

What are the recommended options for the treatment of syphilis when penicillin therapy is not feasible?

Citation	Study Design	Study Population	Exposure/Intervention	Outcome	Findings	Design Analysis Quality/Biases
Doxycycline and Ceftriaxone						
Chotmongkol V , et al. <i>STI</i> 2012; 88:177-178	Case series (retrospective)	19 patients with otosyphilis	Doxycycline 400mg orally daily X 21 days (N=19)	Subjective and audiogram changes	Subjective improvement in 47.3% and improved audiogram in 36.8% (similar to historical reports)	Small sample size without control group. Specificity of otosyphilis diagnosis
Psomas KC , et al. <i>Med Malad Infect</i> 2012; 42:15-19	Observational (retrospective)	116 (93 HIV+) with early syphilis (89 secondary stage)	BPG 2.4-7.2 MU (N=52) Ceftriaxone 1g IV X 10d (N=49) Doxycycline? dose (N=15)	4-fold decline in VDRL titer at 12 months	75% response for BPG 77.6% for ceftriaxone and 73.3% for doxycycline	Heterogeneity in stages and doses; limited information provided
Spornraft-Ragaller P , et al. <i>Eur J Med Res</i> 2011; 16:47-51	Retrospective case series	24 HIV infected MSM with mainly early syphilis (~80%)	12 treated with high dose PCN for 2 weeks; 12 treated with ceftriaxone 1-2g/day IV X 14-21 days	Serological decline in VDRL titers at 18 months	12/12 of PCN and 11/12 of ceftriaxone responded.	Stages differed between two groups; duration of therapy differed; antibiotic doses varied
Wong T , et al. <i>Am J Med</i> 2008; 121:903-8	Observational (retrospective)	445 with primary syphilis	BPG IM 2.4 MU (N=420) Doxycycline 100 mg orally twice daily or tetracycline 500mg orally four times daily (N=25)	4-fold decline in RPR titers at 6 months, 8-fold at 12 months and 16-fold at 24 months	97.4% success for BPG 100% success for doxycycline/tetracycline	HIV information inconsistent
Azithromycin						
Bai ZG et al. <i>Cochrane Rev</i> 2012	Meta-analysis	3 RCTs in persons with early syphilis (N=790)	BPG vs. Azithromycin (0.5g to 4g)	Serological responses at 3, 6, and 9 months	No difference in serological responses between BPG and azithromycin (OR 1.04; 95% CI 0.69-1.56)	Heterogeneity among studies
Hook III EW et al. <i>JID</i> 2010; 201:1729-35	RCT (open label)	517 HIV- persons with early syphilis	Azithromycin 2g PO X1; BPG 2.4 MU IM;	Serological \geq 4-fold decline in titers at 6 m	Cure (ITT): Azithromycin 77.6% vs. BPG 78.5%	HIV+ excluded
Grimes M , et al. <i>STD</i> 2012; 39:954-8	Series (retrospective)	134 specimens from 129 participants in Seattle	Detection of A2058G and A2059G and molecular typing of <i>T. pallidum</i> strains from 2001-2010	Prevalence of mutations and subtypes	Overall prevalence of either mutation was 72% with increased prevalence over time; each mutation was present in distinct	No clinical correlation data with treatment failures included

					strains	
The A2058G Prevalence Workgroup <i>STD</i> , 2012; 39:794-798	Series (retrospective)	<i>T. pallidum</i> specimens (N=141) from 11 cities throughout the US (South, Midwest, West)	Detection of A2058G mutation 2007-2009	Prevalence of mutations	Overall, 53% prevalence of mutation; geographic differences (no mutations in Midwest; 84% prevalence in the West)	No clinical correlation data with treatment failures included; no data on A2509G mutation
Muldoon EG , et al. <i>STD</i> 2012; 39:784-786	Series (retrospective)	<i>T. pallidum</i> specimens (N=29) from Dublin, Ireland	Detection of A2058G mutation 2009-2010	Prevalence of mutations	93.1% prevalence of mutation	No clinical correlation data with treatment failures included; no data on A2509G mutation
Wu H , et al. <i>JCM</i> 2012;50:2299-2304	Series (retrospective)	<i>T. pallidum</i> specimens (N=40) from Taiwan	Detection of A2058G and A2059G mutations 2009-2011	Prevalence of mutations	0% prevalence	Small number of specimens
Muller EE , et al. <i>STI</i> 2012; 88:470-4	Series (retrospective)	<i>T. pallidum</i> specimens (N=100) from southern Africa	Detection of A2058G and A2059G mutations 2005-2010	Prevalence of mutations	1% prevalence	No clinical correlation data with treatment failures included
Molini BJ , et al. <i>ICAAC</i> 2012 Abstract A-1908	Rabbit models	Groups of 3 rabbits were inoculated with <i>Tp</i> wild type and macrolide mutation	Darkfield microscopy of lesions and VDRL titers	Response to therapy with macrolides, fluoroketolide, and BPG	<i>T. pallidum</i> persisted in Street 14- and UW330B-infected rabbits treated with AZ, and VDRL titers were not significantly different from untreated controls.	Animal model
Tipple C , et al. <i>STI</i> 2011; 87:486-8	Series (retrospective)	<i>T. pallidum</i> specimens (N=18) from London	Detection of A2058G and A2059G mutations 2006-2008	Prevalence of mutations	67% prevalence	No clinical correlation data with treatment failures included
Zhou P , et al. <i>STD</i> 2010; 37:726-729	Series (retrospective)	132 patients who failed therapy after receiving a minimum of 4g of azithromycin in Shanghai	Failure defined as persistent signs, lack of 4-fold serological response, or persistently positive darkfield examination. Detection of A2058G on 4 samples only 2001-2009	Description of treatment failure and mutations in a subset	Overall, 4/4 patients who failed therapy and were tested had the A2508G mutation	Limited numbers with mutations tested; reinfection was still possible
Martin IE , et al. <i>CID</i> 2009; 49:515-21	Series (retrospective)	38 patients with primary syphilis in Shanghai	Detection of A2058G mutation 2007-2008	Prevalence of mutation	100% prevalence of mutation	No clinical correlation data with treatment

						failures included; small number of specimens
Martin IE , et al. <i>JCM</i> 2009; 47:1668-1673	Series (retrospective)	14 patients with syphilis in Alberta, CA	Detection of A2058G mutation 2007-2008	Prevalence of mutation	29% prevalence of mutation	No clinical correlation data with treatment failures included; small number of specimens
Matejkova P , et al. <i>J Med Microbiol</i> 2009; 58:832-6	Series (retrospective)	1 patient with spiramycin treatment failure and 22 other specimens from Czech Republic	Detection of A2058G and description of A2509G mutation	Prevalence of mutation	18% prevalence of either mutation	No clinical correlation data with treatment failures included; small number of specimens
Van Damme K , et al. <i>STD</i> 2009; 36:775-776	Series (retrospective)	<i>T. pallidum</i> specimens (N=141) from subset of participants enrolled in a Madagascar efficacy trial	Detection of A2058G from 2000-2009	Prevalence of mutation	0% prevalence of mutation A2058. [Later 1 A2059G mutant was noted]	No clinical correlation data with treatment failures included;

Does enhanced therapy for early syphilis with additional doses of benzathine penicillin G (BPG) provide improved outcomes [either clinical or serological]?

