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CLINICAL REPORT

Serological Response to Treatment of Syphilis with Doxycycline Compared with Penicillin in HIV-infected Individuals

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Serological response to treatment of syphilis with orally administered doxycycline or intramuscularly administered penicillin was assessed in patients with concurrent HIV. All HIV-infected individuals diagnosed with syphilis attending 3 hospitals in Copenhagen, Denmark were included. Odds ratios (ORs) with 95% confidence intervals (CI) associated with serological outcome were modelled using propensity-score-adjusted logistic regression analysis. In total, 202 cases were treated with doxycycline or intramuscular penicillin. At 12 months, serological failure was observed in 12 cases (15%) treated with doxycycline and in 8 cases (17%) treated with penicillin (OR 0.78 (95% CI 0.16–3.88), $p = 0.76$). The serological cure rate at 12 months was highest in patients with primary syphilis (100%), followed by patients with secondary (89%), early latent (71%) and late latent (67%) syphilis ($p = 0.006$). In conclusion, this study provides evidence for the use of doxycycline as a treatment option when treating a HIV-infected population for syphilis. ***Key words: syphilis; HIV; penicillin; doxycycline; serology.***

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Since its introduction in the 1940s, penicillin has been used for treatment of syphilis. Penicillin G, administered parenterally, is the recommended first-line treatment for all stages of syphilis in Europe and the USA; however, the preparation, dosage and length of treatment depend on disease stage and whether there is central nervous system (CNS) involvement (1, 2). In the 1950s, successful use of tetracycline derivatives for treatment of syphilis was reported (3, 4). Doxycycline, a tetracycline derivative with increased bioavailability and fewer side-effects, was then introduced. An uncontrolled observational study from 1979 evaluated the serological response to doxycycline treatment of syphilis during the course of one year and found excellent response rates for patients with primary (100%), secondary and early latent syphilis (90%) (5). In a more recent retrospective case-control study, doxycycline was compared with benzathine penicillin G in doses recommended by the Centers for Disease Control and Prevention (CDC) and appeared to be an effective agent for treatment of early syphilis (6). Azithromycin has also been used as a treatment alternative, but very high rates of the resistance-conferring A2058G mutation have been reported from Ireland, Eastern Europe, the USA and China (7–10), limiting its usefulness.

Syphilis and HIV co-infection is common in Denmark (11). Since a case report documented neurological relapse after treatment with benzathine penicillin G in an HIV-infected individual (12), the management of syphilis in patients with concurrent HIV has been debated. Although many controversies exist on the impact of HIV on the clinical course of syphilis (13), serologically defined treatment failure has been documented to be more common in patients with primary and secondary syphilis and concurrent HIV (14). However, a recent study found that HIV co-infection had an impact only on the serological response in patients with primary syphilis and a CD4 cell count of < 500 cells/μl (15). Today many HIV-infected individuals are treated with combination antiretroviral therapy (cART) and may have a restored immune system, resulting in reduced rates of serological failure (16). The CDC recommends that HIV-infected individuals are evaluated clinically and serologically for treatment failure at 3, 6, 9, 12 and 24 months after therapy (2). In general, the serological response after treatment with benzathine penicillin G is known to be affected by several factors; for example, the rate of decline is more rapid in patients with high-titre seroreactivity compared with those with low-titre seroreactivity. Moreover, patients with a prior infection with syphilis have a slower reduction in titres (17).

The aim of the present study was to compare the serological response to treatment of primary, secondary, early or late latent syphilis with intramuscularly administered penicillin or orally administered doxycycline in patients with concurrent HIV. Propensity score adjustment and matching were employed to reduce bias between treatment groups owing to the unequal chance of allocation to a treatment group (18, 19).

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METHODS

The study was performed as a retrospective study of HIV-infected individuals ≥18 years of age diagnosed with syphilis between 1 May 2004 and 31 October 2009. All HIV-infected individuals attending the Department of Infectious Diseases at Copenhagen University Hospital, Rigshospitalet, the Department of Infectious Diseases at Copenhagen University Hospital, Hvidovre, and the sexually transmitted disease (STD) clinic at the Department of Dermato-venereology at Copenhagen University Hospital, Bispebjerg, were included. Sociodemographic information, mode of acquisition (e.g. men who have sex with men (MSM) status) and clinical data were extracted from the patient files.

