

SYPHILIS

- A. Causative agent:** *Treponema pallidum*, a spirochete bacterium.
- B. Usual sources and routes of infection:** Humans are the only known hosts. Transmission occurs by direct contact with exudates from moist, early lesions of infected individuals. Sexual intercourse is the most frequent route of transmission, but kissing or touching children with early congenital disease can also transmit disease, and transplacental infection of the fetus may occur when the mother is infected. Transmission may also occur via blood transfusions if the donor is in the early stages of infection. Health care workers have developed primary lesions on the hands after examining lesions of infected patients (syphilitic whitlow).
- C. Incubation period:** Usually 3 weeks, ranges from 10 days to 3 months for primary symptoms.
- D. Period of communicability:** Moist mucocutaneous lesions of primary and secondary syphilis are infectious. However, it is difficult to differentiate between the infectious stage and the noninfectious early latent stage. Transmission beyond the first year is rare and thus syphilis is generally considered noninfectious in the United States, after year one. Transplacental infection of the fetus is more likely if the mother has been recently infected, but can also occur during latent stages.
- E. Investigation of a reported case:**
1. **Form(s):** See Section VI, Investigation and Report Forms by Disease or Condition.
 2. **Investigation should include:**
 - a. **Determination of stage of syphilis.** For each syphilis reactor (positive lab test without morbidity report), a determination of stage of syphilis should be made.
 - i. Case definitions can be found in Section IV.
 - ii. When the stage of syphilis is unknown, an investigation should be conducted to determine if infection took place within the previous 12 months (early syphilis) or before (late syphilis).
 - b. Interview and contact tracing of cases determined to be early syphilis (≤ 12 months duration) should be done aggressively using applicable CDC guidelines. An interview should be performed as early as possible, preferably within 3 days. Early syphilis includes primary syphilis, secondary syphilis, and early latent syphilis, which may be found in the CDC *Recommendations for Partner Services Programs for HIV Infection, Syphilis, Gonorrhea, and Chlamydial Infection*, available at <http://www.cdc.gov/mmwr/pdf/rr/rr57e1030.pdf>. In addition, training and resources are available. Please contact the OEFI Epidemiology Program for available resource material and courses.
 - c. Interview periods:
 - i. **Primary:** 90 days prior to onset of primary lesion through the date of treatment.
 - ii. **Secondary:** 6 ½ months prior to date of onset of secondary symptoms through the date of treatment.

- iii. Early Latent—One year prior to start of treatment. If the patient claims no sex partners in this period, the most recent partner before the interview period should be elicited and notified. Interview periods may be modified if a history of symptoms, a negative test result, or incidental treatment is documented.
 - iv. Undetermined: Many syphilis cases cannot be staged until after the case is investigated. When the stage of syphilis is undetermined at the time of interview, a one-year interview period should be used. That is, epidemiologists should initially interview a patient as early latent syphilis (730) and then, if appropriate, reclassify at case closure as late latent syphilis (745), latent syphilis of unknown duration (740), or not syphilis (serofast). To reclassify an early latent case as late latent or unknown duration, the following criteria must be met: no history of exposure to a known case of syphilis (as determined by interviewing the case and following up on sex partners), no history of symptoms in the last year, no history of a negative blood test in the last year, and no rise in titer of two dilutions or more. A case should be reported even if treatment is not verified.
- d. Completion and mailing, faxing, or secure electronic upload of the Idaho STD/HIV Investigation Form (See Section 6: Investigation Forms) according to instructions within one week of notification of the case. Submitting this form is a requirement of the STD/HIV Prevention Contract. Since most syphilis reports require investigation to determine syphilis stage, at least sections 1–7 should be completed. For early or otherwise interviewed syphilis cases, complete the remaining sections. Keep a copy for your records.
 - e. Contact/partner investigations: the Idaho STD/HIV Investigation Form should be initiated on all sexual partners and other contacts identified in interviews of high priority cases. Each contact should be listed, and ultimately, a disposition documented. Identified potentially at-risk social contacts also should have an Idaho STD/HIV Investigation Form initiated and be listed in the contacts section of the original patient's form. Presumptive treatment should be given to all contacts that have had exposure to an infectious syphilis case within 90 days of diagnosis of early syphilis or syphilis of unknown duration. Contacts exposed >90 days before diagnosis of early syphilis should be presumptively treated if follow-up is uncertain.
 - f. For every pregnant woman diagnosed with any stage of syphilis, a Congenital Syphilis (CS) Case Investigation and Report Form should be completed for the infant within 1 week of report of delivery

F. Laboratory diagnosis: Laboratory testing for syphilis can be confusing. Laboratory tests must always be interpreted together with the clinical history, including symptoms, physical examination, history of possible exposure to syphilis, and country or region of origin.

