

# Syphilis (Last updated December 17, 2015; last reviewed January 12, 2022)

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**NOTE: Update in Progress**

## Epidemiology

Syphilis is associated with an increased risk of sexual acquisition and transmission of HIV.<sup>1-5</sup> In recent years, there has been a resurgence of the disease among men across the United States and in Western Europe (<http://www.cdc.gov/std/stats>).<sup>6-13</sup> Although coexistent HIV infection (particularly in the advanced stages) may modify the diagnosis, natural history, or management of *Treponema pallidum* infection, the principles of syphilis management remain the same for persons with and without coexistent HIV infection.<sup>14-19</sup>

## Clinical Manifestations

The effect of coexistent HIV on the protean manifestations of syphilis have been documented in multiple case reports and small case series, and in a limited number of large studies. In most persons with HIV and syphilis, the clinical manifestations of syphilis are similar to persons without HIV infection. There are some studies that suggest HIV infection may affect the clinical presentation of syphilis, as atypical genital lesions are more apparent, and accelerated progression of syphilis may be seen in persons with advanced immunosuppression.<sup>15,16,20,21</sup> Primary or secondary syphilis also may cause a transient decrease in CD4 T lymphocyte (CD4) count and increase in HIV viral load that improves with recommended syphilis treatment regimens.<sup>19,22-25</sup>

Primary syphilis commonly presents as a single painless nodule at the site of contact that rapidly ulcerates to form a classic chancre; however, multiple or atypical chancres occur and primary lesions may be absent or missed in persons with HIV infection.<sup>15,26</sup> Progression to secondary syphilis typically follows 2 to 8 weeks after primary inoculation. The most common manifestations of secondary syphilis are mucocutaneous lesions that are macular, maculopapular, papulosquamous, or pustular, can involve the palms and soles, and are often accompanied by generalized lymphadenopathy, fever, malaise, anorexia, arthralgias, and headache.<sup>16,17,19</sup> Condyloma lata (moist, flat, papular lesions in warm intertriginous regions) can occur and may resemble condyloma accuminata caused by human papillomavirus. Lues maligna is a rare manifestation of secondary syphilis, characterized by papulopustular skin lesions that can evolve into ulcerative lesions with sharp borders and a dark central crust.<sup>27,28</sup> Manifestations of secondary syphilis involving other organs can occur (e.g., hepatitis, nephrotic syndrome, gastritis, pneumonia), however there is no evidence of increased frequency in persons with HIV infection. Constitutional symptoms, along with nonfocal central nervous system (CNS) symptoms and cerebrospinal fluid (CSF) abnormalities such as lymphocytic pleocytosis with a mildly elevated CSF protein, can be seen in secondary syphilis and acute primary HIV infection.<sup>20,21,26,29-32</sup> Signs and symptoms of secondary syphilis can persist from a few days to several weeks before resolving and evolving to latent stages.

Latent syphilis is defined as serologic reactivity without clinical signs and symptoms of infection. Tertiary syphilis includes cardiovascular syphilis and gummatous syphilis, a slowly progressive disease that can affect any organ system.

Neurosyphilis can occur at any stage of syphilis with different clinical presentations, including cranial nerve dysfunction, auditory or ophthalmic abnormalities, meningitis, stroke, acute or chronic change in mental status, and loss of vibration sense. Manifestations of neurosyphilis in persons with HIV infection are similar to those in individuals who do not have HIV infection. However, clinical manifestations of neurosyphilis, such as concomitant uveitis or meningitis, may be more common in persons with HIV infection.<sup>20,21,32-34</sup> A recent clinical advisory has documented increased reports of ocular syphilis, a clinical manifestation of neurosyphilis that often occurs in during early syphilis.<sup>35</sup>

## Diagnosis

Darkfield microscopy and tests to detect *T. pallidum* in lesion exudates (e.g., DFA-TP) or tissue (e.g., biopsy with silver stain) are definitive for diagnosing early syphilis. Although *T. pallidum* direct antigen

detection tests are no longer commercially available, some laboratories provide locally developed and validated polymerase chain reaction (PCR) tests for the direct detection of *T. pallidum*. A presumptive serologic diagnosis of syphilis is possible based upon non-treponemal tests (i.e., Venereal Disease Research Laboratory [VDRL] and rapid plasma reagin [RPR]) and treponemal tests (i.e., fluorescent treponemal antibody absorbed [FTA-ABS], *T. pallidum* particle agglutination [TP-PA], enzyme immunoassays [EIAs], chemiluminescence immunoassays [CIA], immunoblots, and rapid treponemal assays).

Serologic diagnosis of syphilis traditionally has involved screening for non-treponemal antibodies with confirmation of reactive tests by treponemal-based assays.<sup>19,36</sup> Some laboratories have initiated a testing algorithm using EIA or CIA as a screening test, followed by a reflex-quantitative, non-treponemal test if the EIA or CIA is positive. This latter strategy may identify those with previously treated syphilis infection, persons with untreated or incompletely treated syphilis, or those with a false positive result in persons with a low likelihood of infection.<sup>37</sup>

In persons with a positive treponemal screening test and a negative reflex-quantitative, non-treponemal test, the laboratory should perform a second treponemal test (based on different antigens from the initial test) to confirm the results of the positive initial treponemal test. If a second treponemal test is positive, persons with a history of previous treatment appropriate for the stage of syphilis will require no further treatment unless sexual risk history suggests likelihood of re-exposure. In this instance, a repeat non-treponemal test 2 to 4 weeks after the most recent possible exposure is recommended to evaluate for early infection. Those without a history of treatment for syphilis should be offered treatment. Unless history or results of a physical examination suggest a recent infection (e.g., early stage syphilis), previously untreated persons should be treated for late latent syphilis. If the second treponemal test is negative and the risk of syphilis is low, no treatment is indicated.<sup>19,38</sup> Two studies demonstrated that high quantitative index values from treponemal EIA/CIA tests correlated with TP-PA positivity; however, the range of optical density values varies among different treponemal immunoassays, and the clinical significance of these findings warrant further investigation.<sup>39,40</sup> If the risk of syphilis is high (e.g., high risk population or community with high prevalence), a repeat nontreponemal test in 2 to 4 weeks is recommended to evaluate for early infection. In the absence of neurologic signs or symptoms, risk of neurosyphilis is low in persons with a reactive treponemal test and a non-reactive, non-treponemal test;<sup>39,41</sup> examination of CSF is not recommended.

Early-stage disease (i.e., primary, secondary, and early-latent syphilis) in persons with HIV infection is identified using the same diagnostic tests used in persons without HIV infection: darkfield microscopy of mucocutaneous lesions and standard serologic tests. Results with VDRL and RPR may be higher, lower (in rare instances), or delayed in persons with HIV infection with early-stage syphilis.<sup>42-46</sup> No data indicate that treponemal tests perform differently among persons with HIV infection,<sup>47</sup> although uncommon, false-negative serologic tests for syphilis can occur with documented *T. pallidum* infection.<sup>45,46</sup> Therefore, if serologic tests do not support the diagnosis of syphilis, presumptive treatment is recommended if syphilis is suspected and use of other tests should be considered (e.g., biopsy, darkfield examination, PCR of lesion material, exclusion of prozone phenomenon, repeat serology in 2–4 weeks).

By definition, persons with latent syphilis have serological evidence of syphilis (nontreponemal and treponemal testing) in the absence of clinical manifestations. Early latent syphilis is defined by evidence of infection during the preceding year by

1. A documented seroconversion or four-fold or greater increase in nontreponemal titer; or
2. Symptoms of primary or secondary syphilis; or
3. A sex partner with documented primary, secondary or early latent syphilis.<sup>19</sup>

Late latent syphilis is defined as syphilis in a person who does not have evidence of acquiring infection in the preceding year.