Therapy consisted of oral doxycycline or intramuscular penicillin. Disease stage was based on clinical examination, patient history and the results of serological tests. Patients were classified as having primary syphilis, secondary syphilis, early latent syphilis, late latent syphilis or tertiary syphilis. Serological cure was defined as a ≥4-fold decline in rapid plasma reagin (RPR) titres following therapy. Serological failure was defined as a lack of a 4-fold decline. To capture all available serological data, we obtained the serological test results from Statens Serum Institut, where all serological testing of syphilis was centralized during the study period. The non-treponemal test RPR was determined by agglutination and furthermore, 3 treponemal tests were used: anti-flagellum IgM (AF-M) was determined by a capture enzyme-linked immunoassay (ELISA), anti-flagellum IgG (AF-G) was determined by an indirect ELISA (20–22) and the fluorescent treponemal antibody absorption test (FTA-ABS) was done by immunofluorescence microscopy. For further details see Appendix S1[1].

RESULTS

Clinical and baseline characteristics

From 1 May 2004 to 31 October 2009, a total of 221 cases of syphilis were diagnosed in 172 HIV-infected individuals attending 3 hospitals in the Copenhagen area of Denmark (138 individuals contributed with a single episode, 24 with 2 episodes, 7 with 3 episodes, 1 with 4 episodes and 2 with 5 episodes). Characteristics of the individuals are shown in Table I. The patients were diagnosed with primary, secondary, early and late latent syphilis. No cases of tertiary syphilis were seen in these patients. Patients with neurosyphilis (14 individuals) were excluded from the analysis of serological response to treatment (Fig. 1). In total, 202 cases were treated with doxycycline or intramuscular penicillin. Of these, 126 cases were evaluated at 12 months; 78 cases were treated with doxycycline and 48 cases were treated with penicillin. Table SI[1] summarizes the demographic and clinical characteristics of the doxycycline treatment group and the penicillin treatment group. No statistically significant differences between treatment groups were observed, except for CD4 cell count ≤200 cells/μl, which was less common and proportion on cART, which was higher for the doxycycline-treated group (Table SI[1]).

Table I. *Main characteristics of the study population: 172 HIV-infected individuals contributed with 221 cases of syphilis*

Characteristic	Individuals (n=172)	Cases (n=221)
Age, years, median (range)	40 (20–78)	40 (20–83)
Female, *n* (%)	2 (1)	2 (1)
Male, *n* (%)	170 (99)	219 (99)
MSM, *n* (%)	160 (94)	207 (95)
Danish citizen, *n* (%)	132 (77)	175 (80)
Syphilis stage, *n* (%)		
Primary	14 (8)	21 (10)
Secondary	102 (60)	130 (59)
Early latent	23 (13)	31 (14)
Late latent	31 (18)	36 (16)
Relapse	0 (0)	1 (0)
Unknown	2 (1)	2 (1)
Neurosyphilis, *n* (%)	12 (7)	14 (6)
Syphilis treatment, *n* (%)		
Doxycycline	101 (59)	129 (59)
Penicillin intramuscularly	58 (34)	76 (34)
Penicillin intravenously	4 (2)	6 (3)
Ceftriaxone	6 (3)	7 (3)
Unknown	3 (2)	3 (1)
Infected in Denmark, *n* (%)	104 (60)	127 (57)
History of syphilis, *n* (%)	59 (34)	108 (49)
CD4 cell count, cells/μl, median (IQR)	460 (336–639)	450 (338–630)
≤200	14 (8)	17 (8)
>200	104 (61)	129 (58)
Unknown	54 (31)	75 (34)
HIV RNA, log10 copies/ml, mean (SD)	2.24 (1.66)	2.18 (1.65)
HIV RNA, copies/ml, *n* (%)		
≤200	77 (45)	99 (45)
>200–100,000	30 (18)	36 (16)
≥100,000	11 (6)	13 (6)
Unknown	54 (31)	73 (33)
cART, *n* (%)	117 (68)	153 (69)
Co-infections, *n* (%)		
Hepatitis B virus infection	17 (10)	27 (12)
Hepatitis C virus infection	15 (9)	22 (10)
Gonorrhoea	4 (2)	5 (2)
Chlamydia	4 (2)	6 (3)

Data are presented as *n* (%) unless otherwise indicated.
MSM: men who have sex with men; IQR: interquartile range; SD: standard deviation; cART: combination antiretroviral therapy.

