Guidelines for the Prevention and Treatment of Opportunistic Infections Among HIV-Exposed and HIV-Infected Children

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Syphilis (Last updated November 6, 2013; last reviewed November 6, 2013)

Panel's Recommendations

Congenital Syphilis

- Infants should be evaluated and treated per guidelines for congenital syphilis, given the following maternal factors:
  - Untreated or inadequately treated syphilis (including treatment with erythromycin or any other non-penicillin regimen)
  - Lack of documentation of having received treatment,
  - Receipt of treatment <30 days before delivery,
  - Treatment with penicillin but maternal nontreponemal antibody titer at delivery is fourfold higher than the pretreatment titer, or
  - Fourfold or greater increase in nontreponemal antibody titer suggesting relapse or reinfection **(AII)**.
- **Note:** For comprehensive discussion and recommendations, see Centers for Disease Control and Prevention Sexually Transmitted Disease Treatment Guidelines, 2010.
- Treatment for proven or highly probable congenital syphilis is aqueous crystalline penicillin G for 10 days **(AII)**.
- If congenital syphilis is diagnosed after age 1 month, the dosage of aqueous crystalline penicillin G should be increased per treatment guidelines **(AII)**.
- An alternative to aqueous crystalline penicillin G is procaine penicillin G for 10 days **(BII)**.
- All seroreactive infants (or infants whose mothers were seroreactive at delivery) should receive careful follow-up examinations and serologic testing (a nontreponemal test) every 2 to 3 months until the test becomes nonreactive or the titer has decreased fourfold **(AIII)**. Infants whose initial cerebrospinal fluid (CSF) evaluations are abnormal should undergo repeat lumbar puncture approximately every 6 months until the results are normal **(AII)**.
- After treatment of congenital syphilis, children with increasing or stable nontreponemal titers at ages 6 to 12 months should be evaluated (i.e., including a CSF examination) and treated with a 10-day course of parenteral penicillin **(AIII)**.
- Infants in whom the nontreponemal test is reactive at age 18 months should be fully evaluated or re-evaluated (physical, serological, CSF, radiographic exams) and treated or re-treated for congenital syphilis **(AIII)**.

Sexually-Acquired Syphilis

Early Syphilis

- Acquired syphilis in children and adolescents is treated with a single dose of benzathine penicillin G for early-stage disease (i.e., primary, secondary, and early latent disease) **(AII)**.
- HIV-infected children and adolescents with early syphilis (i.e., primary, secondary, early latent) should receive a single dose of benzathine penicillin G. Those with primary and secondary syphilis should have clinical and serologic response monitored at 3, 6, 9, 12, and 24 months after therapy, and those with early latent syphilis should have clinical and serologic response monitored at 6, 12, 18, and 24 months after therapy **(AIII)**. (For comprehensive discussion and recommendations, see the Centers for Disease Control and Prevention STD Treatment Guidelines, 2010).
- Re-treatment of patients with early-stage syphilis (i.e., primary, secondary, early latent) and evaluation for HIV infection is recommended for those who:
  - Do not experience at least a fourfold decrease in serum nontreponemal test titers 6 to 12 months after therapy,
  - Have a sustained fourfold increase in serum nontreponemal test titers after an initial reduction post-treatment, or
  - Have persistent or recurring clinical signs or symptoms of disease.
- Individuals whose titers do not decline should at a minimum receive additional clinical and serologic follow-up. If such additional follow-up cannot be ensured, re-treatment is recommended. Because occult central nervous system infection may be signaled by persistently elevated serum nontreponemal test titers, evaluation of CSF can be considered in the event of such persistently elevated titers **(BIII)**.
- If initial CSF examination demonstrates pleocytosis, repeat lumbar puncture should be conducted, and then every 6 months until the cell count is normal **(AIII)**.

Late Latent Syphilis

- For late latent disease, 3 doses of benzathine penicillin G should be administered over 3 weeks **(AIII)**.
- Patients with late-latent syphilis should have CSF examination if they have clinical signs or symptoms attributable to syphilis, a fourfold increase in serum nontreponemal test titer, or experience an inadequate serologic response (i.e., less than fourfold decline in nontreponemal test titer) within 12 to 24 months after therapy if initial titer was high (>1:32) **(BIII)**. CSF examination

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Panel's Recommendations, continued

should also be performed. Treatment for neurosyphilis should be initiated if CSF examination is positive for neurosyphilis.

