

# Effectiveness of Syphilis Treatment Using Azithromycin and/or Benzathine Penicillin in Rakai, Uganda

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**Objective:** The goal of this study was to assess azithromycin and/or benzathine penicillin for treatment of syphilis.

**Methods:** In a population-based study, participants with serologic syphilis (TRUST with TPHA confirmation) were offered 2.4 MU benzathine penicillin intramuscularly. Intervention arm participants received 1 g presumptive oral azithromycin. We assessed cure rates with penicillin or azithromycin given alone and in combination. Cure assessed after 10 months was defined as seroreversion or a 4-fold decrease in titer. The rate ratio (RR) of cure and 95% confidence intervals (95% CIs) were estimated by log binomial regression.

**Results:** Among 952 cases with syphilis, 18% received penicillin alone, 17% azithromycin only, and 65% dual treatment. The overall cure rate was 61%. Cure rates were lower in males compared with females (RR, 0.89; 95% CI, 0.80–0.99) and in subjects with initial titers  $\geq 1:4$  compared with  $\leq 1:2$  (RR, 0.77; 95% CI, 0.69–0.86). There was no significant differences in cure rates among HIV-positive and HIV-negative persons. With initial titers  $\leq 1:2$ , there were no differences in cure rates by treatment regimen. However, with initial titers  $\geq 1:4$ , significantly higher cure rates were observed with azithromycin alone (adjusted RR, 1.38; 95% CI, 0.97–1.96), and with dual treatment of azithromycin and benzathine penicillin (RR, 1.38; 95% CI, 1.03–1.87) compared with penicillin alone.

**Conclusion:** Azithromycin alone or in combination with penicillin achieved higher cure rates than penicillin alone in cases with a high initial TRUST titer. In low-titer infections, the 3 drug combinations were equally effective. HIV status did not affect cure rates.

GENITAL ULCER DISEASE (GUD), caused by primary and secondary syphilis has been associated with increased infectious-

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ness of and susceptibility to HIV, and syphilis, particularly in pregnancy, is a major public health problem.<sup>1,2</sup> Benzathine penicillin has long been the standard treatment for syphilis, but studies have established that azithromycin is effective and may be useful for the control of syphilis in high-risk populations or during epidemics.<sup>3–8</sup> Azithromycin has the added advantage of oral administration rather than intramuscular injection. Also, there is limited information on whether HIV infection affects the response to syphilis treatment in developing countries, although previous studies in developed countries suggest that HIV infection has relatively modest effects on cure rates.<sup>9,10</sup>

We assessed the outcomes of syphilis treatment with benzathine penicillin or azithromycin given alone or in combination among HIV-positive and HIV-negative individuals in a rural African population with a predominance of asymptomatic/latent syphilis infection. Previous studies have described the effect of HIV infection and/or treatment in early syphilis among clinic-based populations<sup>11–13</sup>

## Methods

This is a secondary data analysis of a community-randomized trial of sexually transmitted disease (STD) control for HIV prevention in Rakai, Uganda, conducted in 1994–1998.<sup>14,15</sup> In brief, 56 communities were aggregated into 10 clusters, which were randomized into an intervention arm receiving presumptive STD treatment, and a control arm. Persons with serologic syphilis were offered a single intramuscular injection of 2.4 MU benzathine penicillin in both study arms.<sup>16,17</sup> In addition, in the intervention arm, all participants were offered presumptive treatment with a single directly observed dose of 1 g azithromycin. Thus, treatment could be categorized into 3 groups: benzathine penicillin only, azithromycin only, and dual therapy (azithromycin and benzathine penicillin, usually provided within 1 to 2 days of each other).

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Treatment assignment was nonrandom because participants receiving azithromycin alone would have been intervention-arm subjects who declined benzathine penicillin, and participants receiving dual treatment were intervention-arm subjects who accepted both drugs. Participants receiving benzathine penicillin alone were predominantly control-arm subjects or intervention-arm subjects who declined azithromycin.