Citation	Study Design	Study Population	Exposure/Intervention	Outcome	Findings	Design Analysis Quality/Biases
*Dionne-Odom J , et al. <i>CID</i> 2013 (in press)	Retrospective cohort	1321 persons in two African sero-discordant cohorts (Zambia and Rwanda)	Diagnosis and treatment of syphilis	Serological responses at 400 days post therapy	No difference between HIV+ and negatives; by 400 days 67% had responded to therapy and 27% were serofast	Not randomized; subset tested using treponemal test; limited staging information; treatment doses not clearly defined between groups
Taiwan HIV and Syphilis Study Group. CROI 2013 Atlanta, GA	Observational (prospective)	579 HIV-infected participants with early syphilis from 7 hospitals in	BPG 2.4 MU X1 (N=302) vs. BPG 2.4 MU X3 (N=277)	4-fold serological decline at 12 months	70.9% serological responses in BPG X1 group vs. 76.7% in BPG X3	Not randomized; treatment decision at discretion of physician.

Abstract S-119		Taiwan between 2007 and 2012			group. Low CD4 count (<350 cells/ml) was associated with fewer serologic responses	
Cousins DE , et al. <i>Int J STD AIDS</i> 2012; 23:632-634	Retrospective	2 cohorts: 2006 cohort treated with 2 or 3 doses of BPG (N=131; HIV+ N=39) vs. 2007 cohort treated with single dose of BPG (N=128; HIV+ =38)	BPG treatment	Serological responses	No significant differences in outcomes except that HIV+ persons may have been more likely to be reinfected	Limited data on how they differentiated reinfection with treatment failure; observation time may have differed between the two cohorts
Blank LJ , et al. <i>STI</i> 2011; 87:9-16	Systematic review	23 studies assessing treatment responses in HIV-infected persons	Serological and clinical responses to BPG therapy at various stages of syphilis	Serological non-response 6-12 months after treatment for early syphilis, 12 to 24 months after treatment for latent syphilis, and 12 months after treatment for neurosyphilis	Range of failure of BPG X1 for early syphilis from 6.9% to 22.4%; BPG X3 for latent syphilis from 19.4% to 31.1%, and IV PCN for neurosyphilis of about 27%	Limited data mainly of poor quality
Hopkins S , et al. <i>Int J STD AIDS</i> ; 2009; 20:593-594	Prospective	506 persons in Dublin (N=100 HIV+) treated and followed for two years	Syphilis therapy	Serological responses	HIV+ responses were 76% vs. 64% among HIV- (HIV- had more loss to follow-up)	Therapy was extremely variable between HIV+ and HIV- persons. More HIV+ got procaine penicillin
Farhi D , et al. <i>Medicine</i> 2009; 88:331-340	Observational (retrospective)	144 persons with syphilis (HIV+ N=85)	BPG X1 for early syphilis and BPG X3 for latent syphilis	Serological failure (VDRL)	1.7% of HIV- persons failed therapy vs. 8.2% of HIV+ (NS). All failures occurred with early syphilis.	Failure vs. reinfection; small numbers overall;
Warwick Z , et al. <i>Int J STD AIDS</i> 2009; 20:229-230	Observational study (prospective)	HIV-infected (N=128) and uninfected (N=200) participants	BPG therapy in HIV-uninfected and procaine PCN + Probenecid X17d for HIV+	Serological 4-fold decline at 12 months	98% treatment response in both groups at 12 months	No control groups in either arm; not randomized.

What is the minimum and maximum acceptable amount of time between BPG injections when treating late latent syphilis? Should recommendations differ for pregnant women?

Citation	Study Design	Study Population	Exposure/Intervention	Outcome	Findings	Design Analysis Quality/Biases
Janier M et al. STD 2012; 39:359-360	Observational (prospective)	50 participants with latent syphilis	A single 2.4 MU injection versus two 1.2 MU injections given at weeks 1 and 2 respectively	Pain score and patient choice of injection at week 3	No difference in pain scores or patient preferences for either formulation	Not randomized

- Collart P, et al. Kinetic Study of Serum Penicillin Concentrations after Single Doses of Benzathine and Benethamine Penicillins in Young and Old People. *Br J Vener Dis* 1980; 56:355-62.
 - The figure and table below demonstrate the kinetics of 2.4 MU of BPG

