



Treatment of syphilis in HIV-infected subjects: a systematic review of the literature

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ABSTRACT

Background The optimal antimicrobial regimen to treat syphilis in HIV-infected subjects remains controversial.

Objective To systematically assess the literature for studies evaluating syphilis treatment regimens in this population.

Methods Two reviewers independently assessed studies published between 1980 and June 2008 in electronic databases, trial registries and bibliographies (with no language restrictions) for content and quality. Studies that included 10 or more people, with documented HIV status, type and duration of syphilis treatment and at least 6 months of follow-up were included. The primary outcome was syphilis serological or clinical failure stratified by syphilis stage.

Results Of 1380 unique citations, 23 studies (22 published papers and 1 conference abstract) were included in the systematic review. Owing to the significant heterogeneity among studies, pooled summary statistics could not be generated. The range of probabilities for serological failure with 2.4 million units (MU) of intramuscular benzathine penicillin G (BPG) was 6.9% (95% CI 2.6% to 14.4%) to 22.4% (11.7% to 36.6%); that of 7.2 MU of BPG in late latent syphilis was 19.4% (11.9% to 28.9%) to 31.1% (22.3% to 40.9%) and failure estimates with 18–24 MU of aqueous penicillin for the treatment of neurosyphilis were 27.3% (6.0% to 61.0%) to 27.8% (14.2% to 45.2%).

Conclusions The optimal antimicrobial regimen to treat syphilis in HIV-infected subjects is unknown; guideline recommendations in this population are based on little objective data.

INTRODUCTION

Since its introduction in the 1940s, penicillin has remained the preferred drug for treating syphilis. Data from randomised trials comparing the efficacy of the different penicillin-based syphilis treatment regimens are limited.¹ Currently, the Centers for Disease Control and Prevention (CDC) recommend the use of long-acting intramuscular benzathine penicillin G (BPG) for the treatment of early and late latent syphilis and high-dose intravenous aqueous crystalline penicillin G for the treatment of neurosyphilis.² Even though *Treponema pallidum* is isolated in the cerebrospinal fluid of up to 40% of people with early syphilis,^{3 4} and BPG does not achieve treponemicidal levels in the cerebrospinal fluid,⁵ there were very few reports of late manifestations of syphilis in people treated with penicillin in the pre-HIV era.⁶

The optimal treatment regimen for syphilis in HIV-infected subjects has been controversial since

case reports emerged in the late 1980s documenting failures to CDC-recommended treatment regimens.⁷ Several studies have suggested an increased risk of syphilis treatment failure when standard regimens are used while others have not.⁸ The current CDC recommendations suggest using the same treatment regimens as those used in HIV-uninfected subjects with more aggressive post-treatment serological follow-up in those who are co-infected.² Our goal was to systematically assess the literature for studies reporting syphilis serological and clinical treatment responses in HIV-infected subjects stratified by the stage of syphilis infection.

METHODS

Data sources and searches

We searched Medline, SCOPUS, ISI, POPLINE, Excerpta Medica and Cochrane Central Register of Controlled Trials databases from 1980 to June 2008 (or earliest date available within the time range). We used the following search terms: syphilis AND (treatment OR therapy OR management) AND ('HIV infection' OR 'HIV infections' OR 'HIV persons' OR 'HIV patient'). Reference lists of the retrieved articles were also manually searched for other potentially relevant papers. We also reviewed conference abstracts (International Society for Sexually Transmitted Diseases Research, CDC STD Prevention Conferences, Infectious Diseases Society of America meetings, Interscience Conference on Antimicrobial Agents and Chemotherapy, Conference on Retroviruses and Opportunistic Infections). We assessed both English and non-English language articles for eligibility.

Study selection

We evaluated articles for eligibility using a two-stage procedure. In the first stage, all identified abstracts were reviewed. In the second stage, we reviewed the entire text of articles that met the inclusion criteria and articles whose eligibility was uncertain based on review of the abstract. Where information was missing, we attempted to contact either the primary or senior authors on the study to request additional information or clarification. All articles were independently assessed by two reviewers.

The inclusion criteria for studies were (1) syphilis diagnosis based on serological criteria or darkfield microscopy; patients treated based on syndromic management without serological or microscopic confirmation were excluded; (2) 10 or more people with at least one patient documented HIV positive;

(3) the HIV status of the patient was known at or near (± 365 days) the time of syphilis diagnosis; (4) the *type* and *duration* of antimicrobial therapy received was documented; (5) clinical or serological outcome was reported with at least 6 months of follow-up after syphilis treatment. The primary outcome was syphilis serological or clinical failure at or greater than 6 (early-stage syphilis) to 12 (late latent syphilis or neurosyphilis) months after treatment. We used the definition for serological non-response as a fourfold increase in non-treponemal titres 30 or more days after appropriate treatment or lack of a fourfold decline in non-treponemal titres 6–12 months after treatment for early syphilis or 12–24 months for late syphilis (instances where follow-up was less than the times specified above are highlighted in the tables).² For neurosyphilis, the definitions of failure included lack of a fourfold or greater non-treponemal serological response at or after 12 months after treatment and/or the lack of improvement in cerebrospinal fluid abnormalities (white blood cell count, Venereal Disease Research Laboratory test or protein), or clinical signs suggestive of neurosyphilis after 12 months.