Respondents provided serum at 10-month intervals for syphilis testing using the nontreponemal TRUST (Toluidine Red Unheated Serum Test; New Horizons, Columbia, MD) kit followed by TPHA (*Treponema pallidum* hemagglutination assay, Sera-Tek; Fujirebio, Tokyo, Japan) confirmation of TRUST-positive samples. The TRUST assay has been evaluated and is comparable to the rapid plasma reagin (RPR) card test in sensitivity, specificity, intra- and interlaboratory reproducibility.<sup>18</sup> The standard treatment of benzathine penicillin was offered to all persons with confirmed serologic syphilis in the intervention and control arms. Cure was defined as a 4-fold reduction in TRUST titers or seroreversion at 10 months. Participants with serologic syphilis were stratified by initial TRUST titer ( $\leq 1:2$  and  $\geq 1:4$ ), and by probable primary, early latent, and late latent syphilis based on WHO guidelines<sup>19</sup> (primary syphilis if they reported GUD within the 7 days before testing positive for syphilis, secondary or early latent if they reported GUD and a generalized rash in the past 12 months, and late latent syphilis if a respondent was asymptomatic). We also assessed HIV status, number of sex partners in the past 12 months, age, gender, and duration of time since treatment.

The decision to treat all serologically confirmed syphilis with 2.4 MU benzathine penicillin intramuscularly in a single dose rather than isolating latent syphilis of unknown duration for 3 doses of 2.4 MU benzathine penicillin at 1-week intervals was based on feasibility of replicating standard hospital guidelines in a rural African community setting that relied on home-based treatment. Because of the home-based setting, it was not feasible to determine the stage of infection and to provide weekly home visits. However, all government health centers were provided with benzathine penicillin to facilitate access to penicillin injections, if needed. As mentioned, all seropositive study respondents were offered screening and retreatment every 10 months, and this enabled us to treat all reinfections, treatment failures, and/or those who declined treatment at a previous contact. This treatment strategy was discussed with experts and approved by the Institutional Review Boards in Uganda (the Uganda National Council for Science and Technology/AIDS Subcommittee and the Ugandan Ministry of Health/AIDS Control Program), and at Columbia and Johns Hopkins Universities.

Exploratory data analysis used crosstabulation and chi-squared tests. The proportion of cases meeting the criteria for cure was the outcome of interest. In multivariate analyses, we used log-log binomial regression model to estimate the adjusted rate ratios (RR) and 95% confidence intervals (CIs) of cure with patients receiving penicillin alone as the reference group.<sup>20</sup> Confidence interval estimates were adjusted for potential correlation using the Huber-White sandwich estimator of variance for clustering at the individual level.<sup>21</sup> In multivariate adjustments, we fitted variables that were significant in univariate analysis plus variables that were thought to be biologically important in determining cure rates. Statistical computation was done using STATA version 8.<sup>22</sup>

## Results

There were 952 cases of serologically confirmed treated syphilis. Of these, 705 (74%) had a syphilis diagnosis at 1 visit, 195 (20.5%) had syphilis diagnosed at 2 study visits, and 52 (5.5%) had

syphilis at 3 study visits. The repeat episodes of syphilis represent both reinfections and/or persistence of prior syphilis infection. There were 539 females (57%), of whom 117 (22%) were HIV-positive and the average age was 35.5 years ( $\pm 10.7$  standard deviation [SD]). There were 409 males (43%), of whom 81 (20%) were HIV-positive and their mean age was 39.3 ( $\pm 10.7$  SD). There were 181 incident cases of syphilis (19%) and the remainder were prevalent cases at the time of first observation. The distribution of initial TRUST titers were low: 500 (53%) were  $\leq 1:2$ , 383 (40%) were between 1:4 and 1:8, and only 69 (7%) were  $\geq 1:16$ . The interquartile range of TRUST titers was 1:2 to 1:4.

Presumptive primary syphilis based on current GUD was 1.1% (11 of 952), and 13% (122 of 952) had presumptive secondary or early latent syphilis based on reported genital ulcer and/or generalized rash in the preceding 12 months, whereas the majority 86% (818 of 952) were asymptomatic and presumed to be late latent infections. Of the 818 late latent syphilis cases, 27% (212 of 818) were persistent cases over 2 or more visits, whereas the remaining 73% (600 of 818) represented first-time episodes. The majority (67%; 638 of 952) reported having only 1 sex partner in the preceding 12 months.

