Clinical Infectious Diseases

SUPPLEMENT ARTICLE

Management of Adult Syphilis: Key Questions to Inform the 2021 Centers for Disease Control and Prevention Sexually Transmitted Infections Treatment Guidelines

Susan Tuddenham[1] and Khalil G. Ghanem[1]

[1]Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

A panel of experts generated 5 "key questions" in the management of adult syphilis. A systematic literature review was conducted and tables of evidence were constructed to answer these questions. Available data suggest no clinical benefit to >1 dose of benzathine penicillin G for early syphilis in human immunodeficiency virus (HIV)–infected patients. While penicillin remains the drug of choice to treat syphilis, doxycycline to treat early and late latent syphilis is an acceptable alternate option if penicillin cannot be used. There are very limited data regarding the impact of additional antibiotic doses on serologic responses in serofast patients and no data on the impact of additional antibiotic courses on long-term clinical outcomes. In patients with isolated ocular or otic signs and symptoms, reactive syphilis serologic results, and confirmed ocular/otic abnormalities at examination, a diagnostic cerebrospinal fluid (CSF) examination is not necessary, because up to 40% and 90% of patients, respectively, would have no CSF abnormalities. Based on the results of 2 studies, repeated CSF examinations are not necessary for HIV-uninfected patients or HIV-infected patients on antiretroviral therapy who exhibit appropriate serologic and clinical responses after treatment for neurosyphilis. Finally, several important gaps were identified and should be a priority for future research.

Keywords. syphilis; neurosyphilis; treatment guidelines; CDC; Centers for Disease Control and Prevention.

The total number of cases of infectious syphilis reported to the Centers for Disease Control and Prevention (CDC) continues to increase [1]. Two epidemics are ongoing in the United States: a long-standing epidemic among men who have sex with men (MSM) [1] and a more recent epidemic among heterosexuals linked to drug use [2]. As a result of increasing rates in women, congenital syphilis is on the rise [1, 3]. In this context, we systematically assessed the literature to review the evidence and to answer some important unanswered key questions in syphilis management.

METHODS

We surveyed experts in the field of syphilis to help define relevant "key questions" in syphilis management. These included questions related to new data on syphilis treatment strategies, management of patients without demonstrated adequate serologic decline, diagnosis of neurosyphilis, prevention of syphilis, and use of the "reverse sequence algorithm" for syphilis testing. A literature review was then conducted based on these key questions. We searched Pubmed, SCOPUS, ISI, SciFinder, Excerpta Medica, and the Cochrane Central Register of Controlled Trials databases from 29 February 2013 (the date of the last systematic review) to 4 December 2018. We used the following search terms: "*Treponema pallidum*" or "treponemal infections/therapy." Reference lists of the retrieved articles were also manually searched for other potentially relevant articles.

We also reviewed conference abstracts from 2018 (CDC Sexually Transmitted Diseases Prevention Conference, IDWeek, and Conference on Retroviruses and Opportunistic Infections). We assessed English-language articles only and included only articles with primary data. All abstracts were read, and they were if found to be relevant to any of the key questions identified, the full article was reviewed. We assessed relevant guidelines from other countries or regions (United Kingdom, Europe, Canada, and Australia). Based on data reviewed, we constructed "tables of evidence" for each key question. The data collected were presented to a group of syphilis experts at the Centers for Disease Control and Prevention Sexually Transmitted Infections Treatment Guidelines Meeting held in Atlanta in 11–13 June 2019. Preliminary answers to the key questions were drafted based on the tables of evidence, and expert opinion was considered where there was no supporting evidence. A summary of the discussion is also included.

RESULTS AND DISCUSSION

Five key questions were identified and agreed on by a panel of 8 external experts. The literature search yielded 3193 references.

Correspondence: Susan Tuddenham, Johns Hopkins University Bayview Medical Center, Infectious Diseases Division, 5200 Eastern Ave, MFL Center Tower, Ste 381, Baltimore, MD 21224 (studden1@jhmi.edu).

Clinical Infectious Diseases® 2022;74(S2):S127–33

https://doi.org/10.1093/cid/ciac060

Of those, 95 were relevant to the key questions and were included in the tables of evidence. Below is a list of the 5 key questions, a summary of the data from the tables of evidence for each question, an overview of the discussion surrounding each question, and the conclusions reached by the committee.

Key Question 1: Are There Relevant New Data on Syphilis Treatment or Management, Particularly When Penicillin Therapy Is Not Feasible?

Data on 1 versus 3 doses of intramuscular benzathine penicillin G (BPG) for treatment of early syphilis in human immunodeficiency virus (HIV)–infected patients remain limited, though a phase 4 comparative trial (NCT03637660) of 1 versus 3 doses of BPG for treatment of early syphilis in subjects with or without HIV infection was initiated in September 2018; results have yet to be reported [4–9]. All studies relied on serologic outcomes; none provided data on long-term clinical outcomes. One large retrospective cohort [6] suggested no difference in serologic responses between 1 and >1 dose of BPG. One large prospective observational study [9] included in the previous (2015) guidelines as an abstract has now been published and showed no difference between 1 and 3 doses of BPG in the per-protocol analysis, although a subanalysis favored 3 doses. The only randomized trial [4] showed no difference in serologic outcomes but had a small sample size. None of the other (retrospective) studies showed differences in serologic outcomes in HIV-infected patients with early syphilis given 1 versus 3 doses of BPG [5, 7, 8].