Serological outcome

Serological outcome was assessed at 3, 6, 9 and 12 months following therapy and no statistically significant differences were observed between treatment groups at any time-point (all $p>0.05$). At 12 months, the time-point often used to evaluate serological cure rates, 20 cases of serological failure were observed (Table II). All these patients had reactive treponemal tests, which confirmed the diagnosis of syphilis. By logistic regression analysis, only age (OR 1.04 (95% CI 1.00–1.09) per year increment) was associated with failure, whereas sex, syphilis stage, mode of acquisition or cART were not associated with serological outcome. In the doxycycline group, 12 cases (15%) of serological failure were observed. In the penicillin group, 8 cases (17%) of serological failure were observed, resulting in a non-significant difference of 2% (95% CI –1.08–5.08%) and corresponding to an OR of 0.78 (95% CI 0.16–3.88, $p=0.76$) after adjust-

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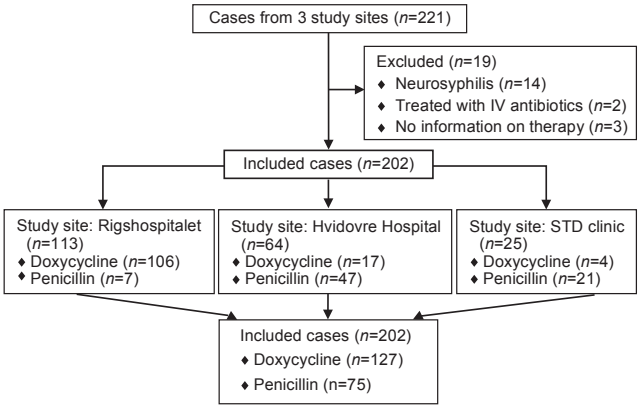

Fig. 1. Inclusion of cases for comparison of serological treatment outcomes. IV: intravenous; STD: sexually transmitted diseases.

ment for age and propensity score. The analysis was repeated including only individuals with one episode of syphilis within the study period; however, this rendered the same result. Among these 20 cases, 2 individuals contributed with more than one episode of serological failure. The first individual contributed with 3 episodes (one episode was treated with procaine penicillin, one episode with benzathine penicillin G and one episode with doxycycline). The other individual contributed with 2 episodes and was diagnosed with relapse due to malaise and persisting seroreactivity one year after treatment of early latent syphilis. This patient had been treated with doxycycline for 14 days, followed by a documented 4-fold decrease in RPR. Titres subsequently stabilized, but did not reverse, and the patient received retreatment with doxycycline for 30 days, but remained seroreactive thereafter. The patient was an 80-year old man with 9 previous episodes of syphilis and re-infection could not be ruled out completely. In all other cases of serological failure the patients did not receive retreatment and no indications of re-infection were found.

When comparing RPR titres between treatment groups at time of diagnosis and 3, 6, 9 and 12 months post-treatment no statistically significant differences were observed (all $p > 0.05$) (Table SI[1]). As a consequence, further analyses were conducted using combined data from the doxycycline and penicillin groups. At the time of diagnosis, there was a statistically significant difference in RPR between syphilis stages ($p = 0.02$). From the descriptive statistics it was evident that the highest titres were observed during the secondary stage (RPR 128) compared with the primary stage (RPR 32), the early latent stage (RPR 64) and the late latent stage (RPR 64). Among the cases with primary and secondary syphilis, 100% and 89% reached serological cure at 12 months, respectively, and of the cases with early and late latent syphilis it was 71% and 67%, respectively ($p = 0.006$). RPR titres at the time of diagnosis were significantly higher in patients with serological failure 12 months after treatment ($p < 0.000$). However, the serological cure rate did not vary by CD4 cell count or HIV RNA (all $p > 0.05$).

Table II. *Serological outcomes 3, 6, 9 and 12 months after treatment (*n*=202 cases). Serological cure was defined as a ≥ 4-fold decline in rapid plasma reagin (RPR). Serological failure was defined as a lack of a 4-fold decline in RPR*

	3 months		6 months		9 months		12 months	
Serological outcome	Doxy (*n*=89)	PC (*n*=58)	Doxy (*n*=74)	PC (*n*=45)	Doxy (*n*=68)	PC (*n*=39)	Doxy (*n*=78)	PC (*n*=48)
Cure, *n* (%)	20 (22)	12 (21)	37 (50)	28 (62)	52 (76)	31 (79)	66 (85)	40 (83)
Failure, *n* (%)	69 (78)	46 (79)	37 (50)	17 (38)	16 (24)	8 (21)	12 (15)	8 (17)

n: number of cases with available serological test results at each time-point. Doxy: doxycycline; PC: penicillin.