Data abstraction, quality assessment and analyses

Both reviewers (LJB and KGG) independently extracted data from all primary studies that fulfilled the inclusion criteria; disagreement was resolved by consensus. The following information was abstracted: study design, syphilis staging, type and duration of syphilis treatment, post-treatment follow-up time and adherence, stage-specific serological and clinical outcomes and assessment of methods to account for re-infection as a cause of syphilis treatment failure. We summarised outcomes for these studies by tabulating the number of failures by the total number of subjects who completed follow-up at the specified time. If studies assessed outcomes at more than one follow-up time, all times beyond the 6-month time point were recorded and the time point with the least amount of loss to follow-up is reported in the tables. We scored the methodological quality of the studies by evaluating study design, allocation concealment, blinding, loss to follow-up and source of funding, as applicable.⁹

Our initial goal was to perform a meta-analysis. However, owing to the significant heterogeneity in treatment used, adherence and follow-up, we were unable to generate meaningful pooled summary statistics. Instead we summarised the data of each individual study and tabulated the results. We calculated probability of serological failure for each study stratified by syphilis stage and treatment regimen used. We provide 95% confidence limits for point estimates to describe the degree of uncertainty surrounding each value.

RESULTS

Of 1380 unique citations, we excluded 1342 on initial screening; 38 studies were fully reviewed: 37 were published articles and one was a conference abstract (figure 1). Fifteen articles did not meet one or more entry criteria and were excluded. The remaining 23 studies, 22 published papers^{10–32} and one conference abstract,³³ which has since been published,³⁴ were included in the systematic review after both reviewers agreed on their validity assessments.

Studies that met inclusion criteria included: six retrospective case series, seven prospective case series, two case–control studies, two retrospective cohort studies, three prospective cohort studies and four randomised trials (table 1). Two of the trials were deemed good quality based on Jadad scores of 5.^{19 27} Two randomised trials compared efficacy of azithromycin with

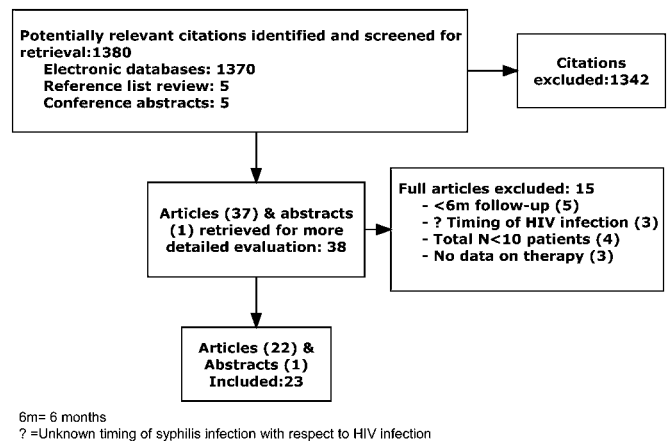


Figure 1 Study flow diagram.

other regimens and included HIV-infected subjects among the recruited participants,^{21 27} one small randomised open-label study in HIV-infected subjects compared penicillin with ceftriaxone in late latent and neurosyphilis,²³ and one randomised open label trial compared BPG with enhanced treatment with additional amoxicillin and probenecid among subjects with early syphilis.¹⁹ The latter trial included subjects with HIV. The remaining studies were descriptive.

Most of the studies reported data on multiple treatment regimens for various stages of syphilis resulting in very small numbers within each category. Some studies only reported failure rates for aggregate data inhibiting our ability to distinguish the efficacy of each individual treatment regimen. Studies that fulfilled entry criteria and reported failures for each regimen with a sample size of >10 HIV-positive persons for that regimen are reported (table 2). The range of probabilities for serological failure with 2.4 million units (MU) of intramuscular BPG was 6.9% (95% CI 2.6% to 14.4%) to 22.4% (11.7% to 36.6%); that of 7.2 MU of BPG in late latent syphilis was 19.4% (11.9% to 28.9%) to 31.1% (22.3% to 40.9%) and failure estimates with 18–24 MU of aqueous penicillin for the treatment of neurosyphilis were 27.3% (6.0% to 61.0%) to 27.8% (14.2% to 45.2%). Only one of the randomised trials²⁷ was included in table 2 because the data from the other three trials were reported in aggregate or because the number of HIV-infected subjects, when stratified by stage and drug regimen, was fewer than 10.