Common non-treponemal syphilis screening tests are the RPR (rapid plasma reagin), and VDRL (venereal disease research laboratory). Blood banks sometimes use the automated PK-TP system microhemagglutination test. Common treponemal confirmatory tests include: FTA-abs (fluorescent treponemal antibody absorption), TP-PA (*Treponema pallidum* particle agglutination), MHA-TP (Microhemagglutination assay). Blood banks use the Captia Syphilis G EIA (enzyme immunoassay) to confirm.

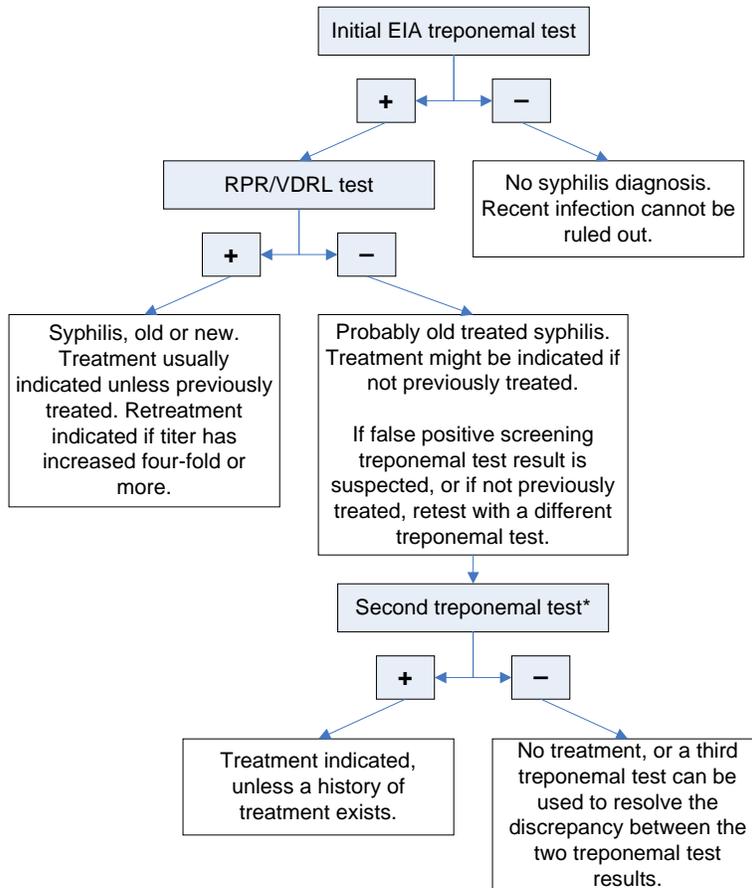
The following is an excerpt from the US Public Health Service Task Force's *Guide to Clinical Preventive Services, Second Edition*:

“Serologic tests are currently the mainstay for syphilis diagnosis and management. Nontreponemal tests are used to screen patients for the presence of nonspecific reagin antibodies that appear and rise in titer following infection. Although VDRL (Venereal Disease Research Laboratory) and RPR (rapid plasma reagin) are the most commonly used nontreponemal tests, others are available. The sensitivity of nontreponemal tests varies with the levels of antibodies present during the stages of disease. In early primary syphilis, when antibody levels may be too low to detect, results may be nonreactive, and the sensitivity of nontreponemal tests is 62-76%. Antibody levels rise as disease progresses; titers usually peak during secondary syphilis, when the sensitivity of nontreponemal tests approaches 100%. In late syphilis, titers decline, and previously reactive results revert to nonreactive in 25% of patients; in untreated late syphilis, test sensitivity averages only 70%. Nontreponemal test titers decline or revert to normal after successful treatment.

Nontreponemal tests can produce sustained or transient false-positive reactions due to preexisting conditions (e.g., collagen vascular diseases, injection drug use, advanced malignancy, pregnancy) or infections (e.g., malaria, tuberculosis, viral and rickettsial diseases), or due to laboratory-associated errors. The specificity of nontreponemal tests is 75-85% in persons with preexisting diseases or conditions, and it approaches 100% in persons without them. Because nontreponemal serodiagnostic tests may be falsely positive, all reactive results in asymptomatic patients should be confirmed with a more specific treponemal test such as fluorescent treponemal antibody absorption (FTA-ABS), which has a sensitivity of 84% in primary syphilis and almost 100% for other stages, and a specificity of 96%. Two less expensive and easier to perform confirmatory tests are the MHA-TP (microhemagglutination assay for antibodies to *Treponema pallidum*) and HATTS (hemagglutination treponemal test for syphilis).