- Benzathine penicillin G should be administered at 1-week intervals for 3 weeks to patients in whom CSF examination does not confirm the diagnosis of neurosyphilis **(AIII)**.

Neurosyphilis

- Neurosyphilis should be treated with aqueous penicillin G for 10 to 14 days **(AII)**.
- If a patient has signs or symptoms consistent with neurosyphilis, and repeat CSF examination is consistent with CNS involvement and cannot be attributable to other ongoing illness, re-treatment for neurosyphilis is recommended **(AIII)**;
- Re-treatment of neurosyphilis should be considered if the CSF white blood cell count has not decreased 6 months after completion of treatment or if the CSF white blood cell count or protein is not normal 2 years after treatment **(BIII)**.

For All Syphilis

- For penicillin-allergic patients or for a discussion of alternative therapies such as doxycycline, ceftriaxone, or azithromycin, please see pages 30, 34, and 38 of the Centers for Disease Control and Prevention STD Treatment Guidelines, 2010.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = One or more randomized trials in children† with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children† from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children† with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion*

† Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents

Epidemiology

Treponema pallidum can be transmitted from mother to child at any stage of pregnancy or during delivery. Among women with untreated primary, secondary, early latent (lacking clinical manifestations within first year after infection), or late latent (lacking clinical manifestations >1 year since infection) syphilis at delivery, approximately 30%, 60%, 40%, and 7% of infants, respectively, will be infected. Treatment of the mother for syphilis ≥30 days before delivery is required for effective *in utero* treatment.

Congenital syphilis has been reported despite adequate maternal treatment. Factors that contribute to treatment failure include maternal stage of syphilis (early stage, including primary, secondary, or early latent syphilis), advancing gestational age at treatment, higher nontreponemal titers at treatment and delivery, and short interval from treatment to delivery (<30 days).[1,2] Since 1991, rates of congenital syphilis have trended downward 92% to 8.5 cases per 100,000 live births in 2011.[3] The continuing decline in the rate of congenital syphilis probably reflects the substantially reduced rate of primary and secondary syphilis in women during the last decade.

Drug use during pregnancy, particularly cocaine use, has been associated with increased risk of maternal syphilis and congenital infection.[4] Similarly, HIV-infected women have a higher prevalence of untreated or inadequately treated syphilis during pregnancy, which places their newborns at higher risk of congenital syphilis.[5] Rates of mother-to-child HIV transmission may be higher when syphilis coinfection is present during pregnancy.[5-7] Risk of HIV transmission does not appear to be higher in mothers whose syphilis is effectively treated before pregnancy.[5]

Although individuals aged 15 to 24 represent one-quarter of the ever-sexually-active population aged 15 to 44, approximately half of sexually transmitted diseases (STDs) diagnosed annually in the United States occur in individuals aged 15 to 24 years.[8,9] Furthermore, individuals in this age group accounted for 28% of primary and secondary syphilis cases during 2011.[3] In 2011, the rate of primary and secondary syphilis was

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highest among individuals aged 20 to 24 years and 25 to 29 years (13.8 and 12.1 cases per 100,000 population, respectively). Nevertheless, the prevalence and incidence of syphilis in HIV-infected youth and of HIV infection in youth with syphilis are appreciable; in a study of 320 HIV-infected and HIV-uninfected U.S. adolescents aged 12 to 19 years, the prevalence of syphilis was 9% in HIV-infected girls and 6% in HIV-infected boys.[10] In a meta-analysis of 30 studies including individuals of all ages, the median HIV seroprevalence in those infected with syphilis in the United States was 15.7% (27.5% in men and 12.4% in women with syphilis).[11] In 2010, coinfection with HIV was reported in 46% of 15- to 29-year-old men who have sex with men with primary and secondary syphilis who knew their HIV status.[12]

Clinical Manifestations

Untreated early syphilis during pregnancy can lead to spontaneous abortion, stillbirth, hydrops fetalis, preterm delivery, and perinatal death in up to 40% of pregnancies.[13] In children with congenital syphilis, two characteristic syndromes of clinical disease exist: early and late congenital syphilis. *Early congenital syphilis* refers to clinical manifestations that appear during the first 2 years of life. *Late congenital syphilis* refers to clinical manifestations that appear in children older than age 2 years.