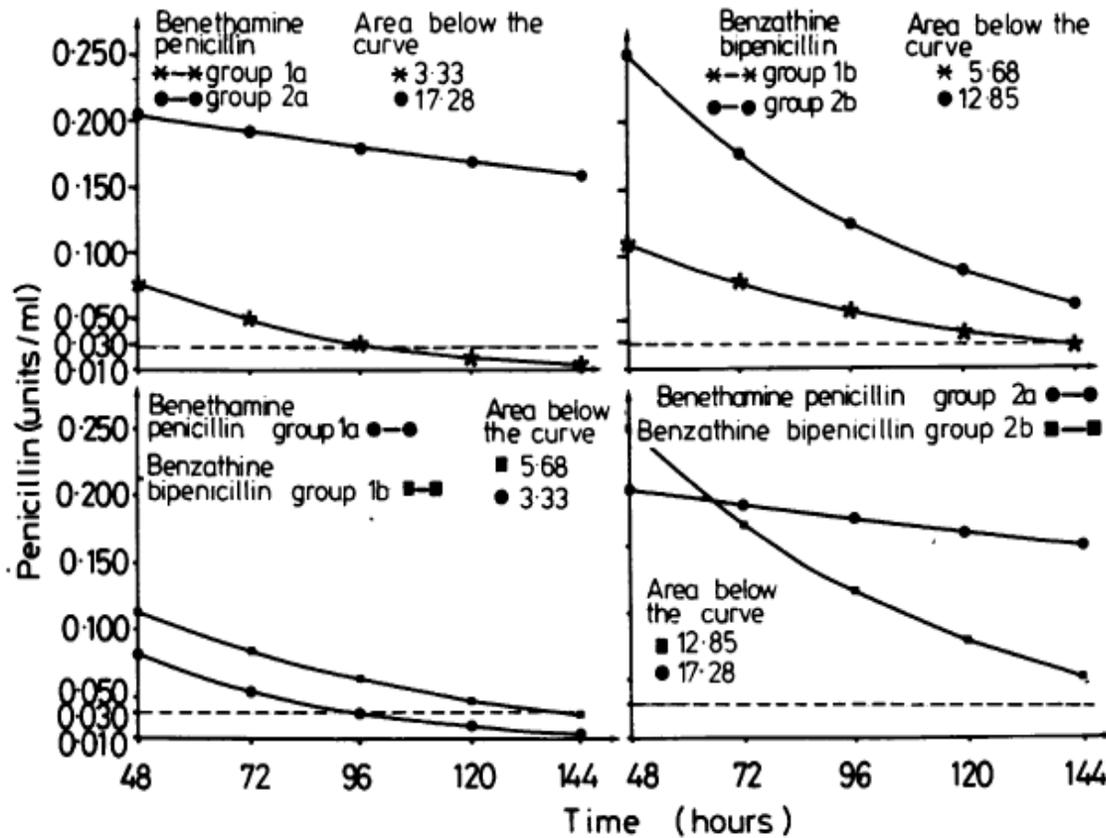


FIG 1 Regression curves of serum penicillin concentrations after a single injection of benethamine penicillin or benzathine bipenicillin in four different groups (groups 1a and 1b, young subjects; groups 2a and 2b, elderly subjects). Results are in weighted values.

TABLE II Comparison of serum penicillin concentrations after injections of benethamine penicillin and benzathine bipenicillin in four different groups of subjects

Subject group	No in group	Mean age (years)	Penicillin complex	Dose (IU)	Mean serum penicillin concentrations (units/ml) at:						
					2 Days	3 Days	4 Days	5 Days	6 Days	13 Days	20 Days
1a (Young)	20	20.5	Benethamine penicillin	3×10^6	0.247	0.139	0.078	0.053	0.035		
2a (Elderly)	36	75	Benethamine penicillin	3×10^6	0.488	0.421	0.351	0.390	0.342	0.104	0.042
1b (Young)	15	22	Benzathine bipenicillin	2.4×10^6	0.340		0.161		0.080	0.037	
2b (Elderly)	25	76	Benzathine bipenicillin	2.4×10^6	0.635		0.216		0.151	0.081	0.064

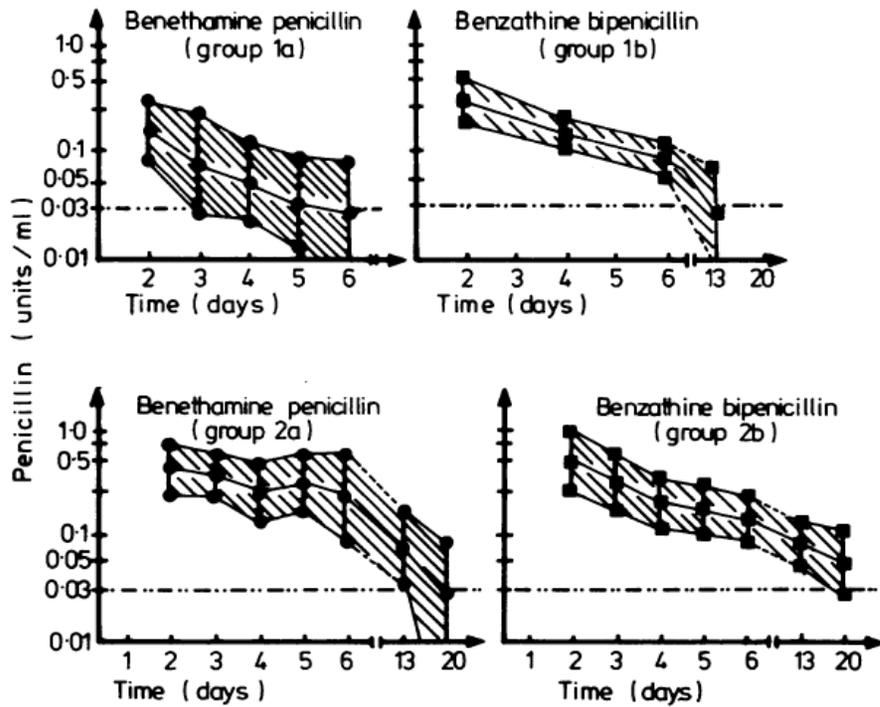


FIG 3 Graphs of the mean serum concentrations of benethamine penicillin and benzathine bipenicillin in four groups of subjects (groups 1a and 1b, young subjects; groups 2a and 2b, elderly subjects).

Additional study by Fretz G, et al. Penicillin Concentrations in Blood and Spinal Fluid After a Single Intramuscular Injection of Penicillin G Benzathine. *Eur J Clin Microbiol* 1984; 3:147-149

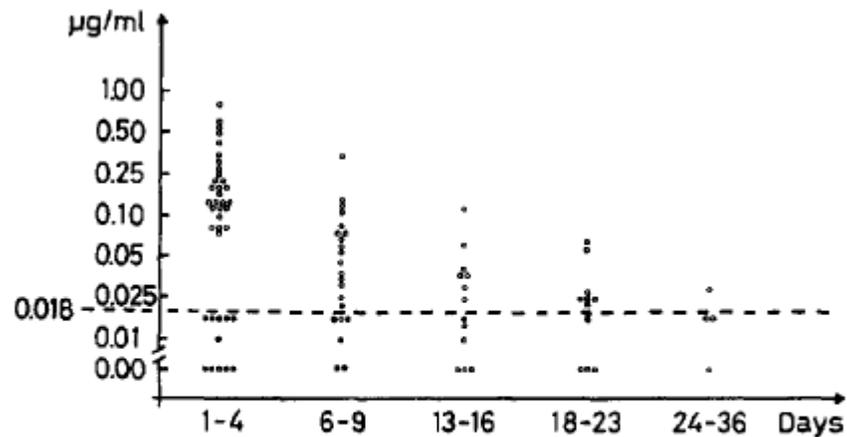


Figure 1: Penicillin concentration in blood (○) and CSF (●) assayed up to 36 days after a single i.m. injection of 1.44 g of penicillin G benzathine.

