicillin (24.4% vs 7.4%; $P < .001$). Three azithromycin recipients (1.3%) vomited within 30 min of taking azithromycin and were classified as having experienced treatment failure in the intent-to-treat analyses. Azithromycin recipients also reported significantly more central nervous system symptoms, such as ageusia, dizziness, and headache, than did the penicillin recipients (6.7% vs 2.5%; $P = .01$). In contrast, skin rash and other cutaneous adverse events were present in 4 (1.4%) of azithromycin recipients and 12 (4.2%) of participants receiving penicillin G ($P = .07$). Administration-related adverse effects (eg, injection site pain and fever) were present in 14 (4.9%) of the azithromycin recipients, compared with 28 (9.8%) of the penicillin recipients ($P = .01$).

Response to therapy. Overall, the response to therapy for azithromycin-treated subjects was similar to that for subjects who received benzathine penicillin G (Table 4). In the intent-to-treat analysis, serological cure was achieved by the 3-month follow-up appointment for 177 (74.4%) of 238 azithromycin recipients, compared with 187 (75.7%) of 247 penicillin recipients (1-sided lower bound of the 95% CI of the difference, −7.8%). At the 6-month follow-up appointment, 180 (77.6%) of 232 azithromycin participants had experienced serological cure, whereas the cure rate was 78.5% (186 of 237 participants) among penicillin recipients (1-sided lower bound of the 95% CI of the difference, −7.2%). Likewise, in the per protocol analysis, the serological cure rates at 3 months were 73.4% (160 of 218 participants) and 74.9% (173 of 231 participants) in the azithromycin group and the penicillin group, respectively (1-sided 95% CI lower bound, −8.3%. As the primary end point, the serological cure rates at 6 months were 77.5% (169 of 218 participants) and 78.9% (180 of 228 participants) in the azithromycin and penicillin groups, respectively. The 1-sided 95% CI lower bound was −7.9%, which indicated that noninferiority of azithromycin to penicillin is achieved with the per protocol definition, as well. Although the predefined criteria for noninferiority were based on a 1-sided 95% CI and a noninferiority margin of 12%, the study actually demonstrated a lower bound for the 2-sided 95% CI of −9.1% for the primary end point in the more conservative per protocol analyses. There were no significant differences in response to therapy noted when serological response to therapy by participants enrolled in Madagascar was compared with the serological responses of US participants.

No participant in either treatment arm had persistent or recurrent clinical manifestations of syphilis. In the course of the study, 4 (1.4%) of the subjects who were enrolled and followed up in Madagascar were defined as having experienced failure of syphilis therapy on the basis of serologic test results with an increase of 2 dilutions (a 4-fold increase) over the study period. Each of these subjects had received azithromycin.

DISCUSSION

In theory, syphilis should be an eradicable disease, because it can be readily diagnosed with affordable serological tests; can be treated with relatively inexpensive single-dose antibiotics (eg, benzathine penicillin G); and has a relatively long, noninfectious incubation period, during which effective partner notification and preventative therapy might interrupt transmission to sexual partners. Thus, failure to successfully control the disease might reveal the "real world" shortcomings of current management strategies. Despite penicillin's proven usefulness for syphilis therapy, clinicians regularly seek alternate therapy for syphilis for many infected persons with a possible penicillin allergy or, in some locales, aversion to parenteral therapy. Ceftriaxone, doxycycline, and several other multiple-dose medications have been shown to have efficacy for syphilis therapy [2]; however, concerns regarding medication adherence have made officials reticent to recommend them except for persons in whom penicillin or de-

Table 3. Phase III Equivalence Trial of Azithromycin vs Benzathine Penicillin for Early Syphilis (DMID99–005), Intent-to-Treat Population

	No. (%) of participants	
Adverse event	Azithromycin group (n = 283)	Penicillin group (n = 285)
Serious	8 (2.8)	10 (3.5)
Nonserious	174 (61.5)	132 (46.3)
Gastrointestinal	69 (24.4)	21 (7.4)
Central nervous system	19 (6.7)	7 (2.5)
Cutaneous	4 (1.4)	12 (4.2)
Administration related	14 (4.9)	28 (9.8)

Table 4. Phase III Equivalence Trial of Azithromycin vs Benzathine Penicillin for Early Syphilis (DMID99–005)

Population, time from treatment	Serological cure rate, proportion (%) of participants with cure		Difference, %	One-sided 95% confidence interval lower bound, %
	Azithromycin group	Penicillin group		
Intent-to-treat				
3 Months	177/238 (74.4)	187/247 (75.7)	−1.3	−7.8
6 Months	180/232 (77.6)	186/237 (78.5)	−0.9	−7.2
Per protocol				
3 Months	160/218 (73.4)	173/231 (74.9)	−1.5	−8.3
6 Months	169/218 (77.5)	180/228 (78.9)	−1.4	−7.9

sensitization is not an option. As a single-dose oral antibiotic that is totally unrelated to penicillin, azithromycin represents a potentially appealing alternate therapy.