All persons with syphilis and signs or symptoms suggesting neurologic disease (e.g., cranial nerve dysfunction, auditory or ophthalmic abnormalities, meningitis, stroke, altered mental status,) warrant

evaluation for neurosyphilis. An immediate ophthalmologic evaluation is recommended for persons with syphilis and ocular complaints, however a normal CSF evaluation can occur with ocular syphilis. Ocular syphilis should be managed according to the treatment recommendations for neurosyphilis, regardless of CSF results.

CSF abnormalities (i.e., elevated protein and mononuclear pleocytosis) are common in early stage syphilis<sup>48</sup> and in persons with HIV infection, even those with no neurologic symptoms. The clinical and prognostic significance of CSF laboratory abnormalities with early stage syphilis in persons without neurologic symptoms is unknown. Several studies have demonstrated that in persons with syphilis and HIV infection, CSF laboratory abnormalities are associated with CD4 counts  $\leq 350$  cells/mm<sup>3</sup> or in combination with RPR titers  $\geq 1:32$ .<sup>31,32,49,50</sup> However, unless neurologic signs and symptoms are present, a CSF examination has not been associated with improved clinical outcomes.

Laboratory testing is helpful in supporting the diagnosis of neurosyphilis; however, no single test can be used to diagnose neurosyphilis. The diagnosis of neurosyphilis depends on a combination of CSF tests (CSF cell count or protein, and a CSF-VDRL) in the setting of reactive serologic test results and neurologic signs and symptoms. Cerebrospinal fluid (CSF) abnormalities are common in persons with early stage syphilis and are of unknown significance in the absence of neurologic signs or symptoms. CSF examination may indicate mononuclear pleocytosis (6–200 cells/mm<sup>3</sup>), mildly elevated protein concentration, or a reactive CSF-VDRL. Among persons with HIV infection, the CSF leukocyte count can be elevated ( $>5$  white blood cell count [WBC]/mm<sup>3</sup>); using a higher cutoff ( $>20$  WBC/mm<sup>3</sup>) might improve the specificity of neurosyphilis diagnosis.<sup>31</sup> In persons with neurologic signs or symptoms, a reactive CSF-VDRL (in a specimen not contaminated with blood), is considered diagnostic of neurosyphilis. If the CSF-VDRL is negative, but serologic tests are reactive, CSF cell count or protein are abnormal, and clinical signs of neurologic involvement are present, treatment for neurosyphilis is recommended. If the neurologic signs and symptoms are nonspecific, additional evaluation using FTA-ABS testing on CSF can be considered. The CSF FTA-ABS test is less specific for neurosyphilis than the CSF-VDRL but is highly sensitive; in the absence of specific neurological signs and symptoms, neurosyphilis is unlikely with a negative CSF FTA-ABS test.<sup>51,52</sup> RPR tests on the CSF have been associated with a high false negative rate and are not recommended.<sup>53</sup> PCR-based diagnostic methods are not currently recommended as diagnostic tests for neurosyphilis.

## Preventing Exposure and Disease

The resurgence of syphilis in men who have sex with men (MSM) with HIV infection in the United States underscores the importance of primary prevention of syphilis in this population, which should begin with a behavioral risk assessment and routine discussion of sexual behaviors. Health care providers should discuss client-centered risk reduction messages and provide specific actions that can reduce the risk of acquiring sexually transmitted diseases and of transmitting HIV infection.<sup>19,54-58</sup> Routine serologic screening for syphilis is recommended at least annually for all persons with HIV infection who are sexually active, with more frequent screening (i.e., every 3–6 months) for those who have multiple or anonymous partners.<sup>19,59-61</sup> The occurrence of syphilis or any other sexually transmitted infection in a person with HIV infection is an indication of risk behaviors that should prompt intensified risk assessment and counseling messages about the manifestations of syphilis, risk of HIV transmission, and prevention strategies with strong consideration of referral for behavioral intervention.<sup>62</sup> Patients undergoing screening or treatment for syphilis also should be evaluated for other sexually transmitted diseases such as chlamydia and gonorrhea at anatomic sites of exposure in men and for chlamydia, gonorrhea, and trichomonas in women.<sup>19,63</sup>

## Preventing Disease

Frequent serologic screening can identify persons recently infected and in some instances, before infectious lesions develop. Treatment can prevent disease progression in the individual and transmission to a partner. Studies in the pre-HIV era demonstrated that approximately one-third of the sex partners of persons who have primary syphilis will develop syphilis within 30 days of exposure, and empiric treatment of incubating

syphilis will prevent the development of disease in those who are exposed and onward syphilis transmission to their partners.<sup>64-67</sup> Those who have had recent sexual contact with a person with syphilis in any stage should be evaluated clinically and serologically and treated presumptively with regimens outlined in current recommendations.

Persons who have had sexual contact with a person who receives a diagnosis of primary, secondary, or early latent syphilis within 90 days preceding the diagnosis should be treated presumptively for early syphilis, even if serologic test results are negative (**AIII**). Persons who have had sexual contact with a person who receives a diagnosis of primary, secondary, or early latent syphilis more than 90 days before the diagnosis should be treated presumptively for early syphilis if serologic test results are not immediately available and the opportunity for follow-up is uncertain. If serologic tests are negative, no treatment is needed. If serologic tests are positive, treatment should be based on clinical and serologic evaluation and stage of syphilis. Long-term sex partners of persons who have late latent syphilis should be evaluated clinically and serologically for syphilis and treated on the basis of the evaluation's findings. Sexual partners of infected persons considered at risk of infection should be notified of their exposure and the importance of evaluation.<sup>19</sup> The following sex partners of persons with syphilis are considered at risk for infection and should be confidentially notified of the exposure and need for evaluation:

- Partners who have had sexual contact within 3 months plus the duration of symptoms for persons who receive a diagnosis of primary syphilis,
- Partners who have had sexual contact within 6 months plus duration of symptoms for those with secondary syphilis, and
- Partners who have had sexual contact within 1 year for persons with early latent syphilis.

## Treating Disease

Treatment regimens for syphilis demonstrate that most persons with HIV infection respond appropriately to single dose benzathine penicillin for primary, secondary, and early latent syphilis.<sup>18,19,43</sup> Closer follow-up is recommended, however, because serologic nonresponse and neurologic complications may be higher in persons with HIV infection.<sup>21,68,69</sup>

Penicillin G remains the treatment of choice for syphilis. Persons with HIV infection with early-stage (e.g., primary, secondary, or early-latent) syphilis should receive a single intramuscular (IM) injection of 2.4 million Units (U) of benzathine penicillin G (**AII**).<sup>19</sup> The available data demonstrate that high-dose amoxicillin given with probenecid in addition to benzathine penicillin G in early syphilis is not associated with improved clinical outcomes.<sup>43</sup> Persons with a penicillin allergy whose compliance or follow-up cannot be ensured should be desensitized and treated with benzathine penicillin (**AIII**).

The efficacy of alternative non-penicillin regimens in persons with HIV infection and early syphilis has not been well studied. The use of any alternative penicillin treatment regimen should be undertaken only with close clinical and serologic monitoring. Several retrospective studies support use of doxycycline, 100 mg orally twice daily for 14 days, to treat early syphilis (**BII**).<sup>70,71</sup> Limited clinical studies, mainly in persons without HIV infection suggest that ceftriaxone, 1 g daily either IM or intravenously (IV) for 10 to 14 days, is effective for treating early stage syphilis (**BII**), but the optimal dose and duration of therapy have not been defined.<sup>72</sup> A single 2-g oral dose of azithromycin has been shown to be effective for treating early syphilis.<sup>73-75</sup> However *T. pallidum* chromosomal mutations associated with azithromycin resistance and treatment failures have been reported most commonly in MSM.<sup>76-81</sup> Azithromycin treatment has not been well studied in persons with HIV infection with early stage syphilis and it should be used with caution in instances when treatment with penicillin or doxycycline is not feasible (**BII**). Azithromycin has not been studied in pregnant women. Therefore, azithromycin should not be used in MSM or in pregnant women (**AII**).