Several retrospective studies [10–15] were published which, while limited, provide additional reassurance about the efficacy of doxycycline or other tetracyclines for the treatment of early and late latent syphilis, suggesting that they are acceptable alternate agents when penicillin therapy is not feasible. Available data on azithromycin suggest comparable efficacy [16, 17], and perhaps lower rates of Jarisch-Herxheimer reaction [18] as compared to BPG for treatment of early syphilis in areas with low rates of macrolide resistance. However, previous data suggest that mutations associated with macrolide resistance are highly prevalent in many settings, including in the United States. Given concerns regarding macrolide resistance, experts agreed that despite these data, azithromycin should not be a recommended treatment for syphilis in the United States.

One randomized trial suggests comparable efficacy for treatment of early syphilis with 1 g/d of intravenous ceftriaxone for 10 days compared with 2 intramuscular doses of 2.4- million units (MU) BPG [19]. These data may provide added reassurance that 1-g intravenous/intramuscular ceftriaxone for 10 days is a reasonable treatment for early syphilis. Data from a retrospective observational study [20] suggests that oral amoxicillin 3 g plus oral probenecid may be a viable option for treatment of syphilis in HIV-infected patients, but there were many limitations to the study (retrospective nature, small sample size, heterogeneity in regimens given, and lack of a comparator group), and as such it was felt that there is insufficient data to recommend this regimen.

Conclusions

Limited data suggest no benefit, in terms of serologic outcomes, to >1 dose of BPG for early syphilis in HIV-infected patients. While penicillin remains the drug of choice to treat syphilis, doxycycline is an acceptable alternate option for treating early and late latent syphilis if penicillin cannot be used. Azithromycin as a single 2-g oral dose has been effective for treating early syphilis in some settings. However, *Treponema pallidum* chromosomal mutations associated with azithromycin (and other macrolide) resistance and treatment failures have been documented in multiple geographic areas in the United States, and azithromycin should therefore not be a recommended treatment for syphilis in the United States. Ceftriaxone (intravenous or intramuscular; 1 g/d for 10 days) is a reasonable alternative treatment for early syphilis. There is insufficient evidence to recommend oral amoxicillin plus probenecid for the treatment of syphilis. (See Supplementary Table 1 for additional details on reviewed studies.)

Key Question 2: Are There Relevant New Data on Managing Patients Without Demonstrated Adequate Serologic Decline or Seroreversion After Stage-Appropriate Therapy?

The first point of discussion focused on terminology—specifically the definition of *serofast* and how this term should be used in the guidelines. In the literature, the term has been used to refer to failure of nontreponemal antibody titers to serorevert (ie, become nonreactive), failure of nontreponemal antibody titers to demonstrate a ≥4-fold decline 6–12 months after therapy for early syphilis and 12–24 months after therapy for late syphilis (sometimes referred to as *serologic nonresponse*), or both. While attendees agreed that the only clinically relevant definition of the serofast state in modern times was serologic nonresponse, there was concern that the heterogeneity of definitions in the literature would confuse readers. It was agreed that the term *serofast* should be clearly defined and then used consistently throughout the guidelines. For the purposes of this section, we will define the term as failure to achieve a 4-fold decline in nontreponemal antibody titers after stage-appropriate therapy.

Multiple studies suggest that a substantial proportion of patients with syphilis (whether HIV infected or not) will remain serofast and that an even larger proportion will not serorevert. One study [25] showed that a strategy of pairing serum samples for rapid plasma regain (RPR) testing (ie, simultaneous testing of acute and convalescent samples) did not result in fewer serofast diagnoses. Several studies assessed factors that predict the serofast state [26–35]. As in previous studies, earlier syphilis stage and higher baseline nontreponemal titers are associated with increased likelihood of serologic cure and seroreversion.

In addition, several studies showed that older age and female sex were associated with a higher probability of remaining serofast [29, 30, 32, 33].

Two studies sought to evaluate whether retreatment with additional doses of BPG would affect titers in serofast patients. One study [36] found no difference but was limited by its retrospective nature. A second study had no comparison group [37]. Neither study evaluated whether additional treatment resulted in improved long-term clinical outcomes. There are limited modern data to assess whether serofast patients (in whom reinfection has been ruled out) experience worse long-term clinical outcomes than those who are serologically cured. One study [38] did not find a difference in the proportion of asymptomatic patients with cerebrospinal fluid (CSF) findings consistent with neurosyphilis between patients who were serofast and those who had a 4-fold decline in nontreponemal test titers. A second study in HIV-infected patients [39] found that 41.7% (n = 5) of those who were serofast at 12 months (n = 12) had asymptomatic neurosyphilis. However, the small numbers and lack of a comparator group make it difficult to gauge the significance of these data.

Conclusions

When the term *serofast* is used in the guidelines, it should be clearly defined and used consistently throughout the document. Older age should be added as a predictor of the serofast state. There are very limited data regarding the impact of additional antibiotic doses on serologic responses in serofast patients, and no data on the impact of additional antibiotic courses on long-term clinical outcomes (see Supplementary Table 2).

Key Question 3: What Are the Optimal Diagnostic and Management Approaches for Neurosyphilis, Ocular Syphilis, and Otic Syphilis?

Several studies assessed predictors of asymptomatic and symptomatic neurosyphilis in HIV-infected and HIV-uninfected persons. Consistently, higher serum nontreponemal titers were associated with increased risk of neurosyphilis. In a study conducted in HIV-uninfected persons [38], there was no difference in the prevalence of neurosyphilis between those who had a ≥4-fold decline in nontreponemal titers after therapy and those who did not. This finding calls into question the current recommendation to consider performing a CSF examination in asymptomatic persons without a 4-fold decline in nontreponemal titers.