At birth, infected infants may manifest signs such as hepatosplenomegaly, jaundice, mucocutaneous lesions (e.g., skin rash, nasal discharge, mucous patches, condyloma lata), lymphadenopathy, pseudoparalysis of an extremity, anemia, thrombocytopenia, pneumonia, and skeletal lesions (e.g., osteochondritis, periostitis, or osteitis). In a study of 148 infants born to mothers with untreated or inadequately treated syphilis, 47% had clinical, radiographic, or conventional laboratory findings consistent with congenital syphilis, and 44% had a positive rabbit infectivity test, polymerase chain reaction assay, or immunoglobulin M (IgM) immunoblot of serum, blood, or cerebrospinal fluid (CSF).[14] Manifestations of congenital syphilis in infants of HIV-infected women are expected to be similar to those in HIV-unexposed infants. However, as many as 60% of infants with congenital syphilis do not have any clinical signs at birth.[15] If untreated, these asymptomatic infants can develop clinically apparent disease in the ensuing 3 weeks to 6 months. In addition, fever, nephrotic syndrome, and hypopituitarism can occur. Clinical manifestations of late congenital syphilis are similar to late manifestations of syphilis in adults (e.g., involvement of bone and soft tissue, eyes, ears, and the central nervous system [CNS]).

The manifestations of sexually acquired syphilis in older children and adolescents are similar to those in adults (see *Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults*).[16] HIV-infected individuals with early syphilis may be at increased risk of neurologic complications and may have higher rates of serologic treatment failure.[17]

Diagnosis

The standard serologic tests for syphilis are based on measurement of immunoglobulin G (IgG) antibody. Because IgG antibody in an infant reflects transplacental passively transferred antibody from the mother, interpretation of reactive serologic tests for syphilis in infants is difficult. Therefore, the diagnosis of neonatal congenital syphilis depends on a combination of results from physical, laboratory, radiographic, and direct microscopic examinations.

All infants born to women with reactive nontreponemal and treponemal test results should be evaluated with a quantitative nontreponemal test (e.g., Venereal Disease Research Laboratory [VDRL] slide test, rapid plasma reagin [RPR], the automated reagin test) from the infant and compared with the same test done at the same laboratory on the mother's serum. Umbilical cord specimens should not be tested because of the potential for maternal blood contamination. Specific treponemal tests, such as the fluorescent treponemal antibody absorption (FTA-ABS) test and *T. pallidum* particle agglutination (TP-PA) test, are not necessary to evaluate congenital syphilis in the neonate. There is no commercially available IgM test recommended for diagnostic use. **Note:** Some laboratories use treponemal tests (e.g., enzyme immunoassay, chemiluminescence) for initial screening, and nontreponemal tests for confirmation of positive specimens.[18] However, such an approach with congenital syphilis has not been published.

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Congenital syphilis can be definitively diagnosed if *T. pallidum* is detected by using darkfield microscopic examination or special stains of lesions or body fluids such as umbilical cord, placenta, nasal discharge, or skin lesion material from an infant. Failure to detect *T. pallidum* does not definitively rule out infection because false-negative results are common.[19] A quantitative nontreponemal serologic titer in an infant that is fourfold higher than the mother's is suggestive of infection. Infection also should be assumed in infants born to mothers who were untreated or inadequately treated for syphilis prior to delivery (e.g., non-penicillin regimen or treatment completion <30 days before delivery), regardless of lack of physical, radiographic, or laboratory findings in the infants suggestive of congenital syphilis.

Evaluation of suspected cases of congenital syphilis should include a careful and complete physical examination. Physical signs and symptoms of congenital syphilis include, but are not limited to, non-immune hydrops, jaundice, hepatosplenomegaly, rhinitis, skin rash, and pseudoparalysis of an extremity. Further evaluation to support a diagnosis of congenital syphilis depends on maternal treatment history for syphilis, findings on physical examination, and planned infant treatment. and may include a complete blood count and differential and platelet count, long bone radiographs, and CSF analysis for VDRL, cell count, and protein. A positive CSF VDRL test, elevated CSF protein, and/or elevated CSF white blood cell (WBC) count without other causes may be due to congenital syphilis. Other tests should be performed as clinically indicated (e.g., chest radiograph, liver-function tests, cranial ultrasound, ophthalmologic examination, auditory brainstem response). Individuals with latent syphilis who have neurologic or ophthalmologic signs or symptoms, active tertiary syphilis, or serologic treatment failure should have a CSF examination. Different scenarios indicating clinical management and follow-up recommendations for congenital syphilis are provided on page 36 through 37 of the Centers for Disease Control and Prevention STD Treatment Guidelines, 2010.