Treponemal tests should not be used as initial screening tests in asymptomatic patients, as they are considerably more expensive and remain reactive in patients with previous, treated infection. Used in concert with nontreponemal tests, however, the positive predictive value of treponemal tests is high, and reactive results are likely to represent true infection with syphilis. Treponemal tests may also be useful in patients with suspected late syphilis and nonreactive nontreponemal tests, since declining antibody titers may produce false-negative nontreponemal tests. All test results should be evaluated in concert with a clinical diagnosis and history.

Infection with HIV may alter the clinical presentation and performance of serologic tests for syphilis. Co-infection with HIV and syphilis does not generally impair the sensitivity of syphilis testing, although there are anecdotal reports of absent or delayed response to nontreponemal tests. In contrast, HIV infection may reduce the specificity of syphilis testing; several studies have noted increased reactivity to nontreponemal tests among HIV-infected persons without syphilis. Persistence of elevated nontreponemal titers after treatment for syphilis has also been reported in some HIV-infected persons, making it difficult to confirm the adequacy of treatment. At the same time, treponema-specific tests may become nonreactive after treatment of syphilis in HIV-infected persons, limiting the ability to document past infection.”



*Using *Treponema pallidum* particle agglutination (TPPA) or fluorescent treponemal antibody (FTA) tests.

Adapted from: Centers for Disease Control and Prevention. Syphilis Testing Algorithms Using Treponemal Tests for Initial Screening — Four Laboratories, New York City, 2005–2006. MMWR 2008;57:872-875

Figure 1. Algorithm for interpretation of syphilis test results using EIA as the initial screening test.

ruled-out (see below). However, again, the majority of syphilis serological tests are reliable and accurate in HIV-infected patients.

Of note, any confirmed case of syphilis should receive STD screening, including HIV testing. It is important to rule-out the possibility of HIV co-infection for the aforementioned diagnostic reasons, but also because coinfection leads to increased transmissibility of both infections and more rapid progression from early syphilis to neurosyphilis (which includes meningitis, optic neuritis, uveitis, and deafness).

- 1. False Negatives:** Be aware false negative results may be encountered due to the prozone reaction. The prozone reaction is a false negative non-treponemal syphilis screening (e.g., RPR, Venereal Disease Research Laboratory [VDRL] test resulting from excess antibody in undiluted serum inhibiting the antigen-antibody reaction

Overall, the incidence of the prozone reaction is thought to be very low ($\leq 2\%$) (Source: Tramont E. *Treponema pallidum* (syphilis). In: Mandell GL, Bennett JE,

A shift in preference of syphilis screening tests has occurred at large reference laboratories in recent years. Enzyme immunoassays (EIAs) to detect *Treponema pallidum* IgG antibody are highly automated and less costly to perform than RPR to perform as initial screening tests at many large laboratories. A positive result from EIA cannot distinguish between old, previously treated, or new infection. Clinicians should seek a quantitative reflexive RPR/VDRL result (titer) and possibly a second treponemal test to guide management. See the algorithm (Figure) for help with interpreting results using EIA as the initial screening test.

When syphilis is strongly suspected in an HIV-infected person, but serologic tests are nonreactive, repeat serology in 1-2 weeks, biopsy of skin lesions with silver staining, darkfield examination, or DFA staining should be considered. Possible prozone phenomena should also be

Dolin R, eds. Principles and Practice of Infectious Diseases. Philadelphia, Churchill Livingstone, 2000, ed 6: 2778). The prozone reaction can occur when antibody titer is very high (e.g., secondary syphilis, pregnancy) and may be more common with HIV infection. Case reports have described the prozone reaction being present in specimens from HIV positive patients up to 1:64 dilution (Source: Smith G, Holman R. The prozone phenomenon with syphilis and HIV-1 coinfection. *Southern Medical Journal*. 97(4):379-382).

Because of the possibility of the prozone reaction, clinicians should specifically request titration in addition to the screening test when the index of suspicion is high. This may be requested later if initial screening results are reported as negative by contacting the testing laboratory.