DISCUSSION

The current treatment guidelines in both the USA² and the UK³⁵ recommend BPG as first-line treatment for early and late latent syphilis in both HIV-infected and uninfected subjects. Assuming lack of heterogeneity, were we to pool data from the 23 studies included in this systematic review, serological outcomes of people treated with BPG (2.4 MU intramuscularly for early syphilis and 7.2 MU intramuscularly for late latent syphilis) could be assessed in a total of 197 people with early and 245 people with late latent syphilis. There are even fewer data available on the use of doxycycline (100 mg orally twice a day) to treat early syphilis in HIV-infected subjects: 20 total cases. For neurosyphilis, outcomes on 68 people treated with intravenous aqueous penicillin (18–24 MU intravenously for 10–14 days) and 19 people treated with ceftriaxone (2 g intramuscularly or intravenously daily for 10–14 days) could be assessed. Our study entry criteria were not overly restrictive. In fact, we chose criteria that would allow for the least restrictive clinically meaningful

Table 1 Studies that met entry criteria stratified by syphilis stage and type of treatment

Study	Study design	Median follow-up time (months)	Re-infection	Initial N (HIV-/HIV+)*	Stage (HIV status)	Follow-up N†	Treatment	Serological failures	Clinical failures
Dowell (1992) ¹⁰	Retrospective series	≥6	Y	56 (0/56)	L (+)	49	13 BPG X 3 36 Cef X 10–14 doses	4	0
Gourevitch (1993) ¹¹	Retrospective cohort	11.4	N	50 (19/31)	N (+) E (-)	7 4	7 Cef X 10–14 doses 1 BPG X 1 3 BPG X 1 enhanced§ 7 BPG X 3	1	0
					L (-)	12	3 BPG X 1 enhanced§ 3 Less than BPG X 3 1 Doxy X 28d 1 Tetra X 14d 1 APG X 10–14d 1 BPG X 1 10 BPG X 1 enhanced§ 9 BPG X 3 1 Less than BPG X 3 2 BPG X 3 enhanced§ 1 Erythro X 28d 2 APG X 10–14d 5 BPG X 2 5 BPG X 3 1 Doxy X 14–15d 1 Erythro X 21d 1 APG X 10–14d 11 APG X 10d 78 BPG X 1 or Doxy X 14d 28 BPG X 1 or Doxy 34 BPG X 3 26 BPG 2.4 X 3 11 BPG 2.4 X 3 7 CPG + P X 10–14d 3 APG X 10–14d 19 BPG X 3 1 Cef? Dose 2 CPG + P X 10–14d 8 APG X 10–14d 5 APG X 10–14d 5 APG X 10d 3 CPG + P X 10–14d 1 CPG + P X 9d 9 APG X 10d 4 CPG + P X 10–14d 22 BPG X 1 1 BPG X 3 3 Other 24 BPG X 3	0	0
Caumes (1994) ¹²	Prospective series	24	N	13 (0/13)	N (+) E (+) L (+)	2 12 13		0	0
Gordon (1994) ¹³	Prospective series	10	N	11 (0/11)	N (+)	1	1 APG X 10d	3	1
Hutchinson (1994) ¹⁴	Case–control	<12	N	309 (239/70)	E (-)	78	78 BPG X 1 or Doxy X 14d	11	0
Goeman (1995) ¹⁵	Prospective cohort	24	N	120 (73/47)	E (+) U (-) U (+)	28 34 26	28 BPG X 1 or Doxy 34 BPG X 3 26 BPG 2.4 X 3	5	0
Malone (1995) ¹⁶	Retrospective series	24 (mean)	N	59 (0/59)	E (+)	21	11 BPG 2.4 X 3 7 CPG + P X 10–14d 3 APG X 10–14d 19 BPG X 3 1 Cef? Dose 2 CPG + P X 10–14d 8 APG X 10–14d 5 APG X 10–14d 5 APG X 10d 3 CPG + P X 10–14d 1 CPG + P X 9d 9 APG X 10d 4 CPG + P X 10–14d 22 BPG X 1 1 BPG X 3 3 Other 24 BPG X 3	3	0
Marra (1996) ¹⁷	Retrospective series	~3–6	N	22 (9/13)	N (+) N (-)	5 9		3	1
Yinnon (1996) ¹⁸	Case–control	~12 (mean)	N	128 (64/64)	E (-)	26		1	0
					L (-)	26		15 of 52	0