For diagnosis of acquired syphilis, a reactive nontreponemal test must be confirmed by a specific treponemal test such as FTA-ABS or TP-PA. Treponemal tests usually remain positive for life, even with successful treatment. The prozone phenomenon (a weakly reactive or falsely negative) reaction is more common in HIV-infected patients.[20] Treponemal antibody titers do not correlate with disease activity and should not be used to monitor treatment response.

Prevention Recommendations

Preventing Exposure

Congenital Syphilis

Effective identification and treatment of congenital syphilis depends on the identification of syphilis in pregnant women and, therefore, on routine serologic screening of pregnant women during the first prenatal visit. In communities and populations in which the risk of congenital syphilis is high, serologic testing and a sexual history also should be obtained at 28 weeks' gestation and at delivery. Moreover, as part of management of pregnant women who have syphilis, information about treatment of sex partners should be obtained to assess the risk of reinfection. Serologic testing at delivery of the mother's serum is preferred over testing of the infant's serum because the serologic tests performed on infant serum can be non-reactive if the mother's serologic test result is of low titer or the mother was infected late in pregnancy. No HIV-exposed infant should leave the hospital unless the maternal syphilis serologic status has been documented at least once during pregnancy and at delivery in communities and populations in which the risk of congenital syphilis is high.[21,22] Routine screening of serum from newborns or umbilical cord blood is not recommended.

Acquired Syphilis

Primary prevention of syphilis includes routine discussion of sexual behaviors that may place individuals at risk of infection. Providers should discuss risk reduction messages that are client-centered and provide specific actions that can reduce the risk of STD acquisition and HIV transmission.[23-25]

Routine serologic screening for syphilis is recommended at least annually for all sexually active HIV-

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infected individuals, with more frequent screening (i.e., 3–6 months) depending on individual risk behaviors (e.g., as multiple partners, sex in conjunction with illicit drug use, methamphetamine use, partners who participate in such activities).[17,26] Syphilis in an HIV-infected individual indicates high-risk behavior and should prompt intensified counseling messages and consideration of referral for behavioral intervention. Patients undergoing screening or treatment for syphilis also should be evaluated for other STDs.[27]

Discontinuing Primary Prophylaxis

Not applicable.

Treatment Recommendations

Treating Disease

Penicillin remains the treatment of choice for syphilis, congenital or acquired, regardless of HIV status **(AI*)**.

Congenital Syphilis

Data are insufficient to determine whether infants who have congenital syphilis and whose mothers are coinfected with HIV require different evaluation, therapy, or follow-up for syphilis than that recommended for infants born to mothers who are not HIV-coinfected. Response to standard treatment may differ in HIV-infected mothers. For example, some studies in adults have shown a lag in serologic improvement in appropriately treated HIV-infected patients.[28,29]

Treatment for congenital syphilis should be administered to infants whose mothers:

- Have been untreated or inadequately treated for syphilis (including treatment with erythromycin or any other non-penicillin regimen),
- Have no documentation of receiving treatment,
- Received treatment <30 days before delivery, or
- Have experienced a fourfold or greater increase in nontreponemal antibody titer suggestive of relapse or reinfection **(AII)** (proven or highly probable disease). (Sexually Transmitted Disease Treatment Guidelines, 2010)[27]

Infants should be treated regardless of maternal treatment history if they have an abnormal physical examination consistent with congenital syphilis, positive darkfield or fluorescent antibody test of body fluid(s), or serum quantitative nontreponemal serologic titer that is at least fourfold greater than maternal titer **(AII)** (proven or highly probable disease).[27]

Treatment for proven or highly probable congenital syphilis is aqueous crystalline penicillin G 100,000 to 150,000 units/kg body weight/day, administered as 50,000 units/kg body weight/dose intravenously (IV) every 12 hours during the first 7 days of life and every 8 hours thereafter for a total of 10 days **(AII)**. If congenital syphilis is diagnosed after age 1 month, the dosage of aqueous penicillin G should be increased to 200,000 to 300,000 units/kg/day IV, administered as 50,000 units/kg body weight/dose IV every 4 to 6 hours for 10 days **(AII)**. If 1 day of therapy is missed, the entire course should be restarted. An alternative to aqueous penicillin G is procaine penicillin G 50,000 units/kg body weight/dose intramuscularly (IM) in a single dose daily for 10 days **(BII)**. However, aqueous penicillin G is preferred because of its higher penetration into the CSF. Insufficient data are available on the effectiveness of ampicillin or other therapies for treatment of congenital syphilis.