In persons with HIV infection who have late latent syphilis, treatment with 3 weekly IM injections of 2.4 million units of benzathine penicillin G is recommended (**AII**). Alternative therapy is doxycycline, 100 mg

orally twice daily for 28 days, however, it has not been sufficiently evaluated in persons with HIV infection (**BIII**). Limited clinical studies and biologic and pharmacologic evidence suggest that ceftriaxone may be effective; however, the optimal dose and duration of therapy have not been determined.<sup>82,83</sup> If the clinical situation requires use of an alternative to penicillin, treatment should be undertaken with close clinical and serologic monitoring.

Persons with HIV infection who have clinical evidence of tertiary syphilis (i.e., cardiovascular or gummatous disease) should have CSF examination to rule out CSF abnormalities before therapy is initiated. If the CSF evaluation is normal, the recommended treatment of late-stage syphilis is 3 weekly IM injections of 2.4 million U benzathine penicillin G (**AII**).<sup>19</sup> However, the complexity of tertiary syphilis management, especially cardiovascular syphilis, is beyond the scope of these guidelines and health care providers are advised to consult an infectious disease specialist.

Persons with HIV infection diagnosed with neurosyphilis or ocular or otic syphilis should receive IV aqueous crystalline penicillin G, 18 to 24 million U daily, administered 3 to 4 million U IV every 4 hours or by continuous infusion for 10 to 14 days (**AII**) or procaine penicillin, 2.4 million U IM once daily plus probenecid 500 mg orally 4 times a day for 10 to 14 days (**BII**).<sup>19,31,32</sup> Persons with HIV infection who are allergic to sulfa-containing medications should not be given probenecid because of potential allergic reaction (**AIII**). Although systemic steroids are used frequently as adjunctive therapy for otologic syphilis, such therapy has not been proven beneficial.

Because neurosyphilis treatment regimens are of shorter duration than those used in late-latent syphilis, 2.4 million U benzathine penicillin IM once per week for up to 3 weeks after completion of neurosyphilis treatment can be considered to provide a comparable duration of therapy (**CIII**).<sup>19</sup> Desensitization to penicillin is the preferred approach to treating neurosyphilis in patients who are allergic to penicillin. However, limited data indicate that ceftriaxone (2 g daily IV for 10–14 days) may be an acceptable alternative regimen (**BII**).<sup>83</sup> Other alternative regimens for neurosyphilis have not been evaluated adequately. Syphilis treatment recommendations are also available in the 2015 Centers for Disease Control and Prevention Sexually Transmitted Disease Treatment Guidelines.<sup>19</sup>

### ***Special Considerations with Regard to Starting Antiretroviral Therapy***

There are no special considerations regarding the initiation of antiretroviral therapy (ART) in patients with syphilis. Specifically, there is currently no evidence that treatment with ART needs to be delayed until treatment for syphilis has been completed. Immune reconstitution inflammatory syndrome (IRIS) in association with syphilis and treatment with ART in persons with HIV infection is uncommon.<sup>84</sup>

### ***Monitoring and Adverse Events (Including IRIS)***

Clinical and serologic responses (four-fold decrease from the nontreponemal titer at the time of treatment) to treatment of early-stage (primary, secondary, and early-latent) disease should be performed at 3, 6, 9, 12, and 24 months after therapy to ensure resolution of signs and symptoms within 3 to 6 months and seroconversion or a four-fold decline in nontreponemal titers within 12 to 24 months. Clinical and serologic responses to treatment are similar in persons with HIV infection; subtle variations can occur, however, including a slower temporal pattern of serologic response in persons with HIV infection.<sup>18,19,43,85</sup> Factors associated with the serologic response to treatment in persons without HIV infection include younger age, earlier syphilis stage, and higher RPR titer.<sup>86,87</sup> If clinical signs and symptoms persist, treatment failure should be considered. If clinical signs or symptoms recur or there is a sustained four-fold increase in non-treponemal titers of greater than 2 weeks, treatment failure or re-infection should be considered and managed per recommendations (see Managing Treatment Failure). The potential for re-infection should be based on the sexual history and risk assessment. Clinical trial data have demonstrated that 15% to 20% of persons (including persons with HIV infection) treated with recommended therapy for early stage syphilis will not achieve the four-fold decline in nontreponemal titer used to define treatment response at one year.<sup>19,43</sup> Serum non-treponemal test titers may remain reactive at a stable level (serofast), usually  $\leq 1:8$ , although rarely may be higher, for prolonged periods. In addition, persons treated for early stage syphilis who have a four-fold decline in titer may not sero-revert to a negative nontreponemal test

and may remain serofast. These serofast states probably do not represent treatment failure.

Response to therapy for late latent syphilis should be monitored using non-treponemal serologic tests at 6, 12, 18, and 24 months to ensure at least a four-fold decline in titer, if initially high ( $\geq 1:32$ ), within 12 to 24 months of therapy. However, data to define the precise time intervals for adequate serologic responses are limited. Most persons with low titers and late latent syphilis remain serofast after treatment often without a four-fold decline in the initial titer. If clinical symptoms develop or a four-fold increase in non-treponemal titers is sustained, then treatment failure or re-infection should be considered and managed per recommendations (see Managing Treatment Failure). The potential for reinfection should be based on the sexual history and risk assessment.<sup>19</sup>

The earliest CSF indicator of response to neurosyphilis treatment is a decline in CSF lymphocytosis. The CSF-VDRL may respond more slowly. If CSF pleocytosis was present initially, a CSF examination should be repeated at 6 months. Limited data suggest that changes in CSF parameters may occur more slowly in persons with HIV infection, especially with advanced immunosuppression.<sup>20,31</sup> If the cell count has not decreased after 6 months or if the CSF WBC is not normal after 2 years, re-treatment should be considered. In persons on ART with neurosyphilis, declines in serum RPR titers after treatment correlate with normalization of CSF parameters.<sup>88</sup> Use of ART in persons with syphilis has also been associated with a reduced risk of serologic failure of syphilis treatment,<sup>20</sup> and a lower risk of developing neurosyphilis.<sup>20</sup>

The Jarisch-Herxheimer reaction is an acute febrile reaction frequently accompanied by headache and myalgia that can occur within the first 24 hours after initiation of treatment for syphilis. Antipyretics can be used to manage symptoms but have not been proven to prevent this reaction. The Jarisch-Herxheimer reaction occurs most frequently in persons with early syphilis, high non-treponemal antibody titers, and prior penicillin treatment.<sup>89</sup> Persons with syphilis should be warned about this reaction, instructed how to manage it, and informed it is not an allergic reaction to penicillin.

## Managing Possible Treatment Failure or Re-infection

Re-treatment should be considered for persons with early-stage syphilis who have persistent or recurring clinical signs or symptoms of disease, or a sustained four-fold increase in serum non-treponemal titers after an initial four-fold decrease following treatment. The assessment for potential reinfection should be informed by a sexual history and syphilis risk assessment including information about a recent sexual partner with signs or symptoms or recent treatment for syphilis. One study showed that 6% of MSM had a repeat early stage syphilis infection within 2 years of initial infection; HIV infection, Black race, and having multiple sexual partners were associated with increased risk of reinfection.<sup>10</sup> Serologic response should be compared to the titer at the time of treatment. However, assessing serologic response to treatment can be difficult, as definitive criteria for cure or failure have not been well established. Person with HIV infection may be at increased risk of treatment failure, but the magnitude of these risks is not precisely defined and is likely low.<sup>19,30,69</sup>

Persons who meet the criteria for treatment failure (i.e., signs or symptoms that persist or recur or a four-fold increase or greater in titer sustained for more than 2 weeks) and who are at low risk for reinfection should be managed for possible treatment failure. Persons whose non-treponemal titers do not decrease four-fold with 12 to 24 months of therapy can also be managed as a possible treatment failure. Management includes a CSF examination and retreatment with benzathine penicillin G, 2.4 million U at 1-week intervals for 3 weeks (**BIII**), unless the CSF examination is consistent with CNS involvement. If titers do not respond appropriately after re-treatment, the value of repeated CSF examination or additional therapy is unclear, but it is generally not recommended. Treatment with benzathine penicillin, 2.4 million U IM without a CSF examination unless signs or symptoms of syphilis, and close clinical follow-up can be considered in persons with recurrent signs and symptoms of primary or secondary syphilis or a four-fold increase in non-treponemal titers within the past year who are at high risk of syphilis re-infection (**CIII**).