All patients but one had treponemicidal blood concentrations 6-9 days after injection, while five had blood concentrations below 0.018 microg/ml after 13-16 days.

Additional study by Hagdrup HK, et al. Penicillin concentrations in serum following weekly injections of benzathine penicillin G. *Chemotherapy*. 1986;32(2):99-101.

Twelve patients with syphilis were treated weekly with injections of 1.44 g (2.4 X 10⁶ IU) of BPG for up to 3 weeks. Almost daily, serum penicillin concentrations were measured by a sensitive microbiological agar cup method. Inter-individual variation was found. Concentrations below the recommended 0.018 micrograms/ml were found 7 days after the first or second injection in 5 samples. Shorter intervals between injections are recommended.

What is the appropriate approach to managing patients who do not demonstrate an adequate serological decline following stage-appropriate therapy? Should recommendations differ for persons with HIV?

Citation	Study Design	Study Population	Exposure/Intervention	Outcome	Findings	Design Analysis Quality/Biases
Sena AC et al. <i>CID</i> 2013;56:420-2	Intervention nested in RCT	HIV- persons who remained serofast at 6 months after treatment of early syphilis with 2.4 MU BPG or 2g oral azithromycin	Retreatment at 6 months with 2.4MU BPG	Titer decline	82 participants were serofast; after retreatment, 13% exhibited serological decline (27% if compared to baseline titer). Persons who remained serofast had lower RPR titers	No assessment of long-term outcomes; no CSF examinations
Holman KM et al. <i>STD</i> 2012; 39:645-647	Nested in RCT	470 persons with early syphilis from U.S. and Madagascar	RPR titers at days 0, 7, and 14	RPR titer variations	20% had titer increases in the first 14 days following therapy. 88% had 1 titer dilution increase. 35% had primary syphilis. Using the peak titer in the first 14 days instead of initial titer change, 6-month serological outcomes only changed in 3% of participants	No HIV-infected participants; participants with primary syphilis and non-reactive nontreponemal tests were excluded
Zhou P et al. <i>STI</i> 2012; 88:342-345	Case series (retrospective)	17 HIV-uninfected persons with secondary syphilis whose titers declined 4-fold following therapy but who progressed to neurosyphilis (N=4 symptomatic)	Progression to NS (positive CSF VDRL) despite serological response following therapy (at least 25 months since therapy) for secondary syphilis (different regimens used)	Neurosyphilis	Of the 17 who had positive CSF VDRLs, 14 were asymptomatic; 3 were symptomatic (I CVA and 2 'cognitive deficits). All symptomatic cases were treated with BPG	No denominator; selection bias; small sample size; most were asymptomatic.; no data on long-term outcomes

Knaute FK , et al. <i>CID</i> 2012; 55:1615-22 and F/U letter <i>CID</i> 2013; 56:56	Observational (retrospective)	264 patients (112 HIV+) with syphilis (223 with early syphilis)	Comparing IgM Ab detection to VDRL and TPPA serologies	VDRL, IgM ELISA, and TPPA serologies	Slower responses among HIV+ with primary stage and CD4 <500; secondary and latent syphilis had slower responses overall; IgM responses were slower than VDRL; TPPA titers seroreverted in 13% (HIV+ was risk factor)	Treatment regimens varied;
Pastuszczak M , et al. <i>STI</i> 2012; 88:312	Observational (prospective)	71 subjects with early syphilis treated with 2.4 MU BPG	Follow-up at 3, 6, and 12 month following therapy	Treatment failure detected at 3 month visit	The 3-month visit did not detect treatment failure. 93.3% achieved serological cure by 12 months (vs. 71.4% at 3 months)	HIV status not known; no control group
Lin L , et al. <i>Diagn Microbiol Infect Dis</i> 2011; 201-7	Observational (retrospective)	1208 persons with syphilis who were treated and had appropriate responses to therapy.	4 groups: (1) +TRUST + TPPA (2) –TRUST and + TPPA (3) –TRUST – TPPA; (4) negative controls	IgM antibodies in serum	33% of Group 1 had IgM antibodies, 10% in group 2, and 0% in Groups 3 and 4	No clinical outcomes to correlate with IgM data; no HIV+ persons
Sena AC et al. <i>CID</i> 2011; 53:1092-1099	Nested in RCT	465 participants with early syphilis: 369 achieved serological cure (>= four-fold decline in titers) and 96 were serofast	Treatment of BPG vs. Azithromycin	Serological responses	Age, RPR titer, JH reaction , syphilis stage, and number of sex partners were associated with serological responses	No HIV-infected patients were included
Gonzalez-Lopez J , et al. <i>CID</i> 2009; 49:1505-11	Observational (retrospective)	347 cases of syphilis (49.3% HIV+)	Treatment (1 to 3 doses of BPG)	Serological responses at 13 months	Men, late stages, and HIV+ status decreased the risks of serological responses while cART increased the risk of	Treatment data not very clear; reinfection may have been a problem

					serological response	
Day S, et al. <i>STI</i> 2009; 85:561-2	Observational (retrospective)	114 persons with early syphilis (60% HIV+)	Treatment (94% BPG)	Serological and clinical responses at 1, 2, 3, 6, and 12 months after therapy	32% of patients achieved serological cure by 2 months ; 2/114 persons at the two-month F/U had suspected treatment failure	

Who should have a CSF examination to evaluate for neurosyphilis and what is the role of follow-up CSF examination after the treatment of neurosyphilis?