Table 1 summarizes the characteristics of the syphilis cases by HIV status. The mean age of HIV-positive subjects with syphilis ( $34 \pm 9$  years) was significantly lower than the mean age of HIV-negative subjects with syphilis ( $38 \pm 11$  years,  $P < 0.001$ ). HIV-positive cases had a higher proportion of primary, secondary, or early latent syphilis compared with HIV-negative subjects (22% and 12%, respectively,  $P < 0.001$ ). There were no statistically significant differences between HIV-positive and HIV-negative syphilis cases in initial TRUST titers or treatment received.

Overall, 18% (168 of 952) of subjects received benzathine penicillin alone, 17% (165 of 952) received azithromycin only, and 65% (619 of 952) received both azithromycin and benzathine penicillin.

Table 2 shows characteristics of subjects in the 3 treatment groups. More women received benzathine penicillin alone compared with men (20% vs. 14%,  $P = 0.017$ ), with almost equal proportions among women and men receiving dual treatment (65% and 66%, respectively). The mean duration between time of treatment and subsequent serologic assessment was lowest among those who received penicillin alone ( $6 \pm 3$  months) compared with those who received either azithromycin alone or azithromycin and benzathine penicillin ( $11 \pm 3$  months in both groups).

As shown in Table 3, the overall cure rate was 61% (580 of 952). The remaining 26% (250 of 952) of cases had either no change or less than a 4-fold reduction in titer or an increase in TRUST titer (13%; 122 of 952). In unadjusted analyses, there were no significant differences in the proportions cured between HIV-positive and HIV-negative individuals by age or number of sex partners. However, cure rates were lower in males than females (56.9% vs. 64%, respectively; RR, 0.89; 95% CI, 0.80–0.99) and in persons with higher titer syphilis  $\geq 1:4$  (52.7%) than low-titer syphilis (68.4%; RR, 0.77; 95% CI, 0.69–0.89). There were 181 cases of incident syphilis of whom 121 were cured (67%). There were 534 who were syphilis-seropositive on first observation, among whom 339 were cured (63%). No significant differences were observed in cure rates by treatment group, but in subanalyses, there was evidence of interaction in cure rates between treatment group and titer. After adjustment for interactions between initial titer and cure rate, persons with high titer  $\geq 1:4$  syphilis who received azithromycin alone had significantly higher cure rates (RR, 1.54; 95% CI, 1.03–2.30) compared with persons receiving penicillin alone. Similarly, patients with titers  $\geq 1:4$  receiving both azithromycin and penicillin also had significantly higher cure rates (RR, 1.39; 95% CI, 1.01–1.94).

TABLE 1. Characteristics of Syphilis Cases by HIV Status

	All		HIV-Negative		HIV-Positive		P Value
	No.	(%)	No.	(%)	No.	(%)	
No. of syphilis cases	952		754		198		
No. of female cases	539	(57)	422	(56)	117	(59)	
Age group (y)							
15–19	35	(4)	33	(4)	2	(1)	<0.05
20–29	235	(25)	171	(23)	64	(32)	<0.01
30–39	314	(33)	225	(30)	89	(45)	<0.001
40+	368	(38)	325	(43)	43	(22)	<0.001
Initial TRUST titers							
≤1:2	500	(53)	397	(53)	103	(52)	
≥1:4	452	(47)	357	(47)	95	(48)	
Syphilis stage*							
Primary /secondary/early latent	133	(14)	88	(12)	45	(22)	<0.001
Late latent	818	(86)	666	(88)	152	(77)	<0.001
No. of sex partners in the past year							
None	172	(18)	145	(19)	27	(14)	
One	638	(67)	506	(67)	132	(67)	
Two+	141	(15)	103	(14)	38	(19)	
Treatment received							
Benzathine penicillin	168	(18)	136	(18)	32	(16)	
Azithromycin only	165	(17)	135	(18)	30	(15)	
Both benzathine penicillin and azithromycin	619	(65)	483	(64)	136	(69)	
TRUST titer changes at follow up							
TRUST-negative/≥4-fold decrease	580	(61)	451	(60)	129	(65)	
No change in titer/2-fold decrease	250	(26)	200	(27)	50	(25)	
Increased titers	122	(13)	103	(14)	19	(10)	
Duration since treatment†							
<6 mo	31	(3)	26	(3)	5	(3)	
6–<12 mo	616	(65)	487	(65)	129	(65)	
≥12 mo	204	(21)	161	(21)	43	(22)	

\*One case had missing classification data.