For infants who do not meet criteria for proven or highly probable disease, treatment options are influenced by several factors, including maternal treatment, maternal serologic results, and response to therapy, and infant physical exam, infant serologic results, and other laboratory test results. Scenarios that include variations of these factors with treatment recommendations are provided in detail in on pages 36 and 37 of the Centers for Disease Control and Prevention STD Treatment Guidelines, 2010.[27] In the setting of maternal

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and possible infant HIV infection, the more conservative choices among scenario-specific treatment options may be preferable.

Acquired Syphilis

Acquired syphilis in children and adolescents is treated with a single dose of benzathine penicillin G 50,000 units/kg body weight IM (up to the adult dose of 2.4 million units) for early-stage disease (i.e., primary, secondary, and early latent disease) **(AII)**. For late latent disease, three doses of benzathine penicillin G 50,000 units/kg body weight (up to the adult dose of 2.4 million units) should be administered IM once weekly for 3 doses (total 150,000 units/kg body weight, up to the adult total dose of 7.2 million units) **(AIII)**. Alternative therapies (e.g., ceftriaxone, azithromycin) should be administered to HIV-infected patients only when treatment with penicillin is not feasible, and with close clinical and serologic monitoring because data on their use are limited **(BII)**. See the *Sexually Transmitted Disease Treatment Guidelines*, 2010.[27] Neurosyphilis should be treated with aqueous penicillin G 200,000 to 300,000 units/kg body weight per dose IV every 4 to 6 hours (maximum dosage: 18–24 million units/day) for 10 to 14 days **(AII)**.[30] See *Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults* for dosing recommendations for older HIV-infected adolescents with acquired syphilis.[16]

Monitoring and Adverse Events (Including IRIS)

All infants with a reactive nontreponemal test for syphilis (or infants whose mothers were seroreactive at delivery) should receive careful follow-up examinations and serologic testing (i.e., a nontreponemal test) every 2 to 3 months until the test becomes non-reactive or the titer has decreased fourfold **(AIII)**. Nontreponemal antibody titers should decline by age 3 months and should be non-reactive by age 6 months in infants who were not infected (i.e., if the reactive test result was caused by passive transfer of maternal IgG antibody) or who were infected but have been adequately treated. The serologic response after therapy may be slower in infants treated after the neonatal period. Whether children with congenital syphilis who also are HIV-infected take longer to become nonreactive and require retreatment is unknown.

Treponemal tests should not be used to evaluate treatment response because in infected children, the results can remain positive despite effective therapy or be related to maternal infection. Passively transferred maternal treponemal antibodies can be present in infants until age 15 months. A reactive treponemal test after age 18 months is diagnostic of congenital syphilis. If the nontreponemal test is non-reactive at that time, no further evaluation or treatment is necessary. Infants in whom the nontreponemal test is reactive at age 18 months should be fully (re)evaluated and (re)treated for congenital syphilis **(AIII)**.

Infants whose initial CSF evaluations are abnormal should undergo repeat lumbar puncture approximately every 6 months until the results are normal **(AII)**. A repeat reactive CSF VDRL test or abnormal CSF indices that cannot be attributed to other ongoing illness requires retreatment for possible neurosyphilis.

HIV-infected children and adolescents with acquired primary and secondary syphilis should have clinical and serologic response monitored at 3, 6, 9, 12, and 24 months after therapy **(AIII)**; nontreponemal test titers should decline by at least fourfold by 6 to 12 months after successful therapy, with examination of CSF and re-treatment strongly considered in the absence of such decline. For acquired syphilis of longer duration (e.g., early and late latent syphilis), follow up is indicated at 6, 12,18, and 24 months; fourfold decline should be expected by 12 to 24 months. If initial CSF examination demonstrated pleocytosis, repeat lumbar puncture should be conducted at 6 months after therapy, and then every 6 months until the cell count is normal **(AIII)**. Follow-up CSF examinations also can be used to evaluate changes in the CSF-VDRL or CSF protein levels after therapy, but changes in these parameters occur more slowly than changes in CSF cell counts. Data from HIV-infected adults with neurosyphilis suggest that CSF abnormalities may persist for extended times, and close clinical follow up is warranted.[31]

Syphilis in HIV-infected children (congenital or acquired) manifesting as immune response inflammatory syndrome (IRIS) has not been reported, and only very rare reports of syphilis-associated IRIS in adults

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(primarily syphilitic ocular inflammatory disease) have been reported.[32,33]

Managing Treatment Failure

After treatment of congenital syphilis, children with increasing or stable nontreponemal titers at ages 6 to 12 months or children who are seropositive with any nontreponemal titer at 18 months should be evaluated (including with a CSF examination) and considered for retreatment with a 10-day course of parenteral penicillin G **(AIII)**.