Citation	Study Design	Study Population	Exposure/Intervention	Outcome	Findings	Design Analysis Quality/Biases
Diagnostics						
Gu W, et al. <i>BMJ Open</i>; 2013; 3:e002204	Cross sectional prospective	STD clinic patients	Measurement of CSF TRUST and VDRL	Positivity of CSF TRUST vs. CSF VDRL	Overall agreement between CSF TRUST and CSF VDRL was 97.3% but the TRUST was more likely to be negative than the VDRL. 97% of samples that were reactive by both tests had identical titers.	No gold standard
Marra CM, et al. <i>STD</i> 2012; 39:453-457	Nested in observational study	A convenience sample selected to over-represent syphilis and neurosyphilis (83.2% HIV+)	Measurement of CSF VDRL, RPR, and modified RPR	Comparing CSF VDRL to CSF RPR and CSF RPR-V	Compared to the CSF VDRL, the CSF RPR and RPR-V were less sensitive for laboratory diagnosed and symptomatic neurosyphilis	Few HIV uninfected persons Convenience sample
Harding AS, et al. <i>STD</i> 2012; 39:291-297	Systematic review	18 studies assessing 7 treponemal CSF	Performance characteristics of CSF treponemal tests	Sensitivity, specificity, positive predictive value	The negative predictive value of CSF treponemal	Heterogeneity of studies

		tests		and negative predictive value	tests depended on the specificity of the test and the pre-test probability of neurosyphilis	
Jiang Y , et al. <i>STD</i> 2011; 38:244-245	Retrospective case series	41 cases of HIV-uninfected neurosyphilis (36 symptomatic) and 34 non-neurologic syphilis	Reactivity of CSF treponemal and nontreponemal tests-particular focus on utility of CSF TRUST	CSF VDRL, TPPA, and TRUST	The sensitivity of TRUST was 95% and specificity was 100%. TPPA specificity was 60%	No gold standard for neurosyphilis; no HIV+ persons
Marra CM , et al. <i>STD</i> 2010; 37:283-287	A convenience sample selected to over-represent syphilis and neurosyphilis	199 persons with syphilis and HIV suspected of having neurosyphilis	Measurement of serum and CSF CXCL13	Levels of CSF and serum CXCL13	CXCL13 levels were higher in patients with neurosyphilis and levels were independent of CSF pleocytosis. Levels of CXCL13 declined after therapy	Selection bias; no HIV uninfected persons
Predisposing Factors						
Marra C , et al. <i>CROI</i> 2013, Atlanta, GA Paper 398	Observational	645 patients (532 HIV+) with syphilis	3 common TLR SNP	Association between TLR polymorphisms and clinical risk of neurosyphilis	Both clinical and laboratory-defined neurosyphilis risks were increased in those with SNP in 3 TLR genes that impair innate immune responses to lipoproteins	
Marra CM , et al. <i>JID</i> , 2010; 202:1380-88	Case series	158 patients (US, China, Ireland, and Madagascar) with syphilis and 15 <i>Tp</i> isolates	Enhanced typing of <i>Tp</i>	Association between type and clinical syndrome	21/42 patients with type 14 d/f had neurosyphilis compared to 10/41 of the other types	Small sample of patients with neurosyphilis
Indication for CSF Examination						
Muldoon EG , et al. <i>Int J STD AIDS</i> 2012; 23:676-678	Case series (prospective)	35 HIV+ persons treated for syphilis pre-2007	CSF examination	Prevalence of CSF abnormalities	34/35 persons had normal neurological examination and CSF parameters. 1	No data on past treatment.

					person had pleocytosis but no symptoms.	
Chang CC et al. <i>Sexual Health</i> 2011; 8:207-213	Retrospective series	18 HIV-infected MSM in Australia diagnosed with neurosyphilis (13/18 were symptomatic)	Descriptive	Clinical and serological responses	17/18 had + CSF FTA; 18/18 had RPR >1:32. Treatment with 14 days of IV PVN resulted in 75% cure within 1 year	Reinfection vs. relapse; selection biases
Matteelli A , et al. <i>CROI</i> 2011, Boston, MA abstract #980	Retrospective case series	HIV and syphilis co-infected persons	CSF examination	Neurosyphilis diagnosis (positive CSF VDRL or CSF WBC >10 + positive CSF TPPA) based on various staging methods	17/122 cases of neurosyphilis. All cases of symptomatic NS (N=4) had early syphilis. 5 cases of asymptomatic neurosyphilis occurred in late latent stage (all had a positive serum RPR)	Limited data in abstract; used old CDC recommendations for neurosyphilis that included late latent stage for CSF examination; unclear what the significance of asymptomatic CSF abnormalities
Choe PG , et al. <i>STI</i> , 2010; 86:39-40	Case series prospective	HIV-uninfected persons with untreated late latent syphilis (N=70)	CSF examination	Prevalence of neurosyphilis	None had clinical findings of neurosyphilis; all had serum VDRL <1:16; all had negative CSF VDRLs; 4 had elevated CSF WBCs (>5 cells/ml); 3 had positive CSF treponemal tests; 57 had elevated CSF protein concentrations	HIV-infected persons were excluded; limited data on neurosyphilis diagnostic criteria available
Neurological Consequences of Syphilis						
Marra CM , et al. <i>CROI</i> , 2011 Boston, MA poster #397	Nested in CHARTER	HIV-infected persons with (N=101) and without (N=65) prior syphilis	Neurocognitive testing	Neuropsychological test domains	Participants with prior syphilis performed more poorly on neuropsychological	

					testing after adjusting for confounders. This was not related to treatment history of syphilis.	
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Are there interventions that improve syphilis outcomes among HIV-infected and at-risk persons?

Citation	Study Design	Study Population	Exposure/Intervention	Outcome	Findings	Design Analysis Quality/Biases
Screening and Reinfections						
Ganesan A, et al. <i>CROI</i> 2013, Atlanta, GA	Retrospective	Military HIV Natural History Study	Assess the number of repeat syphilis infections	Repeat syphilis infections	40% of all cases of syphilis were repeat infections.	Limited risk factor data
Hoare A, et al. <i>Sexual Health</i> 2012; 9:144-51	Modeling transmission dynamics of syphilis and HIV in MSM	MSM reflecting epidemic in Victoria, Australia	Determine if syphilis action plan could reduce new syphilis and HIV infections. Plan includes frequent screening and enhanced partner services	HIV incidence	Implementation of this plan could decrease incident HIV cases by 48% in 10 years	Modeling data
White DAE, et al. <i>STD</i> 2012;39:286-290	Retrospective cohort	Urban ED Oakland CA	Screening for syphilis in persons screened for GC/CT	Syphilis screening and positivity probability	31% of the GC/CT-tested persons were screened for syphilis and 1.4% were positive and 0.7% were newly diagnosed	External validity; feasibility; cost-effectiveness
Brewer TH, et al. <i>STD</i> 2011; 38:367-371	Retrospective	Male syphilis cases in NYC, Miami, Philadelphia	None	Prevalence and risks from 2000-2008	More minority adolescents (particularly African American young men); many MSM; some HIV+ (15-25%)	PH data limited
Lewis, FMT, et al. <i>J Publ Health Management Practice</i> 2011; 17:513-21	Retrospective cost analysis from PH data	Data on syphilis screening from 6 states	Cost assessment	Crude cost per new case	926,258 tests were performed to detect 4671 new syphilis cases. Jail screening had the	Heterogeneity of data quality