Continued

Table 1 Continued

Study	Study design	Median follow-up time (months)	Re-infection	Initial N (HIV-/HIV+)*	Stage (HIV status)	Follow-up N†	Treatment	Serological failures	Clinical failures
							2 other		
					E (+)	26	4 BPG X 1		
							18 BPG X 3		
					L (+)	21	4 other	21 of 48	0
							2 BPG X 1		
					N (+)	1	19 BPG X 3		
					E (-)	257	5 other		
Rofis (1997) ¹⁹	RCT	6	Y	541 (440/101)			NA BPG X 1	42 of 257	0
							NA BPG X 1+		
					E (+)	69	amox/P X 10d		
							NA BPG X 1	15 of 69	1
							NA BPG X 1+		
					E (+)	4	amox/P X 10d		
Bordón (1999) ²⁰	Prospective series	21	N	13 (0/13)			4 BPG X 3	0	0
					L (+)	5	1 CPG X 14d	1 of 5	0
							4 BPG X 3		
					N (+)	4	4 APG X 14d	0	0
					E (-)	71	19 BPG X 1 or 2	0	0
Hook (2002) ²¹	Randomised open label	6	Y	74 (71/3)			21 Azithro X 1	0	0
					E (+)	3	31 Azithro X 2	3	0
							2 BPG X 1 or 2	0	0
					L (+)	11	1 Azithro X 2	0	0
Tattevin (2002) ²²	Prospective cohort	~6	N	23 (0/23)			11 Biclinocilline 2MU		
							IM X 1 daily X 10d	7 of 12‡	0
					N (+)	1	1 Biclinocilline 2MU		
					L (+)	15	8 CPG + P X 15d	1	0
Smith (2004) ²³	Randomised open label	18–32	N	31 (0/31)			7 Cef X 15d	1	0
					N (+)	9	2 CPG + P X 15d	1	0
					E (+)	5	7 Cef X 15d	2	0
Gutiérrez-Galhardo (2005) ²⁴	Prospective series	24	Y	24 (0/24)			4 BPG X 3	0	
					L (+)	5	1 Erythro? duration	0	0
					N (+)	14	5 BPG X 3	0	0
					E (-)	88	3 APG X 14d	4 of 14	0
Kiddugavu (2005) ²⁵	Prospective cohort	~9 (mean)	N	952 (754/198)			10 Cef X 14d		
					L (-)	666	1 BPG X 3		
					E (+)	45	136 BPG X 1		
					L (+)	152	135 Azithro X 1	303 of 754	NA
							483 BPG X 1 + Azithro		
					E (+)	32	32 BPG X 1		
					L (+)	152	30 Azithro X 1	69 of 198	NA
Nhoruka (2005) ²⁶	Prospective series	12	N	31 (0/31)			136 BPG X 1 + Azithro		
					E (+)	9	9 BPG X 3	5 of 10	2 of 10
					L (+)	1	1 Doxy X 15d		

Continued

Table 1 Continued

Study	Study design	Median follow-up time (months)	Re-infection	Initial N (HIV-/HIV+)*	Stage (HIV status)	Follow-up N†	Treatment	Serological failures	Clinical failures
Riedner (2005) ²⁷	Randomised double-blinded	9	N	328 (157/171)	E (-)	157	78 BPG X 1	3	0
Chauhan (2006) ²⁸	Retrospective series	12	N	40 (34/6)	E (+)	171	Azithro X 1	0	0
							BPG X 1	6	0
							Azithro X 1	4	0
							BPG X 1	0	0
							BPG X 2	0	0
							BPG X 1 + Doxy X 14d	0	0
							Doxy X 14d	0	0
							CPG X 10d	0	0
							BPG X 3	0	0
							Doxy X 14d	0	0
Kofoid (2006) ²⁹	Prospective series	7	N	41 (0/41)	E (+)	5	BPG X 3	0	0
							Doxy X 14d	0	0
							CPG + P X 17d	0	0
							BPG X 3	0	0
							Doxy X 14d	0	0
							CPG X 3	0	0
							Doxy X 14d	1	0
							CPG X 10d	1	0
							BPG X 3	0	0
							Doxy X 14d	2	2
Ghanem (2007) ³⁰	Retrospective series	9	Y	297 (168/129)	E (-)	152	BPG X 1	4	0
							Doxy X 14d	0	0
							BPG X 3	1	0
							BPG X 1	1	0
							BPG X 1	4	0
							BPG X 1	32	0
							Doxy X 14d	0	0
							BPG X 3	18	0
							Doxy X 28d	0	0
							BPG X 1	181	0
Manavi (2007) ³¹	Retrospective series	24	Y	371 (242/129)	E (-)	61	BPG X 2	58 of 161	HIV- @ 24m
							BPG X 3	0	0
							Doxy X 21d	0	0
							CPG X 17d	0	0
							Unknown	0	0
							BPG X 1	67	0
							BPG X 2	62	0
							BPG X 3	0	0
							Doxy X 21d	0	0
							Azithr1 g X15d	0	0
CPG X 17d	0	0							
Ghanem (2008) ³²	Retrospective cohort	63.6	Y	231 (0/231)	E (+)	62	APG x 14d	11	0
							Unknown	4 of 11	0
							BPG X 1	0	0
							BPG X 2	0	0
							BPG X 3	0	0
							Doxy X 14d	0	0
							APG X 10-14d	0	0
							30 of 100 HIV+ @ 24m	0	0
							1	0	0
							15	0	0

Continued

Table 1 Continued

Study	Study design	Median follow-up time (months)	Re-infection	Initial N (HIV-/HIV+)*	Stage (HIV status)	Follow-up N†	Treatment	Serological failures	Clinical failures
Warwick (2008) ³³	Retrospective series	6	N	257 (132/125)	L (+) N (+) E (-) E (+)	128 41 132 125	5 BPG X 1 4 BPG X 2 103 BPG X 3 7 Doxy X 21d 1 Cef X 10d 7 Unknown 36 APG X 10-14d 5 Cef X 10d 132 BPG X 1 105 CPG+P X 17d 20 Other	0 0 32 2 0 0 10 1 3 1 1	0 0 0 0 0 0 1 0 N/A N/A N/A