Persons treated for late latent syphilis should have a CSF examination and be re-treated if they develop clinical signs or symptoms of syphilis or have a sustained four-fold increase in serum non-treponemal test

titer and are low risk for infection; this can also be considered if they experience an inadequate serologic response (i.e., less than four-fold decline in an initially high  $\geq 1:32$  non-treponemal test titer) within 12 to 24 months of therapy. If CSF examination is consistent with CNS involvement, re-treatment should follow the recommendations for treatment of neurosyphilis. Persons with a normal CSF examination should be treated with benzathine penicillin 2.4 million U IM weekly for 3 doses (**BIII**). As with early stage syphilis, the value of repeated CSF examination or additional therapy is unclear, but is generally not recommended. Treatment with benzathine penicillin 2.4 million U IM without a CSF examination unless signs or symptoms of neurosyphilis, and close clinical follow-up can be considered in persons with signs or symptoms of primary or secondary syphilis or a four-fold increase in non-treponemal titers within the past year who are at high risk of re-infection (**CIII**).

Re-treatment for neurosyphilis should be considered if the CSF cell count has not decreased 6 months after completion of treatment or if the CSF cell count or protein is not normal after 2 years.<sup>19</sup>

## Preventing Recurrence

No recommendations indicate the need for secondary prophylaxis or prolonged chronic maintenance antimicrobial therapy for syphilis. Targeted mass treatment of high-risk populations with azithromycin has not been demonstrated to be effective.<sup>90</sup> Azithromycin is not recommended as secondary prevention because of azithromycin treatment failures reported in persons with HIV infection and reports of chromosomal mutations associated with macrolide-resistant *T. pallidum*.<sup>76-78,80,81</sup> A small pilot study has demonstrated that daily doxycycline prophylaxis was associated with a decreased incidence of syphilis among MSM with HIV infection.<sup>91</sup>

## Special Considerations During Pregnancy

Pregnant women should be screened for syphilis at the first prenatal visit. In communities and populations in which the prevalence of syphilis is high and in women at high risk of infection, serologic testing should also be performed twice in the third trimester (ideally at 28–32 weeks gestation) and at delivery.<sup>19</sup> Syphilis screening also should be offered at sites providing episodic care to pregnant women at high risk, including emergency departments, jails, and prisons.<sup>92</sup> Antepartum screening with non-treponemal testing is typical but treponemal screening is being used in some settings. Pregnant women with reactive treponemal screening tests should have additional quantitative testing with non-treponemal tests because titers are essential for monitoring treatment response. If a treponemal EIA or CIA test is used for antepartum syphilis screening, all positive EIA/CIA tests should be confirmed with a quantitative, non-treponemal test (RPR or VDRL). If the non-treponemal test is negative and the prozone reaction is ruled out, then the results are discordant; a second treponemal test should be performed, preferably on the same specimen (see Diagnosis section above).<sup>93</sup>

No mother or neonate should leave the hospital without documentation of maternal syphilis serologic status determined at least once during pregnancy.<sup>94</sup> All women who have a fetal death after 20 weeks of gestation also should be tested for syphilis.

Rates of transmission to the fetus and adverse pregnancy outcomes for untreated syphilis are highest with primary, secondary, and early-latent syphilis and decrease with increasing duration of infection. Pregnancy does not appear to alter the clinical course, manifestations, or diagnostic test results for syphilis infection in adults. Concurrent syphilis infection has been associated with increased risk of perinatal transmission of HIV to the infant.<sup>95-100</sup>

Pregnant women with reactive syphilis serology should be considered infected unless an adequate treatment history is documented clearly in the medical records and sequential serologic antibody titers have declined appropriately for the stage of syphilis. In general, the risk of antepartum fetal infection or congenital syphilis at delivery is related to the quantitative maternal nontreponemal titer, especially if it  $\geq 1:8$ . Serofast low antibody titers after documented treatment for the stage of infection might not require additional treatment; however, rising or persistently high antibody titers may indicate reinfection or treatment failure, and treatment should be considered.<sup>19</sup>

Penicillin is recommended for the treatment of syphilis during pregnancy. Penicillin is the only known

effective antimicrobial for preventing maternal transmission to the fetus and for treatment of fetal infection; however evidence is insufficient to determine the optimal penicillin regimen.<sup>101</sup> There is some evidence to suggest that additional therapy (a second dose of benzathine penicillin G, 2.4 million U IM administered 1 week after the initial dose) may be considered for pregnant women with early syphilis (primary, secondary, and early-latent syphilis) **(BII)**.<sup>19,102,103</sup> Because of concerns about the efficacy of standard therapy in pregnant women who have HIV infection, a second injection in 1 week should also be considered for pregnant women with HIV infection **(BIII)**.

Since no alternatives to penicillin have been proven effective and safe for prevention of fetal infection, pregnant women who have a history of penicillin allergy should undergo desensitization and treatment with penicillin **(AIII)**.<sup>19</sup> Erythromycin and azithromycin do not reliably cure maternal or fetal infection **(AII)**; tetracyclines should not be used during pregnancy because of concerns about hepatotoxicity and staining of fetal bones and teeth **(AII)**.<sup>98,104</sup> Data are insufficient on use of ceftriaxone<sup>105</sup> for treatment of maternal infection and prevention of congenital syphilis **(BIII)**.

Treatment of syphilis during the second half of pregnancy may precipitate preterm labor or fetal distress if it is associated with a Jarisch-Herxheimer reaction.<sup>106</sup> Pregnant women should be advised to seek obstetric attention after treatment if they notice contractions or a decrease in fetal movement. During the second half of pregnancy, syphilis management can be facilitated with sonographic fetal evaluation for congenital syphilis, but this evaluation should not delay therapy. Sonographic signs of fetal or placental syphilis indicate a greater risk of fetal treatment failure.<sup>107</sup> Such cases should be managed in consultation with high-risk obstetric specialists. After 20 weeks of gestation, fetal and contraction monitoring for 24 hours after initiation of treatment for early syphilis should be considered when sonographic findings indicate fetal infection.

At a minimum, repeat serologic titers should be performed in the third trimester and at delivery for women treated for syphilis during pregnancy, appropriate for the stage of infection. Data are insufficient on the non-treponemal serologic response to syphilis after stage-appropriate therapy in pregnant women with HIV infection. Non-treponemal titers can be assessed monthly in women at high risk of re-infection. Clinical and non-treponemal antibody titer responses should be appropriate for the stage of disease, although most women will deliver before their serologic response can be definitively assessed. Maternal treatment is likely to be inadequate if delivery occurs within 30 days of therapy, if a woman has clinical signs of infection at delivery, or if the maternal antibody titer is four-fold higher than the pre-treatment titer.<sup>19</sup> The medical provider caring for the newborn should be informed of the mother's serologic and treatment status so that proper evaluation and treatment of the infant can be provided.

### **Recommendations for Treating *Treponema pallidum* Infections (Syphilis) to Prevent Disease** (page 1 of 2)

Empiric treatment of incubating syphilis is recommended to prevent the development of disease in those who are sexually exposed.

#### **Indication for Treatment:**

- Persons who have had sexual contact with a person who receives a diagnosis of primary, secondary, or early latent syphilis within 90 days preceding the diagnosis should be treated presumptively for early syphilis, even if serologic test results are negative **(AIII)**.
- Persons who have had sexual contact with a person who receives a diagnosis of primary, secondary, or early latent syphilis >90 days before the diagnosis should be treated presumptively for early syphilis if serologic test results are not immediately available and the opportunity for follow-up is uncertain **(AIII)**.