†Actual date of treatment was miss on 101 cases treatment with penicillin alone at the penicillin bases.

TABLE 2. Characteristics of Persons by Treatment Group

	Penicillin		Azithromycin		Both Penicillin and Azithromycin		P Value*
	No.	(%)	No.	(%)	No.	(%)	
Syphilis cases	168		165		619		
Female cases	109	(65)	82	(50)	348	(56)	0.02
Age (y)							
15–19	9	(5)	5	(3)	21	(3)	0.43
20–29	46	(27)	42	(25)	147	(24)	0.61
30–39	53	(32)	48	(29)	213	(34)	0.40
40+	60	(36)	70	(42)	238	(38)	0.45
Initial TRUST titers							
≤1:2	93	(55)	94	(57)	313	(51)	0.25
≥1:4	75	(45)	71	(43)	306	(49)	0.25
No. of sex partners in the past year							
None	34	(20)	31	(19)	107	(17)	0.66
One partner	114	(68)	107	(65)	417	(67)	0.79
Two+	20	(12)	27	(16)	94	(15)	0.47
Mean duration since treatment in months (± standard deviation)	6 (± 3)		11 (± 2)		11 (± 2)		

\*P value for the chi-squared test of homogeneity of 3 treatment groups.

TABLE 3. Cure Rates and Unadjusted and Adjusted Rate Ratios of Syphilis Cure and Multivariate Adjusted Cure Rates

Variable	No. Cured/ No. of Cases	(% Cured)	Unadjusted Rate Ratio	95% CI	Adjusted Rate Ratio <sup>‡</sup>	95% CI
HIV status						
HIV-negative	451/754	(60)	1.00		1.00	
HIV-positive	129/198	(65)	1.09	0.96–1.24	1.09	0.98–1.22
Gender						
Female	345/539	(64)	1.00		1.00	
Male	235/413	(57)	0.89	0.80–0.99*	0.91	0.82–1.00
Age group						
15–19	23/35	(66)	1.00			
20–29	147/235	(63)	0.95	0.68–1.33		
30–39	197/314	(63)	0.95	0.68–1.33		
40+	213/368	(58)	0.88	0.63–1.22		
Initial TRUST titers						
≤1:2	342/500	(69)	1.00		1.00	
≥1:4	238/452	(53)	0.77	0.69–0.86 <sup>†</sup>	0.58	0.43–0.78 <sup>†</sup>
Treatment received						
Penicillin only	97/168	(58)	1.00		1.00	
Azithromycin only	93/165	(56)	0.98	0.81–1.18	0.90	0.72–1.12
Azithromycin and penicillin	390/619	(63)	1.09	0.94–1.26	1.00	0.87–1.15
Interaction between treatment and initial TRUST titer						
Azithromycin and ≥1:4					1.54	1.03–2.30*
Azithromycin and benzathine penicillin and ≥1:4					1.39	1.01–1.94*
Syphilis stage						
1°/2°/early latent	78/133	(59)	1.00			
Late latent	501/818	(61)	1.04	0.90–1.22		
Sex partners in the past year						
None	113/172	(66)	1.00			
One partner	388/638	(61)	0.93	0.81–1.06		
Two+	78/141	(55)	0.84	0.70–1.02		

\* $P < 0.05$ .† $P \leq 0.001$ .

‡Adjusted model included HIV status, syphilis case type (incident, new prevalent, persistent prevalent), gender, treatment received, initial TRUST titer, as well as an interaction term of treatment received and initial titer.

As a result of the unusual finding that cases with initial titers  $\geq 1:4$  had lower cure rates compared with cases with initial titers  $\leq 1:2$ , we conducted a subanalysis comparing cases with initial titers  $\geq 1:16$  with the lower titers. Cure rates were 71% (49 of 69) among cases with initial titer  $\geq 1:16$ , 49% (189 of 383) among cases with initial titers 1:4 to 1:8, 60% (189 of 317) among cases with initial titer 1:2, and 84% (153 of 183) in cases with titer  $< 1:2$ . Ignoring the lowest titer group, cases with titer  $\geq 1:16$  had an unadjusted cure rate ratio of 1.32 (95% CI, 1:10–1:57) compared with titers 1:2 to 1:8. The gender- and treatment-adjusted cure rate ratio for initial titer  $\geq 1:16$  was 1.36 (95% CI, 1.16–1.60) com-