*Total number of people who completed follow-up.
 †N—the subset of people who had follow-up data available.
 ‡Serological failure in this study was defined as complete rapid plasma reagin seroreversion. No data on fourfold decline were provided.
 §Enhanced with additional doses of penicillin (but dose not provided).
 ¶Re-infection, the study examined whether failure might have been due to re-infection.
 E, early-stage syphilis (primary, secondary, or early latent); L, late latent syphilis stage or syphilis stage of unknown duration; N, neurosyphilis. Amox, amoxicillin 2 g daily orally; APG, aqueous penicillin 18–24 million units intravenously daily; Azithro, azithromycin 2 g orally unless otherwise noted; BPG, benzathine penicillin G 2.4 million units given intramuscularly; Cef, ceftriaxone 1–2 g intramuscularly or intravenously; CPG, procaine penicillin 2.4 million units intramuscularly; d, days; Doxy, doxycycline 100 mg orally twice a day; erythro, erythromycin 3 g daily orally; IM, intramuscularly; m, months; MU, million units; P, probenecid 500 mg orally four times daily; Tera, tetracycline 500 mg orally four times daily; U, unknown stage.

interpretation of data. Even higher-quality randomised trials did not evaluate the efficacy of syphilis treatment in HIV-positive subjects as a primary outcome. The most commonly cited paper to justify the use of similar treatment regimens in HIV-infected and uninfected subjects is a randomised controlled trial comparing BPG with enhanced treatment (BPG+ amoxicillin and probenecid) in people with early syphilis.¹⁹ A total of 541 people were enrolled, but only 101 were HIV-infected and, of those, only 69 completed follow-up at 6 months. Although no difference in response rate between the treatment regimens used was noted, HIV-infected subjects with primary syphilis were found to have higher serological failure rates than HIV-uninfected subjects. Of note, the augmented treatment consisting of amoxicillin and probenecid chosen for the study had never been shown to be adequate treatment for neurosyphilis.

Of the studies summarised in table 2, only a few had HIV-uninfected controls. Of those, the probability of failure among HIV-uninfected subjects was lower than for HIV-infected subjects, although most comparisons were not statistically significant owing to small numbers. Among HIV-uninfected subjects, the historical estimate of treatment failure with 2.4 MU of BPG is 5%,¹ an estimate similar to those seen among HIV-uninfected subjects in our studies. The estimates among HIV-infected subjects (table 2) range from 1% to 22%—the high estimate was from a cohort study that could not account for the possibility of reinfection.³² The two treatment regimens in table 2 that approach the historical efficacy of 5% are single-dose azithromycin and procaine penicillin plus probenecid. In the past several years, mutations associated with azithromycin resistance have been detected in people infected with syphilis.^{36–38} Thus, the routine use of azithromycin to treat early syphilis is not recommended. The 1% failure rate seen with the procaine penicillin regimen is, by far, the best estimate reported.³⁴ Indeed, among all the regimens for early syphilis, this regimen is the only one approved for the treatment of neurosyphilis. One hypothesis is that the enhanced efficacy of this regimen is due to its potential to treat occult underlying neurosyphilis. Previously, UK treatment guidelines recommended this as the preferred regimen to treat HIV-infected patients with early syphilis; however, the recent updated UK guidelines favour BPG instead.

The estimates for treatment failures among HIV-infected subjects with late latent syphilis and neurosyphilis are much higher than historical estimates from HIV-uninfected subjects, which range from 3% to 10%.¹ One possibility is that the recommended penicillin regimens are less effective in HIV-infected subjects. There are, however, plausible alternate hypotheses. In late latent syphilis, slower serological response times among those with a previous history of treated syphilis³⁹ and among HIV-infected subjects have been reported. In most studies, the median follow-up times were less than the 24 months suggested by the CDC.² This might have inflated the rates of serological failures. When assessing treatment responses for neurosyphilis, HIV-infected subjects, especially those with advanced HIV, can have baseline cerebrospinal fluid abnormalities unrelated to syphilis.⁴⁰ This may have an impact on the case definition and failure rates reported for neurosyphilis. These issues highlight a major factor that has hindered progress in understanding the natural history of syphilis: the main clinical measure of syphilis disease activity, serological titres, are not specific for treponemes and may not reflect the underlying microbiology. Interpretation of serological titres is even more difficult in the setting of HIV where B-cell dysfunction may account for some of the observed variability.⁴¹

Table 2 Probability of treatment failure for various therapeutic regimens stratified by syphilis stage and HIV status (if data on HIV-uninfected subjects were reported). Studies that fulfilled entry criteria and reported failures for each regimen with a sample size of >10 people for that regimen are included