					highest yield. Cost per case identified ranged from \$144 to \$3454	
Marcus JL , et al. <i>STD</i> 2011; 38:24-29	Retrospective analysis using surveillance data	MSM who were treated for early syphilis in San Francisco	Determine if they were retested in the subsequent 1 to 6 months following therapy	Re-testing	One third of MSM treated for syphilis were not retested in the subsequent 6 months	PH data limitations
Brewer TH , et al. <i>STD</i> 2011; 38:12-17	Retrospective	Florida syphilis cases from 2000-2008	What proportion are repeat infections	Prevalence of repeat infection	Of 26,070 syphilis cases, 2.5% were repeat infections; median time to reinfection 3 years. Mostly MSM. Many HIV+	Outcome identification bias (more frequent screening in MSM)
Cohen SE , et al. <i>AJPH</i> 2011 Nov 17: e1-e8	Retrospective	MSM in California	Rates and risks for syphilis reinfection from 2002-2006	Prevalence of repeat infection	5.9% of MSM had repeat early syphilis infection within median of 2 years; AA, HIV+, >10 sex partners were risk factors	Outcome identification bias (more frequent screening in MSM)
Stephens SC , et al. <i>STD</i> 2010; 37:173-176	Prospective survey	MSM in San Francisco	Determine if a social marketing campaign aimed at increasing syphilis testing worked	Recollection of dog-themed social marketing campaign.	Among HIV-MSM, there was no impact of the campaign. HIV+ MSM endorsed recalling the campaign more frequently when tested	Recall bias
Horberg MA , et al. <i>STD</i> 2010;	Retrospective analysis	Kaiser Permanente of	Compare HIV+ and HIV- persons diagnosed with	Prevalence and risks	Incidence of syphilis 86X	Treatment failure vs. reinfection;

37:53-58		N. California	syphilis		higher among HIV+ than HIV-; HIV+ more likely to experience serological failure; Reduction in RPR was higher among those on ART	limited exposure data
Thurnheer MC, et al. <i>AIDS</i> 2010; 24:1907-16	Retrospective cohort study	Prospective Observational Swiss HIV Cohort Study	Describe syphilis rates and risks after the reintroduction of yearly screening	Risk factors and prevalence following routine yearly screening	Risk factors included MSM, younger age, and orogenital exposures. 91% serological response to therapy	Limited data on neurosyphilis cases
Gray RT, et al. <i>STD</i> 2010; 37:298-305	Mathematical model	Describe syphilis transmission among MSM	Screening and contact tracing	Which intervention is highest yield?	Q3m testing among highly active MSM is very high yield. Contact tracing is high yield but costly	Model
Lee D, et al. <i>STD</i> 2010; 37:557-558	Survey	Australian MSM	Syphilis testing using POC test	Survey of preference	MSM liked rapid testing and would get tested more frequently if it were available	No hard outcome; self-reports
Branger J, et al. <i>STD</i> 2009; 36:84-85	Ambispective study	HIV+ persons in the Netherlands	Describe syphilis testing behaviors and yield of screening.	Rates of symptomatic and asymptomatic syphilis infections	Incidence of syphilis in MSM was twice that of all other HIV+ persons	Selection and information biases
Condoms						
Gray RT, et al.	Mathematical	Australian MSM	Impact of condom use	Impact of condom	Short-term	

STD 2011;38: 1151-1158	model		and behaviors on syphilis rates	use and behaviors on syphilis rates	reduction in partners and increases in condom use will have very little impact on long-term changes. It will take large sustained changes in behaviors to impact rates	
Koss CA, et al. STD 2009; 36:401-405	Systematic review	12 studies assessing the impact of condom use on risk of syphilis	Incidence of syphilis with condom use	Association between condom use and syphilis	2 rigorous studies demonstrated the efficacy of condoms in preventing syphilis transmission	Data were of very limited quality
Partner Services/Interventions						
Surie D, et al. <i>Int J STD AIDS</i> , 2012; 23:859-861	Survey	MSM in five US Cities	Educational materials given to increase knowledge of primary and secondary syphilis manifestations	Self and partner examination behaviors	Of 914 MSM, 171 read the materials and reported examining their anus, mouth, penis, and skin and their partners' anus and mouth.	No syphilis outcome data
Ehlman DC, et al. STD 2010; 37:478-485	Retrospective	Washington DC PHD Internet-based partner notification program for early syphilis infection	Location, notification, testing and treatment of partners of patients with early syphilis	Partner localization and treatment if e-mails resulted in additional information	43% of all partners were via IPN. IPN lead to 83% more sex partners notified, 26% more being medically	Not randomized; no control arm

					examined, 8% more patients with at least one treated sex partner	
Taylor MM , et al. <i>STD</i> 2010; 37:767-770	Prospective	Place DIS staff at 3 private clinics with high prevalence of syphilis	DIS placed in 3 clinics	Number of patients interviewed, time to interview, time to treatment, and number of partners located	There was increases in the number of located and treated partners and a reduction in the time to treatment	Expensive intervention; historical control
Marcus JL , et al. <i>STD</i> ; 2010; 37:109-114	Prediction model from retrospective data	San Francisco DH	Validation of model to prioritize interviews	Factors that can limit the number of interviews and increase yield of sex partners	Limiting interviews to patients <50 would ID 92% of partners and decrease interviews by 14% and limiting interviews to P&S cases would ID 68% of partners and decrease interviews by 35%	Information biases
Samoff E , et al. <i>STD</i> 2009; 36:789-793	Retrospective	S. Carolina, Houston, and Jackson MI	ROC curves to compare titers and stage of syphilis	Percent agreement	The agreement between titer and stage was variable with significant titer overlap among the stages	Information biases
Chen SY , et al. <i>STD</i> 2009;36: 445-451	Retrospective	Arizona cases of syphilis 2006-7	None	Predictors of missed and delayed	Untreated syphilis was more likely to occur in a non-	Information biases

				diagnoses and treatment	STD clinic setting and with LL syphilis	
Chemoprophylaxis						
Wilson DP , et al. <i>STD</i> 2011; 38:573-579	Survey, focus groups, and mathematical modeling in Australia	Online survey of 2095 gay men and focus group of 23 MSM.	Survey, focus group, mathematical modeling	Likelihood of using chemoprophylaxis and impact of chemoprophylaxis	52% of 2095 men said they would be slightly or very likely to use chemoprophylaxis for syphilis; 70% use effectiveness of chemo used by 50% of gay men could decrease the # of syphilis cases by 50% in 12m	No hard outcomes

What is the impact of using the 'Reverse Sequence Algorithm' compared with the 'Traditional Algorithm' when screening for syphilis?