Among a prospective cohort of 64 HIV-infected persons with early syphilis and RPR titers ≥1:32 or CD4 cell counts ≤350 cells/μL—in all of whom serologic cure had been achieved a median of 8 months after therapy—only 1 was found to have CSF abnormalities consistent with asymptomatic neurosyphilis [42]. These data lend further support to the current recommendation to treat all patients with early syphilis, using similar antibiotic regimens irrespective of their HIV status.

A study conducted among HIV-uninfected persons with syphilis confirmed prior findings (among both HIV-uninfected and virologically suppressed HIV-infected persons [43]) that the appropriate decline of serum nontreponemal titers in individuals with neurosyphilis predicts CSF normalization [44]. These data suggest that the recommendation to perform follow-up CSF examinations in HIV-uninfected and virologically suppressed HIV-infected persons whose symptoms and nontreponemal serologic titers improve after neurosyphilis treatment should be reconsidered.

Several studies assessed diagnostics for neurosyphilis. Most assessed different treponemal tests performed on CSF. While these tests have high sensitivity, their specificity tends to be lower than the traditionally used CSF VDRL. In a retrospective study that used both training and validation data sets and stringent standards for the diagnosis of neurosyphilis, the CSF *T. pallidum* particle agglutination assay (TPPA) was found to be as sensitive as the CSF fluorescent treponemal antibody test absorption test. More importantly, using a cutoff titer of ≥1:640, the specificity of the CSF TPPA increased significantly and was found to be similar to that of the CSF VDRL [45]. These data suggest that the use of a treponemal-specific antibody assay with titer cutoffs could result in a test that is both sensitive and specific for diagnosing neurosyphilis.

Finally, there were many studies describing case series of ocular syphilis. Only those that reported results for ≥20 participants were included in the review [46–67]. The majority were retrospective case series. Only 1 study was prospective [51]. Most, as expected, used clinical criteria and serologic evidence of syphilis as the case definition for ocular syphilis. The single prospective study was conducted in Britain and found an annual incidence of ocular syphilis of 0.3 per million among UK adults [51]. In general, most studies found that posterior and panuveitis were the most common clinical manifestations; HIV infection may increase the risk for ocular complications, although this finding was inconsistent among the studies.

The prevalence of CSF abnormalities in persons with ocular syphilis ranged from 10% to approximately 60%. Up to 50% of persons with ocular syphilis had a reactive CSF VDRL result. Most studies suggested that response to therapy was high in both HIV-infected and HIV-uninfected persons and that worse visual outcomes were more likely with longer duration of symptoms before treatment and lower baseline visual acuity at the time of treatment. Most patients were treated with intravenous penicillin. No studies addressed what the optimal treatment of ocular syphilis should be and whether steroids improved outcomes, and no studies related to otic syphilis were published during time frame of our systematic review.

Conclusions

There was agreement that the signs and symptoms of neurosyphilis, ocular syphilis, and otic syphilis would be described

separately in the text of the guidelines to ensure that clinicians understood that they represent distinct clinical entities with some overlap. Furthermore, in patients with isolated ocular signs and symptoms, reactive syphilis serologic results, and confirmed ocular abnormalities on examination, attendees agreed that a diagnostic CSF examination was not necessary, as nearly 40% of patients would have no CSF abnormalities. It was believed that CSF analysis may be considered in evaluating individuals with ocular symptoms and reactive syphilis serologic results who do not have ocular findings on examination to rule out occult neurologic involvement. Similarly, a diagnostic CSF examination was not though to be necessary in persons with serologic evidence of syphilis and isolated otic signs and symptoms, because up to 90% will have a normal CSF formula. The urgency of evaluating patients suspected of having neurologic, ocular, and/or otic syphilis would also be highlighted in the updated guidelines to help mitigate serious sequelae.

Despite promising results, it was believed that there was insufficient evidence to recommend specific CSF treponemal antibody cutoff titers at this time as a way to enhance the performance characteristics of neurosyphilis diagnostics (see Research Priorities below). Finally, data from 2 studies suggest that in immunocompetent persons and those with HIV infection receiving effective antiretroviral therapy, normalization of the serum RPR titer predicts normalization of CSF parameters after neurosyphilis treatment. Therefore, it was believed that repeated CSF examinations are not necessary for HIV-uninfected patients or HIV-infected patients receiving antiretroviral therapy who exhibit appropriate serologic and clinical responses after treatment for neurosyphilis (see Supplementary Table 3).

Key Question 4: Are There New Interventions or New Data on Known Interventions for Preventing Syphilis?

Data on doxycycline preexposure prophylaxis (PrEP) or postexposure prophylaxis (PEP) are limited to 1 small pilot feasibility study [85] and 1 pilot randomized trial [86], respectively. While the PEP data in particular suggest a decrease in syphilis (and chlamydia) incidence in MSM taking doxycycline, long-term data regarding the impact on antimicrobial resistance and the microbiome are lacking. Doxycycline PrEP and PEP will be covered in the clinical prevention guidance section, and the syphilis management section will reference this.

One large longitudinal study [87] suggested that circumcision is associated with decreased incident syphilis in men and their female partners, and a smaller retrospective cohort study [88] showed no difference. As such, data are limited, and no changes to the guidelines were recommended.