- 2. Diagnostic Testing for Neurosyphilis:** Patients with syphilis who exhibit signs and symptoms of neurologic diseases (e.g. weakness, pain, hyperreflexia, vibratory or position sensation abnormalities, incontinence, dementia, abnormal gait, hearing loss, or visual disturbances) should undergo CSF analysis and ocular slit-lamp examination to rule-out neurosyphilis. This is particularly important in HIV-coinfected individuals. Other indications for CSF analysis include manifestations of late (tertiary) syphilis (such as aortic aneurysm, aortic regurgitation, or gumma), syphilis treatment failure, or an HIV-infected patient with late latent syphilis. Serum RPR titer greater than or equal to 1:32 or CD4 count less than 350 cells/mm³ in an HIV-infected individual are also suggested indications by some experts

CSF analysis is not universally recommended for all individuals with syphilis, since transient CSF abnormalities without subsequent progression to neurosyphilis are common in primary or secondary syphilis. Regarding the available diagnostic tests and their utility, the following is an excerpt from the CDC 2010 STD Treatment Guidelines:

“Clinical signs of neurosyphilis (i.e., cranial nerve dysfunction, meningitis, stroke, acute or chronic altered mental status, loss of vibration sense, and auditory or ophthalmic abnormalities) warrant further investigation and treatment for neurosyphilis. Laboratory testing is helpful in supporting the diagnosis of neurosyphilis; however, no single test can be used to diagnose neurosyphilis in all instances. Cerebrospinal fluid (CSF) laboratory abnormalities are common in persons with early syphilis. The VDRL in cerebrospinal fluid (CSF-VDRL), which is highly specific but insensitive, is the standard serologic test for CSF. When reactive in the absence of substantial contamination of CSF with blood, it is considered diagnostic of neurosyphilis; however in early syphilis, it can be of unknown prognostic significance. Most other tests are both insensitive and nonspecific and must be interpreted in relation to other test results and the clinical assessment. Therefore, the laboratory diagnosis of neurosyphilis usually depends on various combinations of reactive serologic test results, CSF cell count or protein, and a reactive CSF-VDRL with or without clinical manifestations.

Among persons with HIV infection, the CSF leukocyte count usually is elevated (>5 white blood cell count [WBC]/mm³); using a higher cutoff (>20 WBC/ mm³) might improve the specificity of neurosyphilis diagnosis. The CSF-VDRL might be nonreactive even when neurosyphilis is present; therefore, 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; neurosyphilis is highly unlikely with a negative CSF FTA-ABS test.”

- 3. Blood Donation Screening:** A special circumstance is presented when positive results are received from the American Red Cross (ARC), which performs syphilis screening on donated blood using tests not frequently used by medical providers. The following information was supplied by ARC:
- PKTP:** This automated test for antibodies to *T. pallidum* is used to screen blood donations. Reactive samples are tested further.
 - EIA:** This enzyme immunoassay for IgG antibodies to *T. pallidum* is a confirmatory test for donations with reactive PKTP or RPR screening tests. The EIA results can be positive, negative, or equivocal. The EIA typically remains positive for life following treated infection.
 - RPR:** Is used either to screen blood donations, or as an additional test for donations that test reactive by PKTP or EIA in order to determine whether infection is recent or past.

These tests work together to indicate the likely medical status of the donor (see Table 1., below)

Table 1. American Red Cross syphilis laboratory result interpretation

PKTP screen	EIA	RPR*	Most likely interpretation**
Reactive	Positive	Reactive	Probable active infection
Reactive	Positive	Nonreactive	Probable remote, inactive infection
Reactive	Negative	N/A	Not infected
Reactive	Equivocal or not tested	Reactive	Possible active infection
Reactive	Equivocal or not tested	Nonreactive	Likely not infected; past infection cannot be excluded
Not done	Positive	Reactive***	Probable active infection
Not done	Negative	Reactive***	Not infected; even if quantitative RPR is reactive
Not done	Equivocal or not tested	Reactive***	Possible active infection

*Quantitative RPR testing is performed for samples collected in New York State.

**Clinical evaluation and repeat testing may clarify the infection status.

***Some donations may be screened using RPR instead of PKTP. In cases where screening RPR is reactive, EIA is used as the confirmatory test.