Citation	Study Design	Study Population	Exposure/Intervention	Outcome	Findings	Design Analysis Quality/Biases
RSA						
Hunter MG , et al. <i>JID</i> 2012:1-8	Prospective	Australian general population	Further testing of isolated reactive CIA results with two treponemal assays (TPPA and FTA-ABS)	Description	133 of 28261 specimens were CIA+ RPR-. 80.5% were from high prevalence population; 11/20 patients had previous or subsequent evidence of syphilis. Not all CIA+ RPR- TPPA - tests are false positives	Gold standard issues
Lipinsky D , et al. <i>JCM</i> 2012; 50:1501	Retrospective analysis from Israel	General population	Serum testing using CMIA, RPR, followed by TPPA	Concordance	Of 12,235 specimens: 334 CMIA+/RPR-, 197 were TPPA+ (59%). 65 were RPR+ CMIA-and TPPA-	No clinical data
Gatrix J , et al. <i>STD</i> 2012; 39:528-530	Retrospective	Alberta CA PH	Describe change in epidemiology of syphilis after introduction of the RSA	Syphilis prevalence	After introduction of RSA, 3 cases of primary syphilis were detected; LL cases increased from 36% to 58% (34 cases to 81 cases). Most LL cases were in persons born	Limited clinical data

					outside of Canada. 48% had a negative RPR	
Campbell CS et al. 2012 <i>National STD Prevention Conference</i> , Abstract P32	Prospective	IN HD	Policy instituted to F/U on serodiscordant results. Additional testing and record review	Classification	The “approach” allowed DIS to successfully determine which cases could be closed and which needed further follow-up	Very limited data in abstract. Unclear how further testing was conducted
Binnicker MJ, et al. JCM 2011; 50:148-150	Prospective	Rochester MN population	Direct comparison of RSA and traditional algorithm	Concordance	1000 samples, 15 screened positive: 6 patients had false positive MFI results; 2 patients had latent syphilis missed by traditional algorithm; 4 patients had past treated syphilis	
Park IU, et al. JID 2011; 204:1297-304	Prospective	KPNC	RPR- CIA+ management of patients	Management of patients	21,623 samples: 255 CIA+/ RPR- : 71 were TPPA-. 23% reverted to CIA negative; 1 converted to RPR+. Discordants had a lower CIA index.	No head to head comparison
Owusu-Edusei K, et al. STD 2011; 38:448-456	Cohort decision analysis	Cohort of 10,000 persons with variable prevalence	Health and economic outcomes of Trep-first vs. Nontrep- first	Overtreatment rates and number of confirmatory tests required	2-step algorithms detected and treated same numbers but Non-trep first was	Modeling data

					more cost efficient in low and high prevalence settings	
Owusu-Edusei K , et al. <i>STD</i> 2011; 38:1-7	Cohort decision analysis	Cohort of 200,000 persons with variable prevalence	Cost of Trep-first vs. Nontrep- first	Cost	Trep first: \$1671 Non-trep first: \$1621 per case treated. Trep first resulted in more unnecessary treatment	Modeling data
Mishra S , et al. <i>STD</i> 2011; 38:190-196	Retrospective study	All syphilis tests in Toronto 1998-2008	Describe changes in testing after introduction of EIA Trep-first test	Positive tests	3 million tests: confirmed + increased by 10.3 per 100,000; 0.6% of EIA+ RPR- converted to RPR+ within 2 months; more persons with latent syphilis detected; increased testing in short-term	No clinical data
CDC. MMWR 2011; 60: number 5	Retrospective	5 laboratories in the US	Describe serodiscordancy in high and low prevalence areas.	Serodiscordant test results	140176 specimens: among persons with reactive EIA/CIA: 57% had negative RPR and among those 12-60% were false positives	No clinical data No head to head comparison

Maple PAC , et al. <i>Clin Vaccine Immunol</i> 2010; 17:1718-22	Prospective	UK Public Health Lab	Further characterize EIA+/TPPA-/VDRL- sera using Mercia IgM FTA-ABS, a different EIA, and INNO-LIA Immunoblotting	Prevalence of serodiscordance in 226 samples	18 of 26 EIA+/EIA+/TPPA-/VDRL- sera: most were old or treated cases of HIV+ persons.	
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What are the risks of sexual transmission, vertical transmission, and disease progression in persons with persistently negative nontreponemal tests and positive treponemal tests who do not have a history treated syphilis and how should they (and their sex partners) be managed? Should this recommendation be different if the reactive treponemal test is a CIA/EIA?

Citation	Study Design	Study Population	Exposure/Intervention	Outcome	Findings	Design Analysis Quality/Biases
Vertical Transmission						
Peterman TA , et al. <i>STD</i> 2013; 40:311-315	Retrospective	Pregnant women in the US	Nontreponemal tests persistently negative	Congenital syphilis between 1991-2009	Of 23,863 cases of congenital syphilis, 1? probable case was noted	Limited data from PH records

Miscellaneous Papers of Interest

Citation	Study Design	Study Population	Exposure/Intervention	Outcome	Findings	Design Analysis Quality/Biases
Prozone Phenomenon						
Post JJ , et al. <i>Sexual Health</i> 2012; 9:488-490	Prospective evaluation	Consecutive sera from an Australian laboratory that caters to sexual health clinics	Detection of the prozone phenomenon	Prevalence and risk factors	2 out of 3222 samples; 2 out of 397 reactive samples;	Limited data