Stage	Regimen	Study	Total N (HIV+)	Failures (HIV+)	% Probability of failure HIV+ (95%CI)	Total N (HIV-)	Failures (HIV-)	% Probability of failure HIV- (95% CI)	p Value
Early	BPG X 1	Riedner (2005) ²⁷	87	6	6.9 (2.6 to 14.4)	78	3	3.8 (0.8 to 10.8)	0.3
		Ghanem (2007) ³⁰	31	4	12.9 (3.6 to 29.8)	151	4	2.6 (0.7 to 6.6)	0.03
		Ghanem (2008) ³²	49	11	22.4 (11.7 to 36.6)	—	—	—	—
	CPG+P X 17d	Warwick (2008) ³³	105	1	1.0 (0.3 to 5.4)	—	—	—	—
		Doxy X 14d	Kofoed (2006) ²⁹	15	1	6.7 (0.2 to 31.9)	—	—	—
Late latent	Azithro X 1	Riedner (2005) ²⁷	84	4	4.8 (1.3 to 11.7)	79	0	0 (0 to 4.6)	0.1
		Dowell (1992) ¹⁰	13	4	30.8 (9.1 to 61.4)	—	—	—	—
	BPG X3	Malone (1995) ¹⁶	19	4	21.1 (6.1 to 45.6)	—	—	—	—
		Ghanem (2007) ³⁰	93	18	19.4 (11.9 to 28.9)	14	1	7.1 (0.2 to 33.8)	0.5
		Ghanem (2008) ³²	103	32	31.1 (22.3 to 40.9)	—	—	—	—
Cef X10-14 doses	Dowell (1992) ¹⁰	36	9	25.0 (12.1 to 42.2)	—	—	—	—	
Neurosyphilis	APG X 10-14d	Gordon (1994) ¹³	11	3	27.3 (6.0 to 61.0)	—	—	—	—
		Ghanem (2008) ³²	36	10	27.8 (14.2 to 45.2)	—	—	—	—

APG, aqueous penicillin 18–24 million units intravenously daily; Azithro, azithromycin 2 g; BPG, benzathine penicillin G 2.4 million units given intramuscularly; Cef, ceftriaxone 1–2 g intramuscularly or intravenously; CPG, procaine penicillin 2.4 million units intramuscularly; d, days; Doxy, doxycycline 100 mg orally twice a day; m, months; N, number; P, probenecid 500 mg orally four times daily; —, no data available for HIV-uninfected subjects.

Given the limitations of the data, one approach has been to advocate conservative approaches to managing co-infected people: cerebrospinal fluid examination in all HIV-infected subjects with syphilis or, at least, the use of treatment regimens that are effective at treating underlying occult neurosyphilis irrespective of syphilis stage.^{42–43} The arguments against broad implementation of these strategies include limited resources and lack of studies demonstrating improved long-term outcomes compared with standard management approaches.⁴⁴ Currently, the main recommendation among co-infected people is for aggressive serological and clinical follow-up after stage-appropriate treatment—a logical recommendation, but one not based on objective evidence of efficacy.² Even this goal, however, is not easily achieved. Among co-infected people attending Baltimore City STD clinics, 64% did not have documented evidence of any follow-up serologies after syphilis treatment.³⁰

This study has several limitations: we were unable to pool results owing to significant heterogeneity among the studies; any such attempts would have yielded uninterpretable data. A significant number of studies did not report outcomes for individual treatment regimens. We attempted to contact all first and senior authors listed to try to obtain clarifications. Although most responded to the enquiries, many reported that they no longer had easy access to the primary data given that some of these studies were 10–15 years old. Our study entry criteria were broad. For example, the CDC treatment guidelines suggest that low rapid plasma reagin titres (eg, titres <1:32) in late latent syphilis may not decline fourfold, even after appropriate treatment. Few of the studies we reviewed examined this topic. That is because even the CDC treatment guidelines are fairly opaque about the significance of this finding, suggesting that ‘in these circumstances, the need for treatment or repeated cerebrospinal fluid examinations is unclear’. Finally, there is no simple objective way to distinguish between treatment failure and re-infection and most studies made no attempt to do so (table 1). As such, observed differences in treatment responses between HIV-infected and uninfected subjects may be the result of behavioural confounding.

A recent survey of infectious diseases practitioners highlights the pervading uncertainty among clinicians who manage HIV-infected subjects with syphilis.⁴⁵ Of 375 clinicians who were queried about the treatment of secondary syphilis in

Key messages

- ▶ Studies assessing the treatment of syphilis among HIV-infected subjects are heterogeneous.
- ▶ Current guidelines for the treatment of syphilis among HIV-infected subjects are based on limited objective data.
- ▶ The optimal antimicrobial regimen to treat syphilis in HIV-infected subjects is unknown.

HIV-infected patient, 64% used a non-CDC recommended regimen consisting of three doses of 2.4 MU of intramuscular BPG. In an accompanying editorial titled ‘When guidelines don’t guide the physician’, the author suggested that the inconsistency seen among clinicians is the result of limited evidence to support clear management approaches.⁴⁶ Our study highlights the significant heterogeneity that exists among treatment studies and the difficulty in trying to make use of these data to guide management decisions. Rates of syphilis continue to increase and HIV-infected subjects are disproportionately affected.⁴⁷ The optimal treatment regimen for syphilis in HIV-infected patients is unknown and, consequently, any guideline recommendation in this population is ultimately based on limited objective data.