G. Idaho disease trends: See website at www.epi.idaho.gov.

H. Treatment: In general, penicillin remains the drug of choice for treatment of syphilis. Refer to the most recent CDC Sexually Transmitted Diseases Treatment Guidelines for recommended and alternative regimens, information on follow-up, recommended testing for other STD, and other patient considerations, including pregnancy and HIV infection. The most recent version is available at <http://www.cdc.gov/std/treatment/2010/toc.htm> or visit the CDC web site (www.cdc.gov) and run a search for the guidelines.

Presumptive treatment should be given to contacts of early syphilis cases that were exposed within 90 days preceding diagnosis. Contacts exposed >90 days before diagnosis of early syphilis should be presumptively treated if follow-up is uncertain. For the purposes of contact tracing and presumptive treatment, patients with syphilis of unknown duration with titers $\geq 1:32$ should be assumed to have early syphilis until more information is obtained. Treatment differs depending on stage of infection, patient age (child or infant), and neurologic involvement.

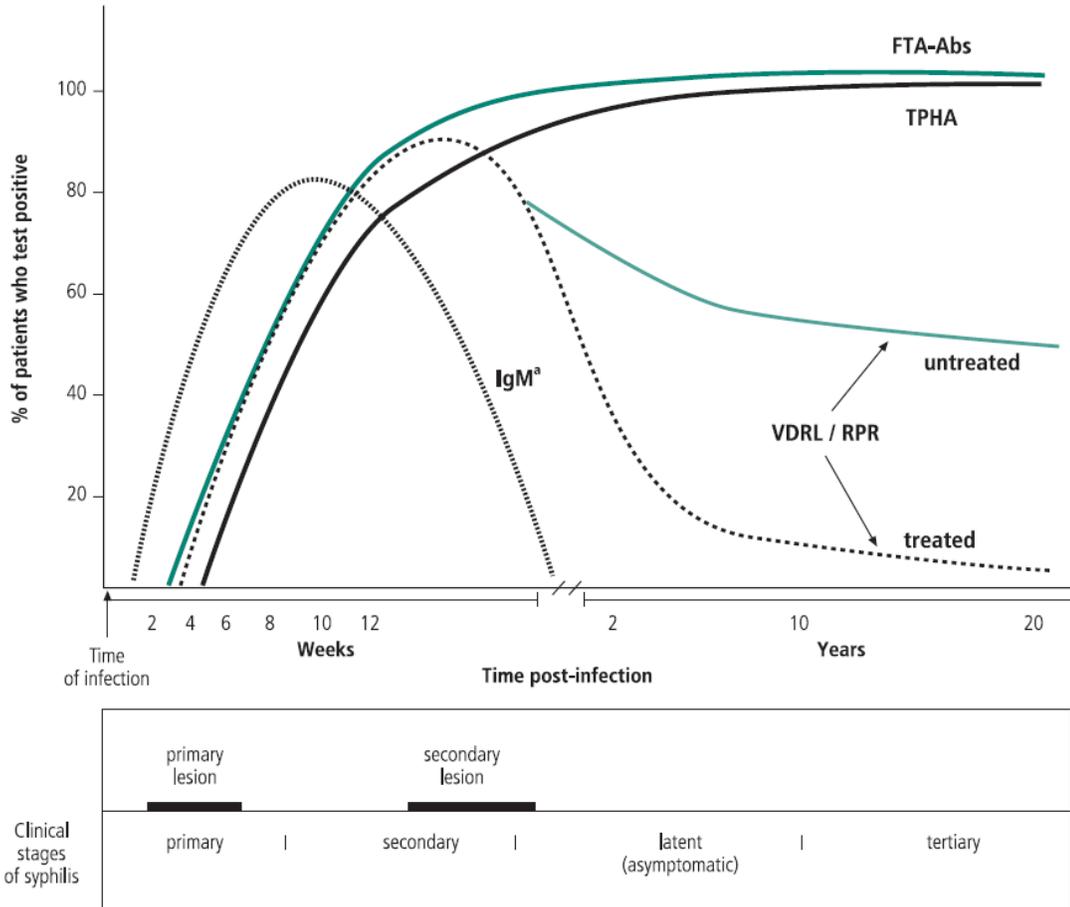
Laboratory testing to assure treatment efficacy is recommended at 3, 6, and 12 months after treatment. The same nontreponemal testing assay – either RPR or VDRL – should be used consistently for all follow-up examinations. No definitive criteria for treatment failure or success exist, as serological response is variable depending on stage of infection and many other factors. Even so, treatment failure is suggested by persistent signs or symptoms or a four-fold increase in nontreponemal test titer (which is equivalent to a change of two dilutions). Treatment success is strongly suggested by a four-fold decline in titer by 6 months post-treatment, eight-fold decline by 12 months, or four-fold decline by 12 months in early latent syphilis. Individuals not meeting these criteria should undergo retreatment and be considered for CSF testing.

