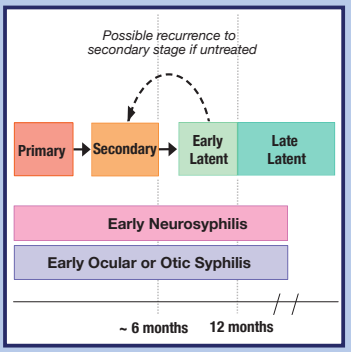
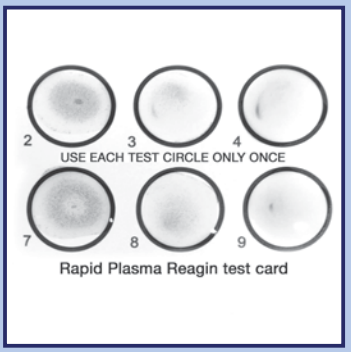
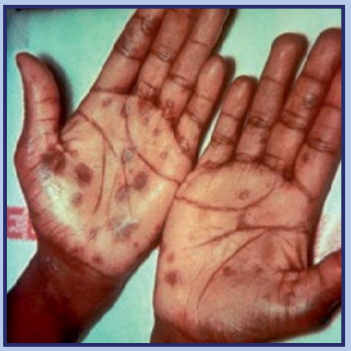
The Diagnosis, Management and Prevention of Syphilis

An Update and Review







Produced by

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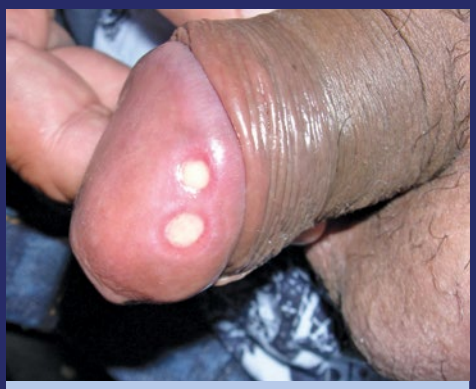
and the New York City STD Prevention Training Center

NYC Health

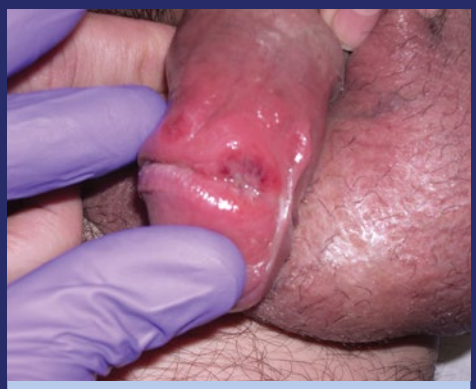
NEW YORK CITY STD HIV PREVENTION TRAINING CENTER

March 2019



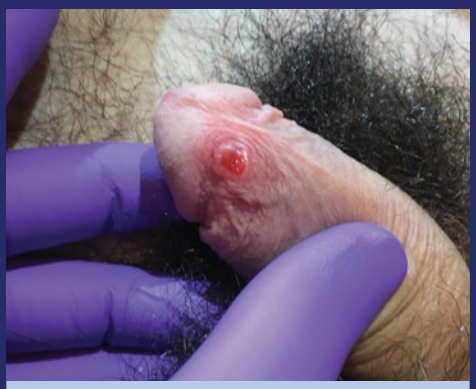
A pair of painless well-demarcated ulcerations with firm rolled edges seen on the penile glans in a patient with primary syphilis; central white areas are a result of early granulation tissue and not exudate.

Source: New York City Department of Health & Mental Hygiene, Sexual Health Clinics



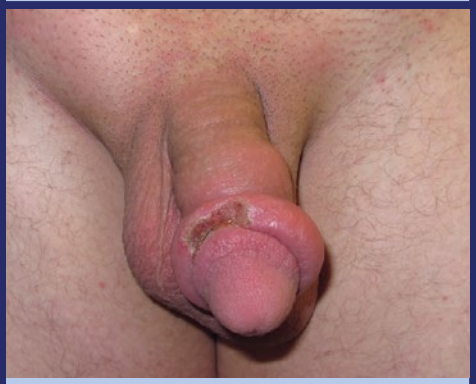
A prominent painless, indurated, primary syphilis ulceration at the penile sulcus with adjacent smaller early ulceration.

Source: New York City Department of Health & Mental Hygiene, Sexual Health Clinics