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REFERENCES

1. Idsoe O, Guthe T, Willcox RR. Penicillin in the treatment of syphilis. The experience of three decades. *Bull World Health Organ* 1972;**47**:1–68.

2. **Workowski KA**, Berman SM; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2006. *MMWR Recomm Rep* 2006;**55** (RR-11):1–94.
3. **Lukehart SA**, Hook EW 3rd, Baker-Zander SA, *et al*. Invasion of the central nervous system by *Treponema pallidum*: implications for diagnosis and treatment. *Ann Intern Med* 1988;**109**:855–62.
4. **Marra CM**, Maxwell CL, Smith SL, *et al*. Cerebrospinal fluid abnormalities in patients with syphilis: association with clinical and laboratory features. *J Infect Dis* 2004;**189**:369–76.
5. **Dunlop EM**, Al-Egaily SS, Houang ET. Penicillin levels in blood and CSF achieved by treatment of syphilis. *JAMA* 1979;**241**:2538–40.
6. **Perdrup A**, Jorgensen BB, Pedersen NS. The profile of neurosyphilis in Denmark: A clinical and serological study of all patients in Denmark with neurosyphilis disclosed in the years 1971–1979 incl. by Wassermann reaction (CWRM) in the cerebrospinal fluid. *Acta Derm Venereol* 1981;**96**:1–14.
7. **Berry CD**, Hooton TM, Collier AC, *et al*. Neurologic relapse after benzathine penicillin therapy for secondary syphilis in a patient with HIV infection. *N Engl J Med* 1987;**316**:1587–9.
8. **Zetola NM**, Klausner JD. Syphilis and HIV infection: an update. *Clin Infect Dis* 2007;**44**:1222–8.
9. **Jadad AR**, Moore RA, Carroll D, *et al*. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;**17**:1–12.
10. **Dowell ME**, Ross PG, Musher DM, *et al*. Response of latent syphilis or neurosyphilis to ceftriaxone therapy in persons infected with human immunodeficiency virus. *Am J Med* 1992;**93**:481–8.
11. **Gourevitch MN**, Selwyn PA, Davenny K, *et al*. Effects of HIV infection on the serologic manifestations and response to treatment of syphilis in intravenous drug users. *Ann Intern Med* 1993;**118**:350–5.
12. **Caumes E**, Minta D, Niel G, *et al*. Syphilis precoce et infection par le VIH: A propos de 13 cas. *Med Mal Infect* 1994;**24**:785–91.
13. **Gordon SM**, Eaton ME, George R, *et al*. The response of symptomatic neurosyphilis to high-dose intravenous penicillin G in patients with human immunodeficiency virus infection. *N Engl J Med* 1994;**331**:1469–73.
14. **Hutchinson CM**, Hook EW 3rd, Shepherd M, *et al*. Altered clinical presentation of early syphilis in patients with human immunodeficiency virus infection. *Ann Intern Med* 1994;**121**:94–100.
15. **Goeman J**, Kivuvu M, Nzila N, *et al*. Similar serological response to conventional therapy for syphilis among HIV-positive and HIV-negative women. *Genitourin Med* 1995;**71**:275–9.
16. **Malone JL**, Wallace MR, Hendrick BB, *et al*. Syphilis and neurosyphilis in a human immunodeficiency virus type-1 seropositive population: Evidence for frequent serologic relapse after therapy. *Am J Med* 1995;**99**:55–63.
17. **Marra CM**, Longstreth WT Jr, Maxwell CL, *et al*. Resolution of serum and cerebrospinal fluid abnormalities after treatment of neurosyphilis. Influence of concomitant human immunodeficiency virus infection. *Sex Transm Dis* 1996;**23**:184–9.
18. **Yinnon AM**, Coury-Doniger P, Polito R, *et al*. Serologic response to treatment of syphilis in patients with HIV infection. *Arch Intern Med* 1996;**156**:321–5.
19. **Rolfs RT**, Joesoef MR, Hendershot EF, *et al*. 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**:307–14.
20. **Bordon J**, Martinez-Vazquez C, de la Fuente-Aguado J, *et al*. Response to standard syphilis treatment in patients infected with the human immunodeficiency virus. *Eur J Clin Microbiol Infect Dis* 1999;**18**:729–32.
21. **Hook EW 3rd**, Martin DH, Stephens J, *et al*. A randomized, comparative pilot study of azithromycin versus benzathine penicillin G for treatment of early syphilis. *Sex Transm Dis* 2002;**29**:486–90.
22. **Tattevin P**, Renault P, Joly V, *et al*. Treatment of latent syphilis in HIV-infected patients with 10 d of benzylpenicillin G benethamine: A prospective study in Maputo, Mozambique. *Scand J Infect Dis* 2002;**34**:257–61.
23. **Smith NH**, Musher DM, Huang DB, *et al*. Response of HIV-infected patients with asymptomatic syphilis to intensive intramuscular therapy with ceftriaxone or procaine penicillin. *Int J STD AIDS* 2004;**15**:328–32.