The majority of successfully treated individuals will experience decline in nontreponemal titers to nonreactivity over time; however, a minority will stabilize to a low level titer and are said to be “serofast.” These individuals should have periodic retesting to assure titers remain at this baseline and should also be ruled-out for HIV infection.

Treponemal test antibody titers, if quantified, should not be used to assess treatment response, since most patients with reactive treponemal tests will remain reactive for life (e.g. only 15-25% of patients treated during the primary stage will become serologically nonreactive after 2-3 years).

HIV-positive individuals may have slightly higher rates of treatment failure with the currently recommended regimens (note that treatment recommendations currently do not differ from those for HIV-negative individuals). As a result, close follow-up is necessary in HIV-positive individuals with clinical and serological evaluation at 3, 6, 9, 12, and 24 months after therapy in the case of primary and secondary syphilis, and re-evaluation at 6, 12, 18, and 24 months in the case of latent syphilis. CSF examination 6 months after therapy may also be considered in HIV-positive patients. If treatment failure occurs, it should be addressed similarly as with HIV-negative patients. Again, extensive guidelines for different scenarios are available at the aforementioned CDC Treatment Guidelines website.

For patients with neurosyphilis, serial CSF testing should be performed at three and six months post-treatment, as well as every six months thereafter until the white blood cell count normalizes and the CSF-VDRL becomes nonreactive.



^a IgM by ELISA or FTA-ABS 195 or immunoblot

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Figure 2. Common patterns of serological reactivity in syphilis patients

Image source: Peeling, R. and Ye, H. Diagnostic tools for preventing and managing maternal and congenital syphilis: an overview. Bulletin of the World Health Organization. June 2004, 82 (6): 439–446.

J. References:

Sexually Transmitted Diseases Treatment Guidelines 2010. These are available at <http://www.cdc.gov/std/treatment/2010/toc.htm> or go to the CDC web site (www.cdc.gov) and run a search for the guidelines. Syphilis recommendations can currently be found under the subtitle “Diseases Characterized by Genital Ulcers” available at <http://www.cdc.gov/STD/treatment/2006/genital-ulcers.htm>

Centers for Disease Control and Prevention. Recommendations for Partner Services Programs for HIV Infection, Syphilis, Gonorrhea, and Chlamydial Infection. MMWR Early Release 2008;57 October 30, 2008.

Sexually Transmitted Diseases Clinical Practice Guidelines, May 1991

Centers for Disease Control and Prevention. Case definitions for infectious conditions under public health surveillance. MMWR 1997;46(No.RR-10):34-38. Available at: http://www.cdc.gov/osels/ph_surveillance/nndss/casedef/syphiliscurrent.htm

U.S. Preventive Services Task Force. Guide to Clinical Preventive Services, 2nd Edition. Screening for Syphilis. Washington, DC: U.S. Department of Health and Human Services, Office of Disease Prevention and Health Promotion, 1996. Update released July 2004. Available at: <http://www.ahrq.gov/clinic/uspstf/uspssyph.htm>

Centers for Disease Control and Prevention. Incorporating HIV prevention into the medical care of persons living with HIV. Recommendations of CDC, the Health Resources and Services Administration, the National Institutes of Health, and the HIV medicine Association of the Infectious Diseases Society of America." MMWR Recomm Rep. 2003 Jul 18; 52 (RR-12): 1-24. Available at: <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5212a1.htm>

Fact Sheet on syphilis from CDC: <http://www.cdc.gov/std/syphilis/STDFact-Syphilis.htm>

Instructions and Code Descriptions for the Idaho STD/HIV Investigation Form. Please contact OEFI Epidemiology Program for a copy if you do not have this resource available at your office.

UpToDate (www.uptodate.com), a clinician reference web site, was used to update parts of this guideline. Articles used:

Rompalo, Anne, "Treatment and prevention of syphilis in the HIV-infected patient." December 3, 2009.

Hicks, Charles. "Laboratory monitoring of patients undergoing treatment for syphilis." September 21, 2009.

Marra, Christina. "Neurosyphilis." February 11, 2010.

Please call the OEFI Epidemiology Program at 208-334-5939 for questions about STD investigations not covered in this document or in references.