pared with cases with initial titers 1:2 to 1:4; however, small numbers limited further analysis. We explored the extent to which our findings were influenced by serofastness of latent syphilis using cure rates among repeat positive cases. Less than half (49%; 105 of 215) of respondents who tested positive for syphilis 10 to 12 months or more after a previous positive test were less likely to respond to retreatment, compared with cure rates among incident syphilis cases (69%; 121 of 181) and among baseline prevalent syphilis cases (64%; 345 of 556), perhaps suggesting serofastness. The results shown in Tables 3 and 4 adjusted for serofast status in the models.

TABLE 4. Adjusted Rate Ratios of Cure in Log Binomial Models Treatment With Treatment Stratified by Initial TRUST Titers\*

	$\leq 1:2$		$\geq 1:4$	
	Cured/No. of Cases (proportions)	Adjusted Relative Risk (95% CI, $P$ value)	Cured/No. of Cases (proportions)	Adjusted Relative Risk (95% CI, $P$ value)
Penicillin	66/93 (0.71)	1.00	31/75 (0.41)	1.00
Azithromycin	55/94 (0.59)	0.87 (0.67–1.13, $P = 0.30$ )	38/71 (0.53)	1.38 (0.97–1.96, $P = 0.07$ )
Azithromycin and penicillin	221/313 (0.71)	0.99 (0.86–1.15, $P = 0.96$ )	169/309 (0.55)	1.38 (1.03–1.87, $P = 0.03$ )

\*Each strata specific model adjusted for gender, HIV status, and syphilis case type (new prevalent, incident, persistent prevalent) and treatment received with initial TRUST titer as the stratifying variable. CI = confidence interval.

To further examine the interaction between treatment-specific cure rates and initial TRUST titer, separate stratified models were fitted for cases with initial titer  $\leq 1:2$  and  $\geq 1:4$  (Table 4). Among low-titer syphilis, cure rates were lower with azithromycin (59%) than with penicillin alone (71%) or penicillin plus azithromycin (71%), but these differences were not statistically significant. In contrast, among persons with initial titers  $\geq 1:4$ , cure rates were only 41% (31 of 75) with penicillin alone, compared with 53% (38 of 71) with azithromycin and 55% with azithromycin plus penicillin (169 of 309). In persons with higher titer syphilis, the adjusted RR of cure, relative to penicillin alone, was greater with azithromycin alone (RR, 1.38; CI, 0.97–1.07;  $P = 0.07$ ) and with azithromycin plus penicillin (RR, 1.38; CI, 1.03–1.87).

## Discussion

The key finding of our study is the apparent differences in cure rates associated with an interaction between initial TRUST titer and treatment regimen. At titers  $\leq 1:2$ , there were no statistically significant difference between benzathine penicillin, azithromycin, and dual treatment with azithromycin and benzathine penicillin (Table 4). However, among cases with TRUST titers  $\geq 1:4$ , persons receiving azithromycin alone or in combination with benzathine penicillin had significantly higher cure rates (RR, 1.38) compared with those receiving penicillin alone (Table 4).

Irrespective of treatment received, cases with higher titer syphilis had lower cure rates than persons with low-titer infections (Tables 3 and 4). This latter finding is in contrast with that of a Zaire study of commercial sex workers that found higher cure rates among cases with titers  $\geq 1:8$  compared with  $\leq 1:4$  at 6, 12, and 24 months.<sup>23</sup> However, the 2 studies are not entirely comparable because of differences in treatment regimens. There were no differences in response to syphilis treatment between HIV-positive and HIV-negative cases, which is in agreement with other studies.<sup>9,23</sup>

About initial TRUST titers, we found that syphilis titers were low in this population; only 7% (69 of 952) had TRUST titers  $\geq 1:16$ . Most other studies are based on clinic populations, and most latent syphilis cases reported tended to have high initial titers making comparison of our findings to other studies difficult.<sup>13</sup> However, other studies in Africa have also found a predominance of low TRUST titer syphilis compared with high-titer syphilis. For example, among female commercial sex workers attending a clinic in Zaire, 55% had initial TRUST titers  $\leq 1:2$  and only 13% had initial TRUST titers  $\geq 1:16$ .<sup>23</sup> Similar findings were reported from a population cohort study in Masaka, Uganda.<sup>24</sup> Looking at changes from the initial TRUST titers in response to treatment, we found that cases with initial TRUST titers of  $\geq 1:4$  were less likely to cure in both unadjusted and adjusted analysis. This finding is unusual and may have resulted from lack of adequate number of cases with titers  $\geq 1:16$ , which showed high cure rates.