Management of failed treatment of acquired syphilis in older children and adolescents is identical to that in adults.[17] Re-treatment of patients with primary or secondary syphilis should be considered for those who:

- Do not experience at least a fourfold decrease in serum nontreponemal test titers 6 to 12 months after therapy,
- Have a sustained fourfold increase in serum nontreponemal test titers after an initial reduction post-treatment, or
- Have persistent or recurring clinical signs or symptoms of disease **(BIII)**.

Adolescents or adults in whom CSF examination does not confirm a neurosyphilis diagnosis should receive benzathine penicillin G 2.4 million units IM, at 1-week intervals for 3 weeks **(BIII)**. If titers fail to respond appropriately after re-treatment, the value of repeat CSF evaluation or re-treatment is unclear, but not recommended.

Re-treatment is warranted for patients with early or late-latent syphilis who have new or sustained clinical signs or symptoms of syphilis, have a fourfold increase in serum nontreponemal test titer, or experience an inadequate serologic response (less than fourfold decline in nontreponemal test titer) within 12 to 24 months after therapy **if initial titer was high (>1:32) (BIII)**. Repeat CSF examination should be performed on these patients, and if the results are consistent with CNS involvement, re-treatment should follow the neurosyphilis recommendations **(AIII)**. Adolescents or adults whose CSF profile is not indicative of CNS disease should receive a repeat course of benzathine penicillin 2.4 million units IM weekly for 3 weeks **(BIII)**; re-treatment of neurosyphilis should be considered in patients whose CSF WBC count has not decreased 6 months after completion of treatment or in whom CSF WBC count or protein is not normal after 2 years **(BIII)**.

Preventing Recurrence

No recommendations have been developed for secondary prophylaxis or chronic maintenance therapy for syphilis in HIV-infected children.

Discontinuing Secondary Prophylaxis

Not applicable.

References

1. Alexander JM, Sheffield JS, Sanchez PJ, Mayfield J, Wendel GD, Jr. Efficacy of treatment for syphilis in pregnancy. *Obstet Gynecol*. Jan 1999;93(1):5-8. Available at http://www.ncbi.nlm.nih.gov/pubmed/9916946.
2. 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.
3. Centers for Disease Control and Prevention. Sexually Transmitted Disease Surveillance 2011. 2012. Available at http://www.cdc.gov/std/stats11/default.htm
4. Sison CG, Ostrea EM, Jr., Reyes MP, Salari V. The resurgence of congenital syphilis: a cocaine-related problem. *J Pediatr*. Feb 1997;130(2):289-292. Available at http://www.ncbi.nlm.nih.gov/pubmed/9042134.
5. Schulte JM, Burkham S, Hamaker D, et al. Syphilis among HIV-infected mothers and their infants in Texas from 1988 to 1994. *Sex Transm Dis*. Jun 2001;28(6):315-320. Available at http://www.ncbi.nlm.nih.gov/pubmed/11403187.

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6. 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.

7. Mwapasa V, Rogerson SJ, Kwiek JJ, Wilson PE, Milner D MM, Kamwendo DD, et al. Maternal syphilis infection is associated with increased risk of mother-to-child transmission of HIV in Malawi. *AIDS*. 2006;20(14):1869-77. Available at http://www.ncbi.nlm.nih.gov/pubmed/16954728

8. Weinstock H, Berman S, Cates W, Jr. Sexually transmitted diseases among American youth: incidence and prevalence estimates, 2000. *Perspectives On Sexual And Reproductive Health*. Jan-Feb 2004;36(1):6-10. Available at http://www.ncbi.nlm.nih.gov/pubmed/14982671.

9. Satterwhite CL, Torrone E, Meites E, et al. Sexually transmitted infections among US women and men: prevalence and incidence estimates, 2008. *Sex Transm Dis*. Mar 2013;40(3):187-193. Available at http://www.ncbi.nlm.nih.gov/pubmed/23403598.