J-H Reaction						
Miller WM, et al. <i>Int J STD AIDS</i> 2010; 21:806-809	Prospective	STD clinic patients in Rio de Janeiro, Brazil	Observation for J-H reaction	J-H reaction	10 of 115 persons had J-H. All occurred in persons with secondary or latent syphilis within 3-6h after Rx; all patients treated with 2-3 doses of BPG.	Non-standard dosage of BPG; duration of latent syphilis not well defined
CNS Gummas						
Fargen KM, et al. <i>Neurosurgery</i> 2009; 64:568-76	Case report and literature review	Persons with CNS gummas	Observation	Clinical presentation and responses	156 cases containing 185 lesions; CSF exam positive in 64%; lesions located in convexities most often; IV penicillin response was excellent; surgery only for non-responders; 83% had reactive serologies; steroids if adjacent edema noted	
Proctocolitis						
Arnold CA et al. <i>Am J Surg Pathol</i> 2013; 37:38-46	Case series	7 patients with syphilitic proctocolitis	Clinical presentation	Clinical outcomes	7/7 HIV+; LGV and syphilitic proctocolitis indistinguishable pathologically; similar to IBD;	Selection bias
Otosyphilis						

Bradshaw D, et al. <i>STI</i> 2012; 88:573	Case series	7 cases in GUM clinic between 2007 and 2011	Clinical presentation	Clinical outcomes	6/7 male; 6/7 HIV+; deafness bilateral in 3/7. 67% had rash and 43% had ocular involvement; 6/7 had CSF exam: 4 of 6 had CSF abnormalities (1 had positive CSF VDRL); 5 treated with steroids. Hearing improved in 3 and stabilized in 4. Significant delay in treatment.	
Ocular Syphilis						
Karunaratne I, et al. <i>Int J STD AIDS</i> 2012; 23:291-6	Case series	GUM clinics in Bristol, UK	7 patients with ocular syphilis	Clinical outcomes	6 HIV-; uveitis, optic neuritis, episcleritis, sclerokeratitis; retinal vasculitis	Selection bias; no consistent management approach
Eandi CM, et al. <i>Retina</i> 2012; 32:1915-41	Case series and literature review	Multicenter study of persons with acute syphilitic posterior placoid chorioretinitis	16 patients in the series and 44 cases from literature	Clinical outcomes	Bilateral in 56.3%; 56% HIV+; 43.8% had secondary syphilis; 25% had CSF changes consistent with neurosyphilis; 15/16 had positive VDRL or RPR; all had positive trep tests; vision improved in	Selection bias; non-uniform approach

					20/25 affected eyes after therapy.	
Tucker JD, et al. <i>STI</i> 2011; 87:4-8	Systematic review	HIV+ with ocular syphilis	101 HIV+ patients from case series/reports	Outcomes	Most with secondary syphilis; 63% bilateral; posterior uveitis more common if CD4<200; ; 3/101 had nonreactive non-trep tests; 97% improved after antibiotics; uveitis most common followed by optic neuritis; only 64 had CSF exam; 57% had positive CSF VDRL and 74% elevated CSF WBC	Heterogeneity
Balaskas K, et al. <i>Br J Ophthalmol</i> 2011;95:1568-1572	Case series (retrospective)	Patients with ocular syphilis in Switzerland	26 patients	Association between visual acuity and various clinical factors	Worse VA associated with macular edema optic neuropathy, and vasculitis on angiography; improvement in VA was associated with vasculitis, neurosyphilis, and anterior uveitis. No difference between PCN and	Selection bias; small sample size

					ceftriaxone; only 19 had CSF exam: 1 had positive CSF VDRL; 48% given steroids; 4/23 relapsed	
Biotti D , et al. <i>STD</i> 2010; 37:41-43	Case series nested in prospective cohort	509 French patients with HIV followed from 05-08	Observation	Outcomes	Among 509 patients, syphilis diagnosed in 3.9% (N=20) and 1/5 th (N=4) had ocular involvement; mainly uveitis; all had early syphilis; ¾ had CSF abnormalities	Selection bias; small numbers
Puech C , et al. <i>Graefes Arch Clin Exp Ophthalmol</i> ; 2010; 248:1623-1629	Case series (retrospective)	Tertiary referral center in Grenoble, France	Observation over a 2.5 year period of ocular syphilis cases	Outcomes	8 cases; 5 HIV+; neurosyphilis diagnosed in 3 of 5 tested; 6/8 were unilateral; most treated with 3 weeks of ceftriaxone; 1 pt given steroids; sequelae: optic nerve atrophy (N=1) and retinal pigment epithelium abnormalities (N=3)	
Fu EX ; et al. <i>Retina</i> 2010; 30:1135-43	Retrospective case series	Multicenter study in US	Describe superficial retinal precipitates	Outcomes of superficial retinal precipitates	8 patients, 9 eyes; 6 HIV+; all had panuveitis and ground-glass	Small numbers; selection bias

					retinitis; 5 had retinal vasculitis; 3 had retinal detachment'; 7 experienced visual recovery after abx; few sequelae	
Muldoon EG , et al. <i>STI</i> 2010; 86:512-513	Case series	Dublin Ireland	Describe the impact of delayed diagnosis of secondary syphilis	Outcomes	5 cases; 4 MSM; 1 HIV+; 3/5 had CSF exam; all had pleocytosis; delayed diagnosis from 4 weeks to 6 months in 4 patients	Small numbers; selection bias
Hughes EH , et al. <i>Clin and Exp Ophthalmol</i> 2010; 38:851-6	Case series	13 patients with optic syphilis in Sydney, Australia	Clinical presentation	Outcomes	13 cases; 12 male; 6 HIV+; 54% had peripheral retinitis with panuveitis; 5/9 had positive CSF VDRL; other manifestations: multifocal choroiditis, scleritis, papillitis; all responded well to IV PCN.	Small numbers; selection bias
Fonollosa A , et al. <i>Ocular Immunology and Inflammation</i> 2009; 17:207-212	Case series	Spanish patients with syphilitic uveitis	Clinical presentation	Outcomes	12 cases; 9 HIV+; all presented with iritis and vitritis; 9/12 had positive CSF VDRL; VA improved in 11 after therapy with	Small numbers; selection bias

					IV PCN;	
Wickremasinghe S, et al. <i>Ophthalmology</i> 2009; 116:1195-1200	Retrospective case series	Australian patients with syphilitic retinitis	Clinical presentation	Outcomes	5 cases; 2 HIV+; all had anterior uveitis and vitritis; all had distinctive inner retinal and pre-retinal white dots	Small numbers; selection bias
Maves RC, et al. <i>CID</i> 2008; 46: e142-5	Retrospective case series	Older patients with ocular syphilis	Clinical presentation	Outcomes	4 cases; age >50; all had secondary syphilis; 2 had prozone phenomenon; 3 had negative CSF VDRL; 3 had CSF pleocytosis all did well after IV PCN; 3 had a delayed diagnosis;	Small numbers; selection bias