Propensity-score-matched case-control study

Seventeen patients in the doxycycline group were matched with the 17 patients in the penicillin group who had the closest propensity scores. Two patients (12%) in the matched doxycycline group and 3 (18%) in the matched penicillin group had serological failure at 12 months (crude OR 0.62 (95% CI 0.09–4.29), $p = 0.5$).

DISCUSSION

In this propensity-score-adjusted and propensity-score-matched case-control study we assessed the serological treatment response in 202 cases of syphilis in HIV-infected individuals; 127 cases were treated with doxycycline and 75 were treated with intramuscular penicillin. Current treatment guidelines in Europe and the USA recommend penicillin as the preferred treatment option, whereas doxycycline is reserved for patients who are allergic to penicillin (1, 2). Our findings suggest that doxycycline can be used as an efficient alternative, at least in an HIV-infected population with close serological and clinical follow-up. In a recent study comparing single dose with multiple doses of benzathine penicillin G for treatment of syphilis in HIV-infected individuals, 91% of the included patients exhibited serological cure by 13 months and 97% by 2 years (23). In addition, a systematic review found a failure rate of 1–22% among HIV-infected individuals (24). In our study, serological cure rates of 85% and 83% for doxycycline and penicillin, respectively, fall within this range and furthermore no difference in serological outcome was observed between treatment groups. Moreover, a previous study from our group with the primary objective to assess the effect of syphilis and HIV coinfection on viral load and CD4 cell count found comparable response rates to treatment with penicillin and doxycycline (25).

A study by Sena et al. (26) demonstrated that persisting non-treponemal titres were common among patients with early syphilis and that re-treatment had only a minor effect

on serofast patients. In keeping with this, one patient in our study was diagnosed with relapse and the patient did not serorevert despite retreatment. Another study showed that patients experiencing their first infection were more likely to serorevert than patients with repeated infection (27). A more recent large study in a HIV-uninfected population assessed factors associated with serological response in patients with early syphilis and found that serological cure at 6 months after treatment was associated with younger age and fewer sex partners, but surprisingly not with a history of syphilis (28). Accordingly, whether persistent seroreactivity represents low-level infection or is caused by variability in the host response remains controversial.

We found a higher rate of serological cure in earlier stages of syphilis. The highest rates of serological cure at 12 months were seen in the primary and secondary stages. Previous studies have also reported slower serological responses in late stages of syphilis (15, 27, 29). Likewise, a study similar to ours, comparing doxycycline and penicillin, corroborated that HIV-infected patients with secondary syphilis were more likely to achieve serological cure than patients in other stages (30). CD4 cell count has also been shown to have an effect on serological treatment outcome; a CD4 cell count of <200 cells/μl at the time of syphilis diagnosis has been associated with an increased risk of serological failure (16). Nevertheless, no such association was demonstrated in our study.

The strengths of the current study include the close follow-up and the detailed demographic, clinical and behavioural data on all patients. Furthermore, to capture all serological data, results of serological tests were obtained from the national provider of serological syphilis testing. The samples were not batched, but all analyses were performed at the same laboratory. All reactive non-treponemal tests were confirmed using treponemal tests, thereby minimizing the risk of false-positive test results. Of note, the use of cART appears to decrease the prevalence of biologic false-positive tests in HIV-infected individuals (31). Also, all patient files were reviewed, enabling us to confirm that seroreactive tests were clinically perceived as a case and to distinguish between relapse and re-infection. Finally, in contrast to others, our study also included patients with late latent-stage syphilis.