10. Vermund SH, Wilson CM, Rogers AS, Partlow C, Moscicki AB. Sexually transmitted infections among HIV infected and HIV uninfected high-risk youth in the REACH study. Reaching for Excellence in Adolescent Care and Health. *J Adolesc Health*. Sep 2001;29(3 Suppl):49-56. Available at http://www.ncbi.nlm.nih.gov/pubmed/11530303.

11. Blocker ME, Levine WC, St Louis ME. HIV prevalence in patients with syphilis, United States. *Sex Transm Dis*. Jan 2000;27(1):53-59. Available at http://www.ncbi.nlm.nih.gov/pubmed/10654870.

12. Su J. Increases in Syphilis Among Young Men in the United States. Paper presented at National STD Prevention Conference, 2012. Minneapolis, MN. Available at https://cdc.confex.com/cdc/std2012/webprogram/Session12901.html

13. Singh R MJ. Syphilis in pregnancy. *Venereology*. 2001;14:121–131.

14. Michelow IC, Wendel GD, Jr., Norgard MV, et al. Central nervous system infection in congenital syphilis. *N Engl J Med*. Jun 6 2002;346(23):1792-1798. Available at http://www.ncbi.nlm.nih.gov/pubmed/12050339.

15. Glaser JH. Centers for Disease Control and Prevention guidelines for congenital syphilis. *J Pediatr*. Oct 1996;129(4):488-490. Available at http://www.ncbi.nlm.nih.gov/pubmed/8859252.

16. Kaplan JE, Benson C, Holmes KH, et al. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep*. Apr 10 2009;58(RR-4):1-207; quiz CE201-204. Available at http://www.ncbi.nlm.nih.gov/pubmed/19357635.

17. Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines. *MMWR*. 2010;59(12). Available at http://www.cdc.gov/std/treatment/2010/genital-ulcers.htm#syphhiv

18. Centers for Disease Control and Prevention. Discordant results from reverse sequence syphilis screening—five laboratories, United States, 2006-2010. *MMWR*. Feb 11 2011;60(5):133-137. Available at http://www.ncbi.nlm.nih.gov/pubmed/21307823.

19. Association of Public Health Laboratories. Laboratory Diagnostic Testing for Treponema pallidum. 2009. Available at http://www.aphl.org/aphlprograms/infectious/std/Documents/LaboratoryGuidelinesTreponemapallidumMeetingReport.pdf

20. Jurado RL, Campbell J, Martin PD. Prozone phenomenon in secondary syphilis. Has its time arrived? *Arch Intern Med*. Nov 8 1993;153(21):2496-2498. Available at http://www.ncbi.nlm.nih.gov/pubmed/7832818.

21. Centers for Disease Control and Prevention. Congenital syphilis—United States, 2002. *MMWR*. Aug 13 2004;53(31):716-719. Available at http://www.ncbi.nlm.nih.gov/pubmed/15306757.

22. Beltrami J, Berman S. Congenital syphilis: a persisting sentinel public health event. *Sex Transm Dis*. Nov 2006;33(11):675-676. Available at http://www.ncbi.nlm.nih.gov/pubmed/16794558.

23. Kamb ML, Fishbein M, Douglas J ea. Efficacy of risk-reduction counseling to prevent human immunodefiency virus and sexually transmitted diseases: a randomized controlled trial. *JAMA*. 1998;280:1161-67. 1998. Available at http://www.ncbi.nlm.nih.gov/pubmed/9777816

24. Fisher JD, Cornman DH, Osborn CY, et al. Clinician-initiated HIV risk reduction intervention for HIV-positive persons: formative research, acceptability, and fidelity of the Options Project. *J Acquir Immune Defic Syndr*. 2004;37(Suppl 2):S88-94. Available at http://www.ncbi.nlm.nih.gov/pubmed/15385903

25. Richardson JL, Milam J SS, et al. Using patient risk indicators to plan prevention strategies in the clinical care setting. *J Acquir Immune Defic Syndr*. 2004;37(suppl 2):S88-94. Available at http://www.ncbi.nlm.nih.gov/pubmed/15385904

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26. CDC, HRSA NIH, HIVMA/IDSA, and the HIV Prevention in Clinical Care Working Group. Recommendations for Incorporating Human Immunodeficiency Virus (HIV) Prevention into the Medical Care of Persons Living with HIV. *Clin Infect Dis*. 2004;38:104-21.

27. Workowski KA, Berman S, Centers for Disease C, Prevention. Sexually transmitted diseases treatment guidelines, 2010. *MMWR Recomm Rep*. Dec 17 2010;59(RR-12):1-110. Available at http://www.ncbi.nlm.nih.gov/pubmed/21160459.