There are several limitations in this study. This was a secondary data analysis, and the trial was not designed to assess the effect of azithromycin and/or benzathine penicillin for treatment of syphilis. Receipt of azithromycin was contingent on randomization to the intervention arm, whereas receipt of penicillin was possible in both study arms. Moreover, receipt of azithromycin alone among intervention-arm subjects was contingent on their refusal to accept penicillin. The study relied on self-reported symptoms for staging the syphilis infection without physical examination for signs of syphilis. Thus, it is possible that there were more cases of early syphilis than we were able to identify. Also, we could only evaluate response to therapy several months after treatment and were not able to adequately evaluate serologic changes at shorter

time intervals, especially in the group that received dual treatment with azithromycin and penicillin. It is possible that our findings are affected by residual serofastness of latent syphilis, although we attempted to adjust for this in the models. We postulate that residual serofast infections will bias our results toward the null hypothesis because serofastness prevents us from measuring cure. This suggests that the true effect of dual treatment may be greater than we were able to detect, but this remains to be proven. Also, potential misclassification of the outcome of interest may have resulted from sera not being tested in pairs or multiples by the TRUST assay as has been observed in rapid plasma reagin.<sup>25</sup> Any misclassification of cure (outcome) resulting from a problem with reproducibility of tests would likely be nondifferential by treatment regimen and thus would bias the results toward a null effect.

This study is limited in its ability to compare single-dose dual treatment of benzathine penicillin and azithromycin with the currently recommended treatment of 3 injections of benzathine penicillin intramuscularly given at weekly intervals for late latent syphilis. Our treatment protocol used single-dose benzathine penicillin in all cases of confirmed syphilis. In this rural population with 49% of people within 5 km of a health facility, and 57% living within 10 km of a health facility (Burton and Wamai, 1994), the research program had to set up penicillin depots close to the study communities and supply free penicillin to all treatment centers to ensure reasonable access to study subjects and their immediate partners. It was not feasible to provide weekly treatment at home and it was not possible to guarantee compliance for referral visits to a health facility or penicillin depots. In such rural communities, single-dose treatment strategies offer the only feasible strategy for treatment.

Studies have documented emergence of azithromycin-resistant *T. pallidum* strains.<sup>26</sup> These findings, although disturbing, have been found in areas where azithromycin use is far more widespread than in sub-Saharan Africa. In this study, we did not evaluate the extent of this problem because the original study was not designed to investigate the effect of azithromycin on syphilis. No resistance was identified for gonorrhea and chlamydia, which were the primary targets of the azithromycin mass treatment. It is imperative that further studies monitor resistance.

The most important finding of this secondary analysis was that azithromycin alone or in combination with penicillin achieved higher cure rates than penicillin alone in cases of high- but not in low-titer syphilis infections. In low-titer infections, the 3 drug combinations were equally effective. This suggests that azithromycin could be substituted for benzathine penicillin for treatment of syphilis and would have the advantage that it is a single-dose oral treatment that is easier to provide and more tolerable than intramuscular benzathine penicillin. These findings have public health relevance. To maximize cure rate among syphilis cases with high TRUST titers, there may be advantages to single-dose azithromycin or dual treatment (azithromycin and benzathine penicillin) given at a single encounter with a health worker. We also found that cure rates were lower with higher titer infections, irrespective of treatment regimen, and that HIV status did not affect cure rates. Among cases with initial titers  $\geq 1:4$ , dual treatment, although statistically significantly better than single-dose benzathine penicillin, was modestly greater than single-dose azithromycin in terms of absolute differences in cure rates (14% and 12%, respectively). Such modest absolute treatment differences are not sufficient to make definitive syphilis treatment recommendations. Well-designed randomized, controlled trials of the conventional treatment for latent syphilis using 3 injections of benzathine penicillin at weekly intervals versus dual therapy of

azithromycin and benzathine given at once are recommended to provide further proof of our findings.

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