#### **Treatment:**

- Same as for early stage syphilis listed below

#### **General Considerations for Treating Syphilis:**

- The efficacy of non-penicillin alternatives has not been well evaluated in persons with HIV infection and should be undertaken only with close clinical and serologic monitoring.
- The Jarisch-Herxheimer reaction is an acute febrile reaction accompanied by headache and myalgias that can occur within the first 24 hours after therapy. It occurs more frequently in persons with early syphilis, high non-treponemal antibody titers, and prior penicillin treatment. Patients should be warned about this reaction and informed it is not an allergic reaction to penicillin.

### Treatment Recommendations Depending on Stage of Disease

#### Early Stage (Primary, Secondary, and Early-Latent Syphilis)

*Preferred Therapy:*

- Benzathine penicillin G 2.4 million U IM for 1 dose (**All**)

*Alternative Therapy (For Penicillin-Allergic Patients):*

- Doxycycline 100 mg PO BID for 14 days (**BII**), *or*
- Ceftriaxone 1 g IM or IV daily for 10–14 days (**BII**), *or*
- Azithromycin 2 g PO for 1 dose (**BII**)

**Note:** Chromosomal mutations associated with azithromycin resistance and treatment failures have been reported, most commonly in MSM. Azithromycin should be used with caution and only when treatment with penicillin, doxycycline or ceftriaxone is not feasible. Azithromycin **is not recommended** for MSM or pregnant women (**All**)

**Note:** Persons with penicillin allergy whose compliance or follow-up cannot be ensured and all pregnant women with penicillin allergy should be desensitized and treated with benzathine penicillin.

For pregnant women with early syphilis, a second dose of benzathine penicillin G 2.4 million units IM after one week the single dose treatment may be considered (**BII**).

#### Late-Latent (>1 year) or Latent of Unknown Duration

*Preferred Therapy:*

- Benzathine penicillin G 2.4 million U IM weekly for 3 doses (**All**)

*Alternative Therapy (For Penicillin-Allergic Patients):*

- Doxycycline 100 mg PO BID for 28 days (**BIII**)

**Note:** Persons with penicillin allergy whose compliance or follow-up cannot be ensured should be desensitized and treated with benzathine penicillin

#### Late-Stage (Tertiary—Cardiovascular or Gummatous Disease)

- Perform CSF examination to rule out neurosyphilis and obtain infectious diseases consultation to guide management

*Preferred Therapy:*

- Benzathine penicillin G 2.4 million U IM weekly for 3 doses (**All**)

#### Neurosyphilis, Otic, or Ocular Disease

*Preferred Therapy:*

- Aqueous crystalline penicillin G, 18–24 million U per day, administered as 3–4 million U IV q4h or by continuous IV infusion for 10–14 days (**All**) +/- benzathine penicillin G 2.4 million U IM weekly for 1 to 3 doses after completion of IV therapy (**CIII**)

*Alternative Therapy:*

- Procaine penicillin G 2.4 million U IM daily plus probenecid 500 mg PO QID for 10–14 days (**BII**) +/- benzathine penicillin G 2.4 million U IM weekly for up to 3 doses after completion of above (**CIII**)
- Persons who are allergic to sulfa-containing medications **should not** be given probenecid, thus the procaine penicillin regimen is not recommended (**AIII**).

*For Penicillin-Allergic Patients:*

- Desensitization to penicillin is the preferred approach; if not feasible, ceftriaxone 2 g IM or IV daily for 10–14 days (**BII**)

**Key to Acronyms:** BID = twice a day; CSF = cerebrospinal fluid; IM = intramuscular; IV = intravenously; MSM = men who have sex with men; PO = orally; QID = four times a day; q(n)h = every “n” hours; U = Units

## References

1. Fleming DT, Wasserheit JN. From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. *Sex Transm Infect*. Feb 1999;75(1):3-17. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10448335>.
2. Rottingen JA, Cameron DW, Garnett GP. A systematic review of the epidemiologic interactions between classic sexually transmitted diseases and HIV: how much really is known? *Sex Transm Dis*. Oct 2001;28(10):579-597. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11689757>.
3. Peterman TA, Newman DR, Maddox L, Schmitt K, Shiver S. High risk for HIV following syphilis diagnosis among men in Florida, 2000-2011. *Public Health Rep*. Mar-Apr 2014;129(2):164-169. Available at <http://www.ncbi.nlm.nih.gov/pubmed/24587551>.
4. Solomon MM, Mayer KH, Glidden DV, et al. Syphilis predicts HIV incidence among men and transgender women who have sex with men in a preexposure prophylaxis trial. *Clin Infect Dis*. Oct 2014;59(7):1020-1026. Available at <http://www.ncbi.nlm.nih.gov/pubmed/24928295>.
5. Patton ME, Su JR, Nelson R, Weinstock H, Centers for Disease C, Prevention. Primary and secondary syphilis—United States, 2005–2013. *MMWR Morb Mortal Wkly Rep*. May 9 2014;63(18):402-406. Available at <http://www.ncbi.nlm.nih.gov/pubmed/24807239>.
6. Chesson HW, Sternberg M, Leichliter JS, Aral SO. Changes in the state-level distribution of primary and secondary syphilis in the USA, 1985–2007. *Sex Transm Infect*. Dec 2010;86 Suppl 3:iii58-62. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20929854>.
7. Torrone EA, Bertolli J, Li J, et al. Increased HIV and primary and secondary syphilis diagnoses among young men—United States, 2004–2008. *J Acquir Immune Defic Syndr*. Nov 1 2011;58(3):328-335. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21826012>.
8. Kerani RP, Handsfield HH, Stenger MS, et al. Rising rates of syphilis in the era of syphilis elimination. *Sex Transm Dis*. Mar 2007;34(3):154-161. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17179773>.
9. Buchacz K, Klausner JD, Kerndt PR, et al. HIV incidence among men diagnosed with early syphilis in Atlanta, San Francisco, and Los Angeles, 2004 to 2005. *J Acquir Immune Defic Syndr*. Feb 1 2008;47(2):234-240. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18340654>.
10. Cohen SE, Chew Ng RA, Katz KA, et al. Repeat syphilis among men who have sex with men in California, 2002-2006: implications for syphilis elimination efforts. *Am J Public Health*. Jan 2012;102(1):e1-8. Available at <http://www.ncbi.nlm.nih.gov/pubmed/22095364>.
11. Centers for Disease Control and Prevention. 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*. Aug 16 2013;62(32):649-650. Available at <http://www.ncbi.nlm.nih.gov/pubmed/23945772>.
12. Centers for Disease Control and Prevention. 2012 Sexually Transmitted Disease Surveillance. 2013. Available at <http://www.cdc.gov/std/stats12/>. Accessed January 7, 2015.
13. Centers for Disease Control and Prevention. Outbreak of syphilis among men who have sex with men—Southern California, 2000. *MMWR Morb Mortal Wkly Rep*. Feb 23 2001;50(7):117-120. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11393490>.
14. Calza L, Manfredi R, Marinacci G, Tadolini M, Fortunato L, Chiodo F. Efficacy of penicillin G benzathine as antimicrobial treatment of cutaneous secondary syphilis in patients with HIV infection. *J Chemother*. Oct 2002;14(5):533-534. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12462435>.
15. Rompalo AM, Lawlor J, Seaman P, Quinn TC, Zenilman JM, Hook EW, 3rd. Modification of syphilitic genital ulcer manifestations by coexistent HIV infection. *Sex Transm Dis*. Aug 2001;28(8):448-454. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11473216>.
16. Musher DM, Hamill RJ, Baughn RE. Effect of human immunodeficiency virus (HIV) infection on the course of syphilis and on the response to treatment. *Ann Intern Med*. Dec 1 1990;113(11):872-881. Available at <http://www.ncbi.nlm.nih.gov/pubmed/2240901>.
17. Radolf JD, Kaplan RP. Unusual manifestations of secondary syphilis and abnormal humoral immune response to *Treponema pallidum* antigens in a homosexual man with asymptomatic human immunodeficiency virus infection. *J Am Acad Dermatol*. Feb 1988;18(2 Pt 2):423-428. Available at <http://www.ncbi.nlm.nih.gov/pubmed/2963840>.