28. Yinnon AM, Coury-Doniger P, Polito R, Reichman RC. Serologic response to treatment of syphilis in patients with HIV infection. *Arch Intern Med*. Feb 12 1996;156(3):321-325. Available at http://www.ncbi.nlm.nih.gov/pubmed/8572843.

29. 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.

30. American Academy of Pediatrics. *Red Book: 2012 Report of the Committee on Infectious Diseases*. Elk Grove Village, IL. 2012.

31. 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*. Jun 29 2007;56(25):625-628. Available at http://www.ncbi.nlm.nih.gov/pubmed/17597693.

32. Moloney G, Branley M, Kotsiou G, Rhodes D. Syphilis presenting as scleritis in an HIV-positive man undergoing immune reconstitution. *Clin Experiment Ophthalmol*. Oct 2004;32(5):526-528. Available at http://www.ncbi.nlm.nih.gov/pubmed/15498066.

33. 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.

Dosing Recommendations for Prevention and Treatment of Syphilis (page 1 of 2)

Preventive Regimen			
Indication	**First Choice**	**Alternative**	**Comments/Special Issues**
Primary Prophylaxis	N/A	N/A	Primary Prophylaxis Indicated for: • N/A Criteria for Discontinuing Primary Prophylaxis: • N/A Criteria for Restarting Primary Prophylaxis: • N/A
Secondary Prophylaxis	N/A	N/A	Secondary Prophylaxis Indicated: • N/A Criteria For Discontinuing Secondary Prophylaxis: • N/A Criteria For Restarting Secondary Prophylaxis: • N/A

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Dosing Recommendations for Prevention and Treatment of Syphilis (page 2 of 2)

Preventive Regimen			
Indication	**First Choice**	**Alternative**	**Comments/Special Issues**
Treatment	Congenital *Proven or Highly Probable Disease:* • Aqueous crystalline penicillin G 100,000–150,000 units/kg body weight per day, administered as 50,000 units/kg body weight per dose IV every 12 hours for the first 7 days of life, and then every 8 hours for 10 days • If diagnosed after 1 month of age, aqueous penicillin G 200,000–300,000 unit/kg body weight per day, administered as 50,000 units/kg body weight per dose IV every 4–6 hours (maximum 18–24 million units per day) for 10 days *Possible Disease:* • Treatment options are influenced by several factors, including maternal treatment, titer, and response to therapy; and infant physical exam, titer, and test results. Scenarios that include variations of these factors are described and treatment recommendations are provided in detail on pages 36–37 of the Centers for Disease Control STD Treatment Guidelines, 2010. Acquired: *Early Stage (Primary, Secondary, Early Latent):* • Benzathine penicillin 50,000 units/kg body weight (maximum 2.4 million units) IM for 1 dose *Late Latent:* • Benzathine penicillin 50,000 units/kg body weight (maximum 2.4 million units) IM once weekly for 3 doses *Neurosyphilis (Including Ocular):* • Aqueous penicillin G 200,000–300,000 units/kg body weight per day administered as 50,000 units/kg body weight per dose IV every 4–6 hours (maximum 18–24 million units per day) for 10–14 days	Congenital *Proven or Highly Probable Disease (Less Desirable if CNS Involvement):* • Procaine penicillin G 50,000 units/kg body weight IM once daily for 10 days *Possible Disease:* • Treatment options are influenced by several factors, including maternal treatment, titer, and response to therapy; and infant physical exam, titer, and test results. Scenarios that include variations of these factors are described and treatment recommendations are provided in detail on pages 36–37 of the Centers for Disease Control STD Treatment Guidelines, 2010.	For treatment of congenital syphilis, repeat the entire course of treatment if >1 day of treatment is missed. Examinations and serologic testing for children with congenital syphilis should occur every 2–3 months until the test becomes non-reactive or there is a fourfold decrease in titer. Children with increasing titers or persistently positive titers (even if low levels) at ages 6–12 months should be evaluated and considered for re-treatment. In the setting of maternal and possible infant HIV infection, the more conservative choices among scenario-specific treatment options may be preferable. Children and adolescents with acquired syphilis should have clinical and serologic response monitored at 3, 6, 9, 12, and 24 months after therapy.

Key to Acronyms: CDC = Centers for Disease Control and Prevention; IM = intramuscular; IV = intravenous; STD = sexually transmitted disease

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