This study is limited by the retrospective non-randomized design. The treatment given was based on local guidelines and the patients at the Department of Infectious Diseases at Rigshospitalet were mainly treated with doxycycline, whereas patients at the Department of Infectious Diseases at Hvidovre Hospital and the STD clinic at Bispebjerg Hospital were mainly treated with penicillin. However, the patients in the 2 treatment groups were comparable, except for the proportion on cART and the CD4 cell count. The patients in this study were all attending either of the 2 departments of infectious diseases for treatment or monitoring of their HIV infection; however, for treatment of syphilis, some of these patients opted for the STD clinic. More HIV-infected individuals not receiving cART opted for treatment at the STD clinic compared with individuals on cART. This explains the lower proportion of patients on cART in the group receiving penicillin (the preferred regimen at the STD clinic). Likewise, even though the median CD4 cell count was comparable between treatment groups, a higher proportion of patients with CD4 cell counts ≤ 200 cells/μl were treated with penicillin. The similar response rates in the treatment groups might be caused by the higher proportion of patients with low CD4 cell counts in the penicillin group because low CD4 cell counts have been associated with increased risk of treatment failure and delayed treatment response in HIV-infected individuals (32). Confounding by indication, i.e. that physicians may tend to use intramuscular penicillin for patients who are more severely ill and less compliant, is a risk when doing a retrospective study of treatment options, but our treatment groups were comparable overall. Using propensity scores to adjust for a skewed use of doxycycline and penicillin can reduce this bias by balancing covariates in the different treatment groups. In our study the results were largely unchanged after adjusting for the propensity score. The propensity score-matched study was small, but the OR was nevertheless very comparable to the propensity score adjusted OR. Also, because benzathine penicillin G does not achieve treponemicidal levels in the cerebrospinal fluid (CSF) and doxycycline conversely penetrates into the CSF (1), patients with asymptomatic neurosyphilis may have benefitted from treatment with doxycycline, resulting in an increased risk of treatment failure in the penicillin group. Finally, the vast majority of the patients in this study were MSM and whether our results are generalizable to other populations is unknown.

Systematic reviews have concluded that guidelines for treatment of HIV-infected individuals are based on very few objective data (24, 33). Whether doxycycline is equipotent to penicillin can only be evaluated definitively in a randomized clinical trial. However, with the well-functioning treatments with penicillin such a study might not counteract the costs of a large clinical trial. Regardless of its observational design, our study provides evidence for the use of doxycycline as an acceptable treatment option for patients with close follow-up, who prefer oral treatment for syphilis. A study similar to ours, comparing doxycycline and penicillin in HIV-infected individuals supports this assumption (30), although their response rates to both penicillin and doxycycline were lower than in our study and lower than previously reported (6). In addition, doxycycline is an effective agent for treatment of multiple STDs (33). Importantly, all our patients had concurrent HIV, but the results may

be generalizable to patients without HIV although the requirement of multiple days of treatment may present a problem in a population less used to daily medication. Taken together, our study supports the use of doxycycline as an efficient treatment option for syphilis when treating an HIV-infected population with close follow-up.