18. Ghanem KG, Workowski KA. Management of adult syphilis. *Clin Infect Dis*. Dec 2011;53 Suppl 3:S110-128. Available at <http://www.ncbi.nlm.nih.gov/pubmed/22080265>.
19. Workowski KA, Bolan GA, with the Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep*. Jun 5 2015;64(RR-03):1-137. Available at <http://www.ncbi.nlm.nih.gov/pubmed/26042815>.
20. Ghanem KG, Moore RD, Rompalo AM, Erbelding EJ, Zenilman JM, Gebo KA. Neurosyphilis in a clinical cohort of HIV-1-infected patients. *AIDS*. Jun 19 2008;22(10):1145-1151. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18525260>.
21. Centers for Disease Control and Prevention. Symptomatic early neurosyphilis among HIV-positive men who have sex with men—four cities, United States, January 2002–June 2004. *MMWR Morb Mortal Wkly Rep*. Jun 29 2007;56(25):625-628. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17597693>.
22. Buchacz K, Patel P, Taylor M, et al. Syphilis increases HIV viral load and decreases CD4 cell counts in HIV-infected patients with new syphilis infections. *AIDS*. Oct 21 2004;18(15):2075-2079. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15577629>.
23. Modjarrad K, Vermund SH. Effect of treating co-infections on HIV-1 viral load: a systematic review. *Lancet Infect Dis*. Jul 2010;10(7):455-463. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20610327>.
24. Palacios R, Jimenez-Onate F, Aguilar M, et al. Impact of syphilis infection on HIV viral load and CD4 cell counts in HIV-infected patients. *J Acquir Immune Defic Syndr*. Mar 1 2007;44(3):356-359. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17159654>.
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*. Mar 2006;33(3):143-148. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16505739>.
26. Rompalo AM, Joesoef MR, O'Donnell JA, et al. Clinical manifestations of early syphilis by HIV status and gender: results of the syphilis and HIV study. *Sex Transm Dis*. Mar 2001;28(3):158-165. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11289198>.
27. Wang H, Wang X, Li S. A case of lues maligna in an AIDS patient. *Int J STD AIDS*. Aug 2012;23(8):599-600. Available at <http://www.ncbi.nlm.nih.gov/pubmed/22930302>.
28. Tucker JD, Shah S, Jarell AD, Tsai KY, Zembowicz A, Kroshinsky D. Lues maligna in early HIV infection case report and review of the literature. *Sex Transm Dis*. Aug 2009;36(8):512-514. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19455078>.
29. Bayne LL, Schmidley JW, Goodin DS. Acute syphilitic meningitis. Its occurrence after clinical and serologic cure of secondary syphilis with penicillin G. *Arch Neurol*. Feb 1986;43(2):137-138. Available at <http://www.ncbi.nlm.nih.gov/pubmed/3947251>.
30. 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*. Jun 18 1987;316(25):1587-1589. Available at <http://www.ncbi.nlm.nih.gov/pubmed/3587291>.
31. Marra CM, Maxwell CL, Smith SL, et al. Cerebrospinal fluid abnormalities in patients with syphilis: association with clinical and laboratory features. *J Infect Dis*. Feb 1 2004;189(3):369-376. Available at <http://www.ncbi.nlm.nih.gov/pubmed/14745693>.
32. Marra CM, Maxwell CL, Tantalos L, et al. Normalization of cerebrospinal fluid abnormalities after neurosyphilis therapy: does HIV status matter? *Clin Infect Dis*. Apr 1 2004;38(7):1001-1006. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15034833>.
33. Biotti D, Bidot S, Mahy S, et al. Ocular syphilis and HIV infection. *Sex Transm Dis*. Jan 2010;37(1):41-43. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20118676>.
34. Tucker JD, Li JZ, Robbins GK, et al. Ocular syphilis among HIV-infected patients: a systematic analysis of the literature. *Sex Transm Infect*. Feb 2011;87(1):4-8. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20798396>.
35. Woolston S, Cohen SE, Fanfair RN, Lewis SC, Marra CM, Golden MR. A Cluster of Ocular Syphilis Cases—Seattle, Washington, and San Francisco, California, 2014–2015. *MMWR Morb Mortal Wkly Rep*. 2015;64(40):1150-1151. Available at <http://www.ncbi.nlm.nih.gov/pubmed/26469141>.
36. Wicher K, Horowitz HW, Wicher V. Laboratory methods of diagnosis of syphilis for the beginning of the third millennium. *Microbes Infect*. Oct 1999;1(12):1035-1049. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10617935>.

37. Centers for Disease C, Prevention. Discordant results from reverse sequence syphilis screening--five laboratories, United States, 2006-2010. *MMWR Morb Mortal Wkly Rep.* Feb 11 2011;60(5):133-137. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21307823>.
38. Centers for Disease C, Prevention. Syphilis testing algorithms using treponemal tests for initial screening--four laboratories, New York City, 2005-2006. *MMWR Morb Mortal Wkly Rep.* Aug 15 2008;57(32):872-875. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18701877>.
39. Park IU, Chow JM, Bolan G, Stanley M, Shieh J, Schapiro JM. Screening for syphilis with the treponemal immunoassay: analysis of discordant serology results and implications for clinical management. *J Infect Dis.* Nov 2011;204(9):1297-1304. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21930610>.
40. Wong EH, Klausner JD, Caguin-Grygiel G, et al. Evaluation of an IgM/IgG sensitive enzyme immunoassay and the utility of index values for the screening of syphilis infection in a high-risk population. *Sex Transm Dis.* Jun 2011;38(6):528-532. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21233789>.
41. Wohrl S, Geusau A. Neurosyphilis is unlikely in patients with late latent syphilis and a negative blood VDRL-test. *Acta Derm Venereol.* 2006;86(4):335-339. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16874420>.
42. Rompalo AM, Cannon RO, Quinn TC, Hook EW, 3rd. Association of biologic false-positive reactions for syphilis with human immunodeficiency virus infection. *J Infect Dis.* Jun 1992;165(6):1124-1126. Available at <http://www.ncbi.nlm.nih.gov/pubmed/1583332>.
43. Rolfs RT, Joesoef MR, Hendershot EF, et al. A randomized trial of enhanced therapy for early syphilis in patients with and without human immunodeficiency virus infection. The Syphilis and HIV Study Group. *N Engl J Med.* Jul 31 1997;337(5):307-314. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9235493>.
44. Augenbraun MH, DeHovitz JA, Feldman J, Clarke L, Landesman S, Minkoff HM. Biological false-positive syphilis test results for women infected with human immunodeficiency virus. *Clin Infect Dis.* Dec 1994;19(6):1040-1044. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7888531>.
45. Hicks CB, Benson PM, Lupton GP, Tramont EC. Seronegative secondary syphilis in a patient infected with the human immunodeficiency virus (HIV) with Kaposi sarcoma. A diagnostic dilemma. *Ann Intern Med.* Oct 1987;107(4):492-495. Available at <http://www.ncbi.nlm.nih.gov/pubmed/3307583>.
46. Kingston AA, Vujevich J, Shapiro M, et al. Seronegative secondary syphilis in 2 patients coinfecting with human immunodeficiency virus. *Arch Dermatol.* Apr 2005;141(4):431-433. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15837859>.
47. Augenbraun M, Rolfs R, Johnson R, Joesoef R, Pope V. Treponemal specific tests for the serodiagnosis of syphilis. Syphilis and HIV Study Group. *Sex Transm Dis.* Nov 1998;25(10):549-552. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9858352>.
48. Lukehart SA, Hook EW, 3rd, Baker-Zander SA, Collier AC, Critchlow CW, Handsfield HH. Invasion of the central nervous system by *Treponema pallidum*: implications for diagnosis and treatment. *Ann Intern Med.* Dec 1 1988;109(11):855-862. Available at <http://www.ncbi.nlm.nih.gov/pubmed/3056164>.
49. Libois A, De Wit S, Poll B, et al. HIV and syphilis: when to perform a lumbar puncture. *Sex Transm Dis.* Mar 2007;34(3):141-144. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16865051>.
50. Ghanem KG. Sensitivity and specificity of lumbar puncture in HIV-infected patients with syphilis and no neurologic symptoms reply. *Clin Infect Dis.* 2009;49:162-163.
51. Jaffe HW, Larsen SA, Peters M, Jove DF, Lopez B, Schroeter AL. Tests for treponemal antibody in CSF. *Arch Intern Med.* Feb 1978;138(2):252-255. Available at <http://www.ncbi.nlm.nih.gov/pubmed/343742>.
52. Harding AS, Ghanem KG. The performance of cerebrospinal fluid treponemal-specific antibody tests in neurosyphilis: a systematic review. *Sex Transm Dis.* Apr 2012;39(4):291-297. Available at <http://www.ncbi.nlm.nih.gov/pubmed/22421696>.
53. Marra CM, Tantalo LC, Maxwell CL, Ho EL, Sahi SK, Jones T. The rapid plasma reagin test cannot replace the venereal disease research laboratory test for neurosyphilis diagnosis. *Sex Transm Dis.* Jun 2012;39(6):453-457. Available at <http://www.ncbi.nlm.nih.gov/pubmed/22592831>.
54. Rietmeijer CA. Risk reduction counselling for prevention of sexually transmitted infections: how it works and how to make it work. *Sex Transm Infect.* Feb 2007;83(1):2-9. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17283359>.
55. Force USPST. Behavioral counseling to prevent sexually transmitted infections: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med.* Oct 7 2008;149(7):491-496, W495. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18701877>.