In this study of HIV-seronegative persons, oral azithromycin administered at a dosage of 2.0 g was found to be equivalent to benzathine penicillin administered via intramuscular injection for early syphilis treatment. Although it was associated with a somewhat increased rate of mild adverse effects, azithromycin was relatively well tolerated. When considered together with prior studies conducted in both North America and sub-Saharan Africa [4, 5], these data suggest that azithromycin may be a useful alternative to penicillin injections for the treatment of early syphilis. Strengths of our study include that it was a randomized, multicenter, multinational study and that it was conducted using the US Food and Drug Administration investigational new drug guidelines. Laboratory-to-laboratory or date-to-date variation in measurement of serological response was minimized by determination of all serological test results simultaneously in a single laboratory.

Although this study found the efficacy of azithromycin and penicillin to be similar, it is not without its limitations. Worldwide, persons with syphilis are commonly coinfected with HIV; however, subjects with HIV infection were excluded from participation in this study. However, in an earlier study conducted in Tanzania, the response rate for patients with syphilis and HIV infection who were treated with azithromycin was similar to the rate for those treated with benzathine penicillin [5]. In light of continuing concerns regarding the usefulness even of currently recommended syphilis-treatment regimens for patients who have HIV infection [2], these data should be extended cautiously for treatment for persons with syphilis and HIV coinfection. In addition, in this and other North American studies of syphilis therapy [4, 8], ~20% of persons with early syphilis did not exhibit meaningful changes in titers of serological tests for syphilis 6 months after therapy [2]. Whether such patients are at risk for subsequent relapse is unknown. Studies that measure response to syphilis therapy beyond the 6-month end point used in this trial would help to address this question.

Azithromycin was relatively well tolerated by study participants. Rates of serious adverse events were similar in both treatment groups, and the serious adverse events that occurred were deemed to be unrelated to the study drugs. Non serious adverse events were more common among the azithromycin group and were most often related to gastrointestinal adverse effects (which are well-described for this medication). Efforts were made to reduce gastrointestinal upset through provision of a small snack (eg, crackers or hard candy) at the time of medication administration, with some apparent success.

In considering these data, an important concern is that recent reports suggest that the prevalence of a 23S rRNA mutation for macrolide resistance, which was first described in patient isolates >30 years ago, has increased substantially [9–12]. Case reports also suggest that persons with this mutation are at increased risk for treatment failure when treated with azithromycin [10]. More-recent case series indicate that the mutation is widespread [12], but there are still limited data regarding the proportion of persons infected with *T. pallidum* who carry this mutation who go on to experience failure of azithromycin therapy. We did not routinely determine the prevalence of the 23S rRNA mutation, which appears to encode for macrolide resistance among *T. pallidum* isolates at study locations. A substudy conducted on specimens from participants enrolled in Madagascar, which is the country where the largest number of subjects was enrolled, found no evidence of this mutation in ~150 isolates [13]. Interestingly, the only 4 serologic treatment failures seen in our study occurred in Madagascar, making it unlikely that this 23S rRNA contributed to the treatment failures. This observation leaves unresolved the important question of the contribution of this mutation to syphilis treatment failure among individuals treated with azithromycin.

Finally and importantly, no pregnant subjects with syphilis were included in the analysis for this study. Because of sub-

stantial evidence of congenital syphilis occurring despite treatment with macrolide antimicrobial agents, pregnant women with early syphilis should definitely not be treated with azithromycin for their infections.

In summary, this study strengthens evidence that suggests that azithromycin administered at a dosage of 2.0 g given as a single dose may be a potentially useful addition to the therapeutic armamentarium for syphilis control. Effective single-dose oral therapy for syphilis could potentially enhance control efforts as a therapeutic option for penicillin-allergic patients and, in selected settings, as field-delivered therapy or partner-delivered therapy for persons with recent exposure to sex partners with infectious syphilis. However, the implications of this result should be tempered by lingering concerns regarding the potential impact of macrolide resistance in *T. pallidum* and the potential for coexisting HIV infection to reduce the effectiveness of syphilis therapy. The adoption of azithromycin for routine syphilis therapy will require translational research studies and monitoring of azithromycin resistance. Further studies building on these observations are needed and should be encouraged.

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