The authors declare no conflicts of interest

REFERENCES

1. Janier M, Hegyi V, Unemo M, Tiplica GS, Potocnik M, French P, et al. 2014 European guideline on the management of syphilis. IUSTI 2014.
2. MMWR. Sexually transmitted diseases treatment guidelines. Centers for Disease Control and Prevention, U.S. Department of Health and Human Services, Atlanta; 2010.
3. Hendricks FD, Greaves AB, Olansky S, Taggart SR, Lewis CN, Landman GS, et al. Terramycin in the treatment of venereal disease; a preliminary report. J Am Med Assoc 1950; 143: 4–5.
4. Kierland RR, Herrell WE, O'Leary PA. Treatment of syphilis with aureomycin administered by mouth. Arch Derm Syphilol 1950; 61: 185–195.
5. Onoda Y. Therapeutic effect of oral doxycycline on syphilis. Br J Vener Dis 1979; 55: 110–115.
6. Ghanem KG, Erbelding EJ, Cheng WW, Rompalo AM. Doxycycline compared with benzathine penicillin for the treatment of early syphilis. Clin Infect Dis 2006; 42: e45–e49.
7. Lukehart SA, Godornes C, Molini BJ, Sonnett P, Hopkins S, Mulcahy F, et al. Macrolide resistance in Treponema pallidum in the United States and Ireland. N Engl J Med 2004; 351: 154–158.
8. Mitchell SJ, Engelman J, Kent CK, Lukehart SA, Godornes C, Klausner JD. Azithromycin-resistant syphilis infection: San Francisco, California, 2000–2004. Clin Infect Dis 2006; 42: 337–345.
9. Martin IE, Gu W, Yang Y, Tsang RS. Macrolide resistance and molecular types of Treponema pallidum causing primary syphilis in Shanghai, China. Clin Infect Dis 2009; 49: 515–521.
10. Tipple C, Taylor GP. Syphilis testing, typing, and treatment follow-up: a new era for an old disease. Curr Opin Infect Dis 2015; 28: 53–60.
11. Salado-Rasmussen K, Katzenstein TL, Gerstoft J, Cowan SA, Knudsen TB, Mathiesen L, et al. Risk of HIV or second syphilis infection in Danish men with newly acquired syphilis in the period 2000–2010. Sex Transm Infect 2013; 89: 372–376.
12. Berry CD, Hooton TM, Collier AC, Lukehart SA. Neurologic relapse after benzathine penicillin therapy for secondary syphilis in a patient with HIV infection. N Engl J Med 1987; 316: 1587–1589.
13. Zetola NM, Klausner JD. Syphilis and HIV infection: an update. Clin Infect Dis 2007; 44: 1222–1228.
14. Rolfs RT, Joesoef MR, Hendershot EF, Rompalo AM, Augenbraun MH, Chiu M, 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: 307–314.
15. Knaute DF, Graf N, Lautenschlager S, Weber R, Bosshard PP. Serological response to treatment of syphilis according to disease stage and HIV status. Clin Infect Dis 2012; 55: 1615–1622.
16. Ghanem KG, Moore RD, Rompalo AM, Erbelding EJ, Zenilman JM, Gebo KA. Antiretroviral therapy is associated with reduced serologic failure rates for syphilis among HIV-infected patients. Clin Infect Dis 2008; 47: 258–265.
17. Brown ST, Zaidi A, Larsen SA, Reynolds GH. Serological response to syphilis treatment. A new analysis of old data. JAMA 1985; 253: 1296–1299.
18. Rubin DB, Thomas N. Matching using estimated propensity scores: relating theory to practice. Biometrics 1996; 52: 249–264.
19. D'Agostino RB, Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. Stat Med 1998; 17: 2265–2281.
20. Pedersen NS, Petersen CS, Axelsen NH. Enzyme-linked immunosorbent assay for detection of immunoglobulin M antibody against the Reiter treponeme flagellum in syphilis. J Clin Microbiol 1982; 16: 608–614.
21. Pedersen NS, Sheller JP, Ratnam AV, Hira SK. Enzyme-linked immunosorbent assays for detection of immunoglobulin M to nontreponemal and treponemal antigens for the diagnosis of congenital syphilis. J Clin Microbiol 1989; 27: 1835–1840.
22. Pedersen NS, Petersen CS, Vejtorp M, Axelsen NH. Serodiagnosis of syphilis by an enzyme-linked immunosorbent assay for IgG antibodies against the Reiter treponeme flagellum. Scand J Immunol 1982; 15: 341–348.
23. Ganesan A, Mesner O, Okulicz JF, O'Bryan T, Deiss RG, Lalani T, 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: 653–660.
24. Blank LJ, Rompalo AM, Erbelding EJ, Zenilman JM, Ghanem KG. Treatment of syphilis in HIV-infected subjects: a systematic review of the literature. Sex Transm Infect 2011; 87: 9–16.
25. Kofoed K, Gerstoft J, Mathiesen LR, Benfield T. 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: 143–148.
26. Sena AC, Wolff M, Behets F, Van DK, Martin DH, Leone P, et al. Response to therapy following retreatment of serofast early syphilis patients with benzathine penicillin. Clin Infect Dis 2013; 56: 420–422.
27. Romanowski B, Sutherland R, Fick GH, Mooney D, Love EJ. Serologic response to treatment of infectious syphilis. Ann Intern Med 1991; 114: 1005–1009.
28. Sena AC, Wolff M, Martin DH, Behets F, Van DK, Leone P, et al. Predictors of serological cure and serofast state after treatment in HIV-negative persons with early syphilis. Clin Infect Dis 2011; 53: 1092–1099.
29. Ghanem KG, Erbelding EJ, Wiener ZS, Rompalo AM. Serological response to syphilis treatment in HIV-positive and HIV-negative patients attending sexually transmitted diseases clinics. Sex Transm Infect 2007; 83: 97–101.
30. Tsai JC, Lin YH, Lu PL, Shen NJ, Yang CJ, Lee NY, 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.
31. Oboho IK, Gebo KA, Moore RD, Ghanem KG. The impact of combined antiretroviral therapy on biologic false-positive rapid plasma reagin serologies in a longitudinal cohort of HIV-infected persons. Clin Infect Dis 2013; 57: 1197–1202.
32. 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.
33. Clement ME, Okeke NL, Hicks CB. Treatment of syphilis: a systematic review. JAMA 2014; 312: 1905–1917.