<http://www.ncbi.nlm.nih.gov/pubmed/18838729>.

56. Kamb ML, Fishbein M, Douglas JM, Jr., et al. Efficacy of risk-reduction counseling to prevent human immunodeficiency virus and sexually transmitted diseases: a randomized controlled trial. Project RESPECT Study Group. *JAMA*. Oct 7 1998;280(13):1161-1167. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9777816>.
57. Richardson JL, Milam J, Stoyanoff S, et al. Using patient risk indicators to plan prevention strategies in the clinical care setting. *J Acquir Immune Defic Syndr*. Oct 1 2004;37 Suppl 2:S88-94. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15385904>.
58. Fisher JD, Cornman DH, Osborn CY, Amico KR, Fisher WA, Friedland GA. Clinician-initiated HIV risk reduction intervention for HIV-positive persons: Formative Research, Acceptability, and Fidelity of the Options Project. *J Acquir Immune Defic Syndr*. Oct 1 2004;37 Suppl 2:S78-87. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15385903>.
59. Branger J, van der Meer JT, van Ketel RJ, Jurriaans S, Prins JM. High incidence of asymptomatic syphilis in HIV-infected MSM justifies routine screening. *Sex Transm Dis*. Feb 2009;36(2):84-85. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18971797>.
60. Aberg JA, Gallant JE, Ghanem KG, et al. Primary care guidelines for the management of persons infected with HIV: 2013 update by the HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis*. Jan 2014;58(1):1-10. Available at <http://www.ncbi.nlm.nih.gov/pubmed/24343580>.
61. Centers for Disease C, Prevention, Health R, et al. Recommendations for incorporating human immunodeficiency virus (HIV) prevention into the medical care of persons living with HIV. *Clin Infect Dis*. Jan 1 2004;38(1):104-121. Available at <http://www.ncbi.nlm.nih.gov/pubmed/14679456>.
62. Guy R, El-Hayek C, Fairley CK, et al. Opt-out and opt-in testing increases syphilis screening of HIV-positive men who have sex with men in Australia. *PLoS One*. 2013;8(8):e71436. Available at <http://www.ncbi.nlm.nih.gov/pubmed/24009661>.
63. Centers for Disease C, Prevention. Recommendations for partner services programs for HIV infection, syphilis, gonorrhea, and chlamydial infection. *MMWR Recomm Rep*. Nov 7 2008;57(RR-9):1-83; quiz CE81-84. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18987617>.
64. Moore MB, Jr., Price EV, Knox JM, Elgin LW. Epidemiologic Treatment of Contacts to Infectious Syphilis. *Public Health Rep*. Nov 1963;78:966-970. Available at <http://www.ncbi.nlm.nih.gov/pubmed/14084872>.
65. Schroeter AL, Turner RH, Lucas JB, Brown WJ. Therapy for incubating syphilis. Effectiveness of gonorrhea treatment. *JAMA*. Nov 1 1971;218(5):711-713. Available at <http://www.ncbi.nlm.nih.gov/pubmed/5171497>.
66. Schober PC, Gabriel G, White P, Felton WF, Thin RN. How infectious is syphilis? *Br J Vener Dis*. Aug 1983;59(4):217-219. Available at <http://www.ncbi.nlm.nih.gov/pubmed/6871650>.
67. Hook EW, 3rd, Marra CM. Acquired syphilis in adults. *N Engl J Med*. Apr 16 1992;326(16):1060-1069. Available at <http://www.ncbi.nlm.nih.gov/pubmed/1549153>.
68. Malone JL, Wallace MR, Hendrick BB, et al. Syphilis and neurosyphilis in a human immunodeficiency virus type-1 seropositive population: evidence for frequent serologic relapse after therapy. *Am J Med*. Jul 1995;99(1):55-63. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7598143>.
69. Walter T, Lebouche B, Mialhes P, et al. Symptomatic relapse of neurologic syphilis after benzathine penicillin G therapy for primary or secondary syphilis in HIV-infected patients. *Clin Infect Dis*. Sep 15 2006;43(6):787-790. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16912958>.
70. Ghanem KG, Erbeling EJ, Cheng WW, Rompalo AM. Doxycycline compared with benzathine penicillin for the treatment of early syphilis. *Clin Infect Dis*. Mar 15 2006;42(6):e45-49. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16477545>.
71. Wong T, Singh AE, De P. Primary syphilis: serological treatment response to doxycycline/tetracycline versus benzathine penicillin. *Am J Med*. Oct 2008;121(10):903-908. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18823862>.
72. Hook EW, 3rd, Roddy RE, Handsfield HH. Ceftriaxone therapy for incubating and early syphilis. *J Infect Dis*. Oct 1988;158(4):881-884. Available at <http://www.ncbi.nlm.nih.gov/pubmed/3171231>.
73. Kiddugavu MG, Kiwanuka N, Wawer MJ, et al. Effectiveness of syphilis treatment using azithromycin and/or benzathine penicillin in Rakai, Uganda. *Sex Transm Dis*. Jan 2005;32(1):1-6. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15614114>.
74. Riedner G, Rusizoka M, Todd J, et al. Single-dose azithromycin versus penicillin G benzathine for the treatment of early syphilis. *N Engl J Med*. Sep 22 2005;353(12):1236-1244. Available at <http://www.ncbi.nlm.nih.gov/>

[pubmed/16177249](http://pubmed/16177249).