24. **Gutierrez-Galhardo MC**, do Valle GF, Sa FC, *et al*. Clinical characteristics and evolution of syphilis in 24 HIV+ individuals in Rio de Janeiro, Brazil. *Rev Inst Med Trop Sao Paulo* 2005;**47**:153–7.
25. **Kiddugavu MG**, Kiwanuka N, Wawer MJ, *et al*. Effectiveness of syphilis treatment using azithromycin and/or benzathine penicillin in Rakai, Uganda. *Sex Transm Dis* 2005;**32**:1–6.
26. **Nnoruka EN**, Ezeoke AC. Evaluation of syphilis in patients with HIV infection in Nigeria. *Trop Med Int Health* 2005;**10**:58–64.
27. **Riedner G**, Rusizoka M, Todd J, *et al*. Single-dose azithromycin versus penicillin G benzathine for the treatment of early syphilis. *N Engl J Med* 2005;**353**:1236–44.
28. **Chauhan M**, Serisha B, Sankar KN, *et al*. Audit of the use of benzathine penicillin, post-treatment syphilis serology and partner notification of patients with early infectious syphilis. *Int J STD AIDS* 2006;**17**:200–2.
29. **Kofoed K**, Gerstoft J, Mathiesen LR, *et al*. Syphilis and human immunodeficiency virus (HIV)-1 coinfection: influence on CD4 T-cell count, HIV-1 viral load and treatment response. *Sex Transm Dis* 2006;**33**:143–8.
30. **Ghanem KG**, Erbeling EJ, Wiener ZS, *et al*. Serological response to syphilis treatment in HIV-positive and HIV-negative patients attending sexually transmitted diseases clinics. *Sex Transm Infect* 2007;**83**:97–101.
31. **Manavi K**, McMillan A. The outcome of treatment of early latent syphilis and syphilis with undetermined duration in HIV-infected and HIV-uninfected patients. *Int J STD AIDS* 2007;**18**:814–18.
32. **Ghanem KG**, Moore RD, Rompalo AM, *et al*. Antiretroviral therapy is associated with reduced serologic failure rates for syphilis among HIV-infected patients. *Clin Infect Dis* 2008;**47**:258–65.
33. Should early syphilis be treated differently in HIV positive and HIV negative individuals? Brooklyn, NY. BASHH ASTDA 3rd Joint Conference, Brooklyn, NY, 2008, Abstract E-08.
34. **Warwick Z**, Dean G, Fisher M. Should syphilis be treated differently in HIV-positive and HIV-negative individuals? Treatment outcomes at a university hospital, Brighton, UK. *Int J STD AIDS* 2009;**20**:229–30.
35. **Kingston M**, French P, Goh B, *et al*. UK National guidelines on the management of syphilis 2008. *Int J STD AIDS* 2008;**19**:729–40.
36. **Stamm LV**, Bergen HL. A point mutation associated with bacterial macrolide resistance is present in both 23S rRNA genes of an erythromycin-resistant *Treponema pallidum* clinical isolate. *Antimicrob Agents Chemother* 2000;**44**:806–7.
37. **Lukehart SA**, Godornes C, Molini BJ, *et al*. Macrolide resistance in *Treponema pallidum* in the United States and Ireland. *N Engl J Med* 2004;**351**:154–8.
38. **Matejkova P**, Flasarova M, Zakoucka H, *et al*. Macrolide treatment failure in a case of secondary syphilis: a novel A2059G mutation in the 23S rRNA gene of *Treponema pallidum* subsp. *pallidum*. *J Med Microbiol* 2009;**58**:832–6.
39. **Romanowski B**, Sutherland R, Fick GH, *et al*. Serologic response to treatment of infectious syphilis. *Ann Intern Med* 1991;**114**:1005–9.
40. **Marra CM**, Maxwell CL, Collier AC, *et al*. Interpreting cerebrospinal fluid pleocytosis in HIV in the era of potent antiretroviral therapy. *BMC Infect Dis* 2007;**7**:37.
41. **De Milito A**. B lymphocyte dysfunctions in HIV infection. *Curr HIV Res* 2004;**2**:11–21.
42. **Marra CM**. Déjà Vu all over again: When to perform a lumbar puncture in HIV-infected patients with syphilis. *Sex Transm Dis* 2007;**34**:145–6.
43. **Ghanem KG**, Moore RD, Rompalo AM, *et al*. Lumbar puncture in HIV-infected patients with syphilis and no neurologic symptoms. *Clin Infect Dis* 2009;**48**:816–21.
44. **Stoner BP**. Current controversies in the management of adult syphilis. *Clin Infect Dis* 2007;**44**(Suppl 3):S130–46.
45. **Dowell D**, Polgreen PM, Beekmann SE, *et al*. Dilemmas in the management of syphilis: a survey of infectious diseases experts. *Clin Infect Dis* 2009;**49**:1526–9.
46. **Gross PA**. When guidelines don't guide the physician. *Clin Infect Dis* 2009;**49**:1530–1.
47. **Centers for Disease Control and Prevention**. *Sexually transmitted disease surveillance, 2008*. Atlanta, GA: Department of Health and Human Services, 2009.