Findings of retrospective studies [89, 90] suggest that screening of MSM populations at increased risk for syphilis is still suboptimal. A large retrospective study in Australia [91] suggests that increased screening of MSM may be reducing infectious (primary and secondary syphilis), but these data are ecological, and as such, limited. Finally, 4 modeling studies [91–95] suggest that more frequent screening of MSM (every 3–6 months) was more cost-effective than increased breadth of screening coverage in controlling incident syphilis in this population.

A case series suggests that methamphetamine and Internet use in MSM [96] are associated with increased numbers of reported sex partners, and consequently, increased risk of infectious syphilis. Another case series [97] described numerous repeated syphilis infections in a cohort of predominantly African American MSM in Baltimore.

One case series [98] demonstrated that syphilitic anogenital lesions may be multiple, and painful, which stands in contradistinction to the single painless lesion that clinicians have been taught to anticipate in early syphilis. Another study highlights cases where oral swab samples were positive for *T. pallidum* via polymerase chain reaction in patients with syphilis, even in the absence of symptoms or oral lesions [99]. While it is unclear whether these patients were infectious, it does highlight the importance of serologic screening of at-risk patients, regardless of symptoms.

Conclusions

Most of the articles covered in key question 4 related to topics covered in other sections. Screening rates remain suboptimal. An important observation was the atypical presentation of primary syphilitic chancres [98] (see Supplementary Table 4).

Key Question 5: Are There Relevant New Data on Using the "Reverse Sequence Algorithm" Versus the "Traditional Algorithm" When Screening/Testing for Syphilis?

The reverse sequence algorithm will be covered extensively in the syphilis laboratory guidelines document that will be released imminently. The syphilis treatment guidelines will harmonize with the laboratory guidelines. Extensive discussion was largely deferred. However, there was a discussion regarding reports that some laboratories (particularly those using automated nontreponemal assays) were not performing complete end titers on nontreponemal antibodies (eg, reporting RPR titers as >1:32 without specifying the end titer). This practice makes it impossible to manage patients effectively. It was discussed that there should be specific language in the guidelines to state that end point nontreponemal antibody titers should always be reported to ensure appropriate management of patients.

RESEARCH PRIORITIES

There are still many fundamental unanswered questions in the management of syphilis. What is the impact of repeated infections on the clinical manifestations of syphilis? What are

the optimal interventions that would impact rising syphilis rates? What is the impact of doxycycline PrEP and/or PEP on the human microbiome and resistome? Are there alternative antimicrobials (especially oral options) to BPG and doxycycline for the treatment of early and latent syphilis? What is the role of high-dose doxycycline for the treatment of neurosyphilis? Does additional antimicrobial therapy affect serologic and clinical outcomes in serofast patients? What is the optimal treatment of patients with otic and ocular syphilis? Will CSF treponemal antibody titers provide enhanced specificity for the diagnosis of neurosyphilis? Finally, a critical gap is the lack of biomarkers to adequately measure syphilis disease activity.

Notes

Acknowledgments. We thank the following for their input and advice: Sheila Lukehart PhD, Christina Marra MD, Ned Hook MD, Arlene Sena MD, MPH, Brad Stoner MD, PhD, and Ina Park MD, MS.

Financial support. S.T. is supported by National Institutes of Health (NIH) grant K23AI125715 (PI: Tuddenham). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Supplement sponsorship. This supplement is sponsored by The Centers for Disease Control and Prevention.

Potential conflicts of interest. S. T. has received royalties from UpToDate, consulted for Luca Biologics and Roche Molecular Diagnostics, and received speaker honoraria from Medscape and Roche. S. T. also reports holding a board member position with the American Sexually Transmitted Diseases Association. K. G. G. reports receiving royalties from UpToDate and is president of the American Sexually Transmitted Diseases Association. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Centers for Disease Control. Sexually transmitted diseases surveillance 2018. Available at: https://www.cdc.gov/std/stats18/STDSurveillance2018-full-report.pdf. Accessed 6 February 2020.
2. Kidd SE, Grey JA, Torrone EA, Weinstock HS. Increased methamphetamine, injection drug, and heroin use among women and heterosexual men with primary and secondary syphilis—United States, 2013-2017. MMWR Morb Mortal Wkly Rep **2019**; 68:144–8.
3. Bowen V, Su J, Torrone E, Kidd S, Weinstock H. Increase in incidence of congenital syphilis—United States, 2012-2014. MMWR Morb Mortal Wkly Rep **2015**; 64:1241–5.
4. Andrade R, Rodriguez-Barradas MC, Yasukawa K, Villarreal E, Ross M, Serpa JA. Single dose versus 3 doses of intramuscular benzathine penicillin for early syphilis in HIV: a randomized clinical trial. Clin Infect Dis **2017**; 64:759–64.
5. Costa-Silva M, Azevedo C, Azevedo F, Lisboa C. Early syphilis treatment in HIV-infected patients: single dose vs. three doses of benzathine penicillin G. J Eur Acad Dermatol Venereol **2016**; 30:1805–9.
6. Ganesan A, Mesner O, Okulicz JF, et al. A single dose of benzathine penicillin G is as effective as multiple doses of benzathine penicillin G for the treatment of HIV-infected persons with early syphilis. Clin Infect Dis **2015**; 60:653–60.
7. Saje A, Tomazic J. Syphilis and HIV co-infection: excellent response to multiple doses of benzathine penicillin. Acta Dermatovenerol Alp Pannon Adriat **2014**; 23:1–3.
8. Tittes J, Aichelburg MC, Antoniewicz L, Geusau A. Enhanced therapy for primary and secondary syphilis: a longitudinal retrospective analysis of cure rates and associated factors. Int J STD AIDS **2013**; 24:703–11.
9. Yang CJ, Lee NY, Chen TC, et al. One dose versus three weekly doses of benzathine penicillin G for patients co-infected with HIV and early syphilis: a multicenter, prospective observational study. PLoS One **2014**; 9:e109667.
10. Dai T, Qu R, Liu J, Zhou P, Wang Q. Efficacy of doxycycline in the treatment of syphilis. Antimicrob Agents Chemother **2016**; 61:e01092-16.
11. Salado-Rasmussen K, Hoffmann S, Cowan S, et al. Serological response to treatment of syphilis with doxycycline compared with penicillin in HIV-infected individuals. Acta Derm Venereol **2016**; 96:807–11.
12. Shao LL, Guo R, Shi WJ, et al. Could lengthening minocycline therapy better treat early syphilis? Medicine **2016**; 95:e5773.
13. Tsai JC, Lin YH, Lu PL, et al. Comparison of serological response to doxycycline versus benzathine penicillin G in the treatment of early syphilis in HIV-infected patients: a multi-center observational study. PLoS One **2014**; 9:e109813.
14. Wu BR, Liu WC, Wu PY, et al. Surveillance study of *Treponema pallidum* harbouring tetracycline resistance mutations in patients with syphilis. Int J Antimicrob Agents **2014**; 44:370–2.
15. Xiao H, Liu D, Li Z, et al. Comparison of doxycycline and benzathine penicillin G for the treatment of early syphilis. Acta Dermatovenerol Croat **2017**; 25:107–11.
16. Li HY, Qu HQ, Wang XM, Zhang YJ, Zhang FR. A meta-analysis of the efficacy of azithromycin and benzathine penicillin in early syphilis. Trop J Pharm Res **2018**; 17:345–50.
17. Yang CJ, Tang HJ, Chang SY, et al. Comparison of serological responses to single-dose azithromycin (2 g) versus benzathine penicillin G in the treatment of early syphilis in HIV-infected patients in an area of low prevalence of macrolide-resistant *Treponema pallidum* infection. J Antimicrob Chemother **2016**; 71:775–82.
18. Tsai MS, Yang CJ, Lee NY, et al. Jarisch-Herxheimer reaction among HIV-positive patients with early syphilis: azithromycin versus benzathine penicillin G therapy. J Int Aids Soc **2014**; 17:18993.
19. Cao Y, Su X, Wang Q, et al. A multicenter study evaluating ceftriaxone and benzathine penicillin G as treatment agents for early syphilis in Jiangsu, China. Clin Infect Dis **2017**; 65:1683–8.
20. Tanizaki R, Nishijima T, Aoki T, et al. High-dose oral amoxicillin plus probenecid is highly effective for syphilis in patients with HIV infection. Clin Infect Dis **2015**; 61:177–83.
21. Liang Z, Chen YP, Yang CS, et al. Meta-analysis of ceftriaxone compared with penicillin for the treatment of syphilis. Int J Antimicrob Agents **2016**; 47:6–11.
22. Liu Y, Liu C, Huang C, Hu L, Wang H. Therapeutic effect of ceftriaxone and penicillin g procaine in patients with early-stage syphilis. Int J Clin Exp Med **2017**; 10:16699–702.
23. Liu HY, Han Y, Chen XS, et al. Comparison of efficacy of treatments for early syphilis: A systematic review and network meta-analysis of randomized controlled trials and observational studies. PLoS One **2017**; 12:e0180001.
24. Drago F, Ciccarese G, Broccolo F, et al. A new enhanced antibiotic treatment for early and late syphilis. J Glob Antimicrob Resist **2016**; 5:64–6.
25. Kenyon CR, Osbak KK, Van Esbroek M, Lynen L, Crucitti T. What is the role of paired rapid plasma reagin testing (simultaneous testing of acute and convalescent samples) in the diagnosis of repeat syphilis and the follow-up of syphilis? Sex Transm Dis **2018**; 45:35–8.
26. Jinno S, Anker B, Kaur P, Bristow CC, Klausner JD. Predictors of serological failure after treatment in HIV-infected patients with early syphilis in the emerging era of universal antiretroviral therapy use. BMC Infect Dis **2013**; 13:605.
27. Li J, Wang LN, Zheng HY. Predictors of serological cure and serofast state after treatment in HIV-negative patients with early syphilis in China. Sex Transm Infect **2013**; 89:69.
28. Luo Z, Zhu L, Ding Y, et al. Factors associated with syphilis treatment failure and reinfection: a longitudinal cohort study in Shenzhen, China. BMC Infect Dis **2017**; 17:620.
29. Qin J, Yang T, Wang H, Feng T, Liu X. Potential predictors for serofast state after treatment among HIV-negative persons with syphilis in China: a systematic review and meta-analysis. Iran J Public Health **2015**; 44:155–69.
30. Sena AC, Wolff M, Behets F, et al. Rate of decline in nontreponemal antibody titers and seroreversion after treatment of early syphilis. Sex Transm Dis **2017**; 44:6–10.
31. Sena AC, Zhang XH, Li T, et al. A systematic review of syphilis serological treatment outcomes in HIV-infected and HIV-uninfected persons: rethinking the significance of serological non-responsiveness and the serofast state after therapy. BMC Infect Dis **2015**; 15:479.
32. Tong ML, Lin LR, Liu GL, et al. Factors associated with serological cure and the serofast state of HIV-negative patients with primary, secondary, latent, and tertiary syphilis. PLoS One **2013**; 8:e70102.
33. Zhang RL, Wang QQ, Zhang JP, Yang LJ. Molecular subtyping of *Treponema pallidum* and associated factors of serofast status in early syphilis patients: identified novel genotype and cytokine marker. PLoS One **2017**; 12:e0175477.
34. King H, Tilghman W, Prakash K, et al. Effect of HIV status on early syphilis treatment response in the era of combination antiretroviral therapy. Presented at: IDWeek 3–7 October 2018; **2018**; San Francisco, CA.
35. Ren MS, Tan D, Walmsley S. Response to syphilis treatment: CDC guidelines in HIV-infected adults on cART. Presented at: Conference on Retroviruses and Opportunistic Infection; 4–7 March **2018**; Boston, MA.

36. Ren RX, Wang LN, Zheng HY, Li J. No improvement in serological response among serofast latent patients retreated with benzathine penicillin. Int J STD AIDS **2016**; 27:58–62.
37. Wang ZS, Liu XK, Li J. Serological response to therapy following retreatment of serofast early syphilis patients with benzathine penicillin. J Antimicrob Chemother **2018**; 73:1348–51.
38. Cai SN, Long J, Chen C, Wan G, Lun WH. Incidence of asymptomatic neurosyphilis in serofast Chinese syphilis patients. Sci Rep **2017**; 7:15456. doi:10.1038/s41598-017-15641-w.
39. Pastuszczak M, Sitko M, Bociaga-Jasik M, Kucharz J, Wojas-Pelc A. Lack of antiretroviral therapy is associated with higher risk of neurosyphilis among HIV-infected patients who remain serofast after therapy for early syphilis. Medicine **2018**; 97:e13171.
40. King H, Tilghman W, Prakash K, et al. Effect of HIV status on early syphilis treatment response in the era of combination antiretroviral therapy. Presented at: ID week; 3–7 October **2018**; San Francisco, CA.
41. Ren M, Szadkowski L, Tan D, Walmsley S. Response to syphilis treatment: CDC guidelines in HIV-infected adults on cART. Presented at: Conference on Retroviruses and Opportunistic Infections; 4–7 March **2018**; Boston, MA.
42. Tomkins A, Ahmad S, Cousins DE, Thng CM, Vilar FJ, Higgins SP. Screening for asymptomatic neurosyphilis in HIV patients after treatment of early syphilis: an observational study. Sex Transm Infect **2018**; 94:337–9.
43. Marra CM, Maxwell CL, Tantalo LC, Sahi SK, Lukehart SA. Normalization of serum rapid plasma reagin titer predicts normalization of cerebrospinal fluid and clinical abnormalities after treatment of neurosyphilis. Clin Infect Dis **2008**; 47:893–9.
44. Xiao Y, Tong ML, Lin LR, et al. Serological response predicts normalization of cerebrospinal fluid abnormalities at six months after treatment in HIV-negative neurosyphilis patients. Sci Rep **2017**; 7:9911. doi:10.1038/s41598-017-10387-x
45. Marra CM, Maxwell CL, Dunaway SB, Sahi SK, Tantalo LC. Cerebrospinal fluid *Treponema pallidum* particle agglutination assay for neurosyphilis diagnosis. J Clin Microbiol **2017**; 55:1865–70.
46. Bollemeijer JG, Wieringa WG, Missotten TO, et al. Clinical manifestations and outcome of syphilitic uveitis. Invest Ophthalmol Vis Sci **2016**; 57:404–11.
47. Fonollosa A, Martinez-Indart L, Artaraz J, et al. Clinical manifestations and outcomes of syphilis-associated uveitis in Northern Spain. Ocul Immunol Inflamm **2016**; 24:147–52.
48. Furtado JM, Arantes TE, Nascimento H, et al. Clinical manifestations and ophthalmic outcomes of ocular syphilis at a time of re-emergence of the systemic infection. Sci Rep **2018**; 8:12071. doi:10.1038/s41598-018-30559-7
49. Hoogewoud F, Frumholtz L, Loubet P, et al. Prognostic factors in syphilitic uveitis. Ophthalmology **2017**; 124:1808–16.
50. Lee SY, Cheng V, Rodger D, Rao N. Clinical and laboratory characteristics of ocular syphilis: a new face in the era of HIV co-infection. J Ophthalmic Inflamm Infect **2015**; 5:56. doi:10.1186/s12348-015-0056-x
51. Mathew RG, Goh BT, Westcott MC. British ocular syphilis study (BOSS): 2-year national surveillance study of intraocular inflammation secondary to ocular syphilis. Invest Ophthalmol Vis Sci **2014**; 55:5394–400.
52. Moradi A, Salek S, Daniel E, et al. Clinical features and incidence rates of ocular complications in patients with ocular syphilis. Am J Ophthalmol **2015**; 159:334–43.e1.
53. Northey LC, Skalicky SE, Gurbaxani A, McCluskey PJ. Syphilitic uveitis and optic neuritis in Sydney, Australia. Br J Ophthalmol **2015**; 99:1215–9.
54. Oliver S, Sahi SK, Tantalo LC, et al. Molecular typing of *Treponema pallidum* in ocular syphilis. Sex Transm Dis **2016**; 43:524–7.
55. Oliver SE, Cope AB, Rinsky JL, et al. Increases in ocular syphilis–North Carolina, 2014-2015. Clin Infect Dis **2017**; 65:1676–82.
56. Oliver SE, Aubin M, Atwell L, et al. Ocular syphilis—eight jurisdictions, United States, 2014-2015. MMWR Morb Mortal Wkly Rep **2016**; 65:1185–8.
57. Pratas AC, Goldschmidt P, Lebeaux D, et al. Increase in ocular syphilis cases at ophthalmologic reference center, France, 2012-2015. Emerg Infect Dis **2018**; 24:193–200.
58. Reekie I, Reddy Y. Use of lumbar punctures in the management of ocular syphilis. Semin Ophthalmol **2018**; 33:271–4.
59. Tsuboi M, Nishijima T, Yashiro S, et al. Prognosis of ocular syphilis in patients infected with HIV in the antiretroviral therapy era. Sex Transm Infect **2016**; 92:605–10.
60. Tuddenham S, Obeng C, Ghanem KG. Neurosyphilis and ophthalmic syphilis in persons with negative rapid plasma reagin and positive treponemal antibody test results. Sex Transm Dis **2015**; 42:347–9.
61. Wells J, Wood C, Sukthankar A, Jones NP. Ocular syphilis: the re-establishment of an old disease. Eye **2018**; 32:99–103.
62. Zhang R, Qian J, Guo J, et al. Clinical manifestations and treatment outcomes of syphilitic uveitis in a Chinese population. J Ophthalmol **2016**; 2016:2797028. doi:10.1155/2016/2797028
63. de Voux A, Kidd S, Torrone EA. Reported cases of neurosyphilis among early syphilis cases–United States, 2009 to 2015. Sex Transm Dis **2018**; 45:39–41.
64. Dombrowski JC, Pedersen R, Marra CM, Kerani RP, Golden MR. Prevalence estimates of complicated syphilis. Sex Transm Dis **2015**; 42:702–4.
65. Kasarskis I, Sundy M, Schafer S, Suhler E, Winthrop K. Ocular syphilis in Oregon, January 2014-March 2016. Presented at: Centers for Disease Control and Prevention Sexually Transmitted Diseases Prevention Conference; 27–30 August **2018**; Washington, DC.
66. Katz S, Workowski K, Barrow R, et al. Molecular detection and genotyping of *Treponema pallidum* strains associated with ocular syphilis. Presented at: Centers for Disease Control and Prevention Sexually Transmitted Diseases Prevention Conference; 27–30 August **2018**; Washington, DC.
67. Quilter L, de Voux A, Downs J, et al. Prevalence of self-reported neurologic and ocular symptoms in early syphilis cases. Presented at: Centers for Disease Control and Prevention Sexually Transmitted Diseases Prevention Conference; 27–30 August **2018**; Washington, DC.
68. Davis AP, Stern J, Tantalo L, et al. How well do neurologic symptoms identify individuals with neurosyphilis? Clin Infect Dis **2018**; 66:363–7.
69. Shi M, Peng RR, Gao Z, et al. Risk profiles of neurosyphilis in HIV-negative patients with primary, secondary and latent syphilis: implications for clinical intervention. J Eur Acad Dermatol Venereol **2016**; 30:659–66.
70. Firlag-Burkacka E, Swiecki P, Cielniak I, et al. High frequency of neurosyphilis in HIV-positive patients diagnosed with early syphilis. HIV Med **2016**; 17:323–6.
71. Ho EL, Maxwell CL, Dunaway SB, et al. Neurosyphilis increases human immunodeficiency virus (HIV)-associated central nervous system inflammation but does not explain cognitive impairment in HIV-infected individuals with syphilis. Clin Infect Dis **2017**; 65:943–8.
72. Marra CM, Deutsch R, Collier AC, et al. Neurocognitive impairment in HIV-infected individuals with previous syphilis. Int J STD AIDS **2013**; 24:351–5.
73. Moulton CD, Koychev I. The effect of penicillin therapy on cognitive outcomes in neurosyphilis: a systematic review of the literature. Gen Hosp Psychiatry **2015**; 37:49–52.
74. Wang Z, Liu L, Shen YZ, et al. The clinical and laboratory features of neurosyphilis in HIV-infected patients: a retrospective study in 92 patients. Medicine **2018**; 97:e0078.
75. Chan Y, Yeung KH, Ho HF, et al. Use of cerebrospinal fluid enzyme immunoassay for diagnosis of neurosyphilis. Int J STD AIDS **2014**; 25:571–8.
76. Dumaresq J, Langevin S, Gagnon S, et al. Clinical prediction and diagnosis of neurosyphilis in HIV-infected patients with early Syphilis. J Clin Microbiol **2013**; 51:4060–6.
77. Guarner J, Jost H, Pillay A, et al. Evaluation of treponemal serum tests performed on cerebrospinal fluid for diagnosis of neurosyphilis. Am J Clin Pathol **2015**; 143:479–84.
78. Noy M, Rayment M, Sullivan A, Nelson M. The utility of cerebrospinal fluid analysis in the investigation and treatment of neurosyphilis. Sex Transm Infect **2014**; 90:451.
79. Pastuszczak M, Wojas-Pelc A, Jaworek AK. Association of CSF glucose concentration with neurosyphilis diagnosis. Cent Eur J Med **2013**; 8:48–51.
80. Vanhaecke C, Grange P, Benhaddou N, et al. Clinical and biological characteristics of 40 patients with neurosyphilis and evaluation of *Treponema pallidum* nested polymerase chain reaction in cerebrospinal fluid samples. Clin Infect Dis **2016**; 63:1180–6.
81. Xiao Y, Tong ML, Liu LL, et al. Novel predictors of neurosyphilis among HIV-negative syphilis patients with neurological symptoms: an observational study. BMC Infect Dis **2017**; 17:310.
82. Zheng S, Lin RJ, Chan YH, Ngan CCL. Biological false-positive venereal disease research laboratory test in cerebrospinal fluid in the diagnosis of neurosyphilis—a case-control study. J Eur Acad Dermatol Venereol **2018**; 32:474–81.
83. Zhu L, Gu X, Peng RR, et al. Comparison of the cerebrospinal fluid (CSF) toluidine red unheated serum test and the CSF rapid plasma reagin test with the CSF venereal disease research laboratory test for diagnosis of neurosyphilis among HIV-negative syphilis patients in China. J Clin Microbiol **2014**; 52:736–40.
84. Zhang X, Du Q, Ma F, Lu Y, Wang M, Li X. Characteristics of syphilitic uveitis in northern China. BMC Ophthalmology **2017**; 17:95. doi:10.1186/s12886-017-0491-6
85. Bolan RK, Beymer MR, Weiss RE, Flynn RP, Leibowitz AA, Klausner JD. Doxycycline prophylaxis to reduce incident syphilis among HIV-infected men who have sex with men who continue to engage in high-risk sex: a randomized, controlled pilot study. Sex Transm Dis **2015**; 42:98–103.
86. Molina JM, Charreau I, Chidiac C, et al. Post-exposure prophylaxis with doxycycline to prevent sexually transmitted infections in men who have sex with men: an open-label randomised substudy of the ANRS IPERGAY trial. Lancet Infect Dis **2018**; 18:308–17.

87. Pintye J, Baeten JM, Manhart LE, et al. Association between male circumcision and incidence of syphilis in men and women: a prospective study in HIV-1 serodiscordant heterosexual African couples. Lancet Global Health **2014**; 2:E664–E71.
88. Qian HZ, Ruan Y, Liu Y, et al. Lower HIV risk among circumcised men who have sex with men in China: interaction with anal sex role in a cross-sectional study. J Acquir Immune Defic Syndr **2016**; 71:444–51.
89. An Q, Wejnert C, Bernstein K, Paz-Bailey G; NHBS Study Group. Syphilis screening and diagnosis among men who have sex with men, 2008-2014, 20 U.S. cities. J Acquir Immune Defic Syndr **2017**; 75:S363–S369.
90. de Voux A, Bernstein K, Bradley H, Kirkcaldy R, Tie Y, Shouse L. Syphilis screening among sexually active men who have sex with men and who are receiving medical care for HIV in the United-States-Medical Monitoring Project, 2013-2014. Presented at: Centers for Disease Control and Prevention Sexually Transmitted Diseases Prevention Conference; 27–30 August **2018**; Washington, DC.
91. Chow EPF, Callander D, Fairley CK, et al. Increased syphilis testing of men who have sex with men: greater detection of asymptomatic early syphilis and relative reduction in secondary syphilis. Clin Infect Dis **2017**; 65:389–95.
92. Tuite A, Fisman D. Go big or go home: impact of screening coverage on syphilis infection dynamics. Sex Transm Infect **2016**; 92:49–54.
93. Tuite AR, Burchell AN, Fisman DN. Cost-effectiveness of enhanced syphilis screening among HIV-positive men who have sex with men: a microsimulation model. PLoS One **2014**; 9:e101240.
94. Tuite AR, Fisman DN, Mishra S. Screen more or screen more often? Using mathematical models to inform syphilis control strategies. BMC Public Health **2013**; 13:606.
95. Tuite AR, Shaw S, Reimer JN, Ross CP, Fisman DN, Mishra S. Can enhanced screening of men with a history of prior syphilis infection stem the epidemic in men who have sex with men? a mathematical modelling study. Sex Transm Infect **2018**; 94:105–10.
96. Chew Ng RA, Samuel MC, Lo T, et al. Sex, drugs (methamphetamines), and the Internet: increasing syphilis among men who have sex with men in California, 2004-2008. Am J Public Health **2013**; 103:1450–6.
97. Chaulk CP, Muvva R, Morgan J, et al. Notes from the field: repeat syphilis infection and HIV coinfection among men who have sex with men—Baltimore, Maryland, 2010-2011. MMWR Morb Mortal Wkly Rep **2013** ; 62: 649–50.
98. Towns JM, Leslie DE, Denham I, Azzato F, Fairley CK, Chen M. Painful and multiple anogenital lesions are common in men with *Treponema pallidum* PCR-positive primary syphilis without herpes simplex virus coinfection: a cross-sectional clinic-based study. Sex Transm Infect **2016**; 92:110–5.
99. Yang CJ, Chang SY, Wu BR, et al. Unexpectedly high prevalence of *Treponema pallidum* infection in the oral cavity of human immunodeficiency virus-infected patients with early syphilis who had engaged in unprotected sex practices. Clin Microbiol Infect **2015**; 21:787.e1–e7.
100. Marra C, Maxwell C, Sahi S, Tantalo L, Dunaway S, Lukehart S. Prior syphilis protects against *T. palldium* dissemination in repeat infection. Presented at: Conference on Retroviruses and Opportunistic Infections; 4–7 March **2018**; Boston, MA.
101. de Voux A, Bernstein KT, Bradley H, Kirkcaldy RD, Tie Y, Shouse RL. Syphilis testing among sexually active men who have sex with men and who are receiving medical care for human immunodeficiency virus in the United States: medical monitoring project, 2013-2014. Clin Infect Dis **2019**; 68:934–9.
102. Shilaih M, Marzel A, Braun DL, et al. Factors associated with syphilis incidence in the HIV-infected in the era of highly active antiretrovirals. Medicine **2017**; 96:e5849. doi:10.1097/MD.0000000000005849