75. Hook EW, 3rd, Behets F, Van Damme K, et al. A phase III equivalence trial of azithromycin versus benzathine penicillin for treatment of early syphilis. *J Infect Dis*. Jun 1 2010;201(11):1729-1735. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20402591>.
76. Centers for Disease C, Prevention. Azithromycin treatment failures in syphilis infections--San Francisco, California, 2002-2003. *MMWR Morb Mortal Wkly Rep*. Mar 12 2004;53(9):197-198. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15017376>.
77. Lukehart SA, Godornes C, Molini BJ, et al. Macrolide resistance in *Treponema pallidum* in the United States and Ireland. *N Engl J Med*. Jul 8 2004;351(2):154-158. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15247355>.
78. Mitchell SJ, Engelman J, Kent CK, Lukehart SA, Godornes C, Klausner JD. Azithromycin-resistant syphilis infection: San Francisco, California, 2000-2004. *Clin Infect Dis*. Feb 1 2006;42(3):337-345. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16392078>.
79. Martin IE, Tsang RS, Sutherland K, et al. Molecular characterization of syphilis in patients in Canada: azithromycin resistance and detection of *Treponema pallidum* DNA in whole-blood samples versus ulcerative swabs. *J Clin Microbiol*. Jun 2009;47(6):1668-1673. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19339468>.
80. Wu H, Chang SY, Lee NY, et al. Evaluation of macrolide resistance and enhanced molecular typing of *Treponema pallidum* in patients with syphilis in Taiwan: a prospective multicenter study. *J Clin Microbiol*. Jul 2012;50(7):2299-2304. Available at <http://www.ncbi.nlm.nih.gov/pubmed/22518868>.
81. Chen CY, Chi KH, Pillay A, Nachamkin E, Su JR, Ballard RC. Detection of the A2058G and A2059G 23S rRNA Gene Point Mutations Associated with Azithromycin Resistance in *Treponema pallidum* by Use of a TaqMan Real-Time Multiplex PCR Assay. *J Clin Microbiol*. Mar 2013;51(3):908-913. Available at <http://www.ncbi.nlm.nih.gov/pubmed/23284026>.
82. Dowell ME, Ross PG, Musher DM, Cate TR, Baughn RE. Response of latent syphilis or neurosyphilis to ceftriaxone therapy in persons infected with human immunodeficiency virus. *Am J Med*. Nov 1992;93(5):481-488. Available at <http://www.ncbi.nlm.nih.gov/pubmed/1442850>.
83. Smith NH, Musher DM, Huang DB, et al. Response of HIV-infected patients with asymptomatic syphilis to intensive intramuscular therapy with ceftriaxone or procaine penicillin. *Int J STD AIDS*. May 2004;15(5):328-332. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15117503>.
84. Bernal E, Munoz A, Ortiz Mdel M, Cano A. Syphilitic panuveitis in an HIV-infected patient after immune restoration. *Enferm Infecc Microbiol Clin*. Oct 2009;27(8):487-489. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19406524>.
85. Long CM, Klausner JD, Leon S, et al. Syphilis treatment and HIV infection in a population based study of persons at high risk for sexually transmitted disease/HIV infection in Lima, Peru. *Sex Transm Dis*. 33:151-55. 2006.
86. Sena AC, Wolff M, Martin DH, et al. Predictors of serological cure and Serofast State after treatment in HIV-negative persons with early syphilis. *Clin Infect Dis*. Dec 2011;53(11):1092-1099. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21998287>.
87. 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. Available at <http://www.ncbi.nlm.nih.gov/pubmed/24369955>.
88. Marra CM, Maxwell CL, Tantalos 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*. Oct 1 2008;47(7):893-899. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18715154>.
89. Yang CJ, Lee NY, Lin YH, et al. Jarisch-Herxheimer reaction after penicillin therapy among patients with syphilis in the era of the hiv infection epidemic: incidence and risk factors. *Clin Infect Dis*. Oct 15 2010;51(8):976-979. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20825309>.
90. Rekart ML, Patrick DM, Chakraborty B, et al. Targeted mass treatment for syphilis with oral azithromycin. *Lancet*. Jan 25 2003;361(9354):313-314. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12559870>.
91. 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*. Feb 2015;42(2):98-103. Available at <http://www.ncbi.nlm.nih.gov/pubmed/25585069>.

92. Wolff T, Shelton E, Sessions C, Miller T. Screening for syphilis infection in pregnant women: evidence for the U.S. Preventive Services Task Force reaffirmation recommendation statement. *Ann Intern Med.* May 19 2009;150(10):710-716. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19451578>.
93. Mmeje O, Chow JM, Davidson L, Shieh J, Schapiro JM, Park IU. Discordant Syphilis Immunoassays in Pregnancy: Perinatal Outcomes and Implications for Clinical Management. *Clin Infect Dis.* Oct 1 2015;61(7):1049-1053. Available at <http://www.ncbi.nlm.nih.gov/pubmed/26063719>.
94. Genc M, Ledger WJ. Syphilis in pregnancy. *Sex Transm Infect.* Apr 2000;76(2):73-79. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10858706>.
95. Berman SM. Maternal syphilis: pathophysiology and treatment. *Bull World Health Organ.* Jun 2004;82(6):433-438. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15356936>.
96. Tess BH, Rodrigues LC, Newell ML, Dunn DT, Lago TD. Breastfeeding, genetic, obstetric and other risk factors associated with mother-to-child transmission of HIV-1 in Sao Paulo State, Brazil. Sao Paulo Collaborative Study for Vertical Transmission of HIV-1. *AIDS.* Mar 26 1998;12(5):513-520. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9543450>.
97. Lee MJ, Hallmark RJ, Frenkel LM, Del Priore G. Maternal syphilis and vertical perinatal transmission of human immunodeficiency virus type-1 infection. *Int J Gynaecol Obstet.* Dec 1998;63(3):247-252. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9989893>.
98. Wendel GD, Jr., Sheffield JS, Hollier LM, Hill JB, Ramsey PS, Sanchez PJ. Treatment of syphilis in pregnancy and prevention of congenital syphilis. *Clin Infect Dis.* Oct 15 2002;35(Suppl 2):S200-209. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12353207>.
99. Kreitchmann R, Fuchs SC, Suffert T, Preussler G. Perinatal HIV-1 transmission among low income women participants in the HIV/AIDS Control Program in Southern Brazil: a cohort study. *BJOG.* Jun 2004;111(6):579-584. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15198786>.
100. Mwapasa V, Rogerson SJ, Kwiek JJ, et al. Maternal syphilis infection is associated with increased risk of mother-to-child transmission of HIV in Malawi. *AIDS.* Sep 11 2006;20(14):1869-1877. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16954728>.
101. Walker GJ. Antibiotics for syphilis diagnosed during pregnancy. *Cochrane Database Syst Rev.* 2001(3):CD001143. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11686978>.
102. Donders GG, Desmyter J, Hooft P, Dewet GH. Apparent failure of one injection of benzathine penicillin G for syphilis during pregnancy in human immunodeficiency virus-seronegative African women. *Sex Transm Dis.* Feb 1997;24(2):94-101. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9111755>.
103. Sheffield JS, Sanchez PJ, Morris G, et al. Congenital syphilis after maternal treatment for syphilis during pregnancy. *Am J Obstet Gynecol.* Mar 2002;186(3):569-573. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11904625>.
104. Ramsey PS, Vaules MB, Vasdev GM, Andrews WW, Ramin KD. Maternal and transplacental pharmacokinetics of azithromycin. *Am J Obstet Gynecol.* Mar 2003;188(3):714-718. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12634646>.
105. Zhou P, Gu Z, Xu J, Wang X, Liao K. A study evaluating ceftriaxone as a treatment agent for primary and secondary syphilis in pregnancy. *Sex Transm Dis.* Aug 2005;32(8):495-498. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16041252>.
106. Klein VR, Cox SM, Mitchell MD, Wendel GD, Jr. The Jarisch-Herxheimer reaction complicating syphilotherapy in pregnancy. *Obstet Gynecol.* Mar 1990;75(3 Pt 1):375-380. Available at <http://www.ncbi.nlm.nih.gov/pubmed/2304710>.
107. Hollier LM, Harstad TW, Sanchez PJ, Twickler DM, Wendel GD, Jr. Fetal syphilis: clinical and laboratory characteristics. *Obstet Gynecol.* Jun 2001;97(6):947-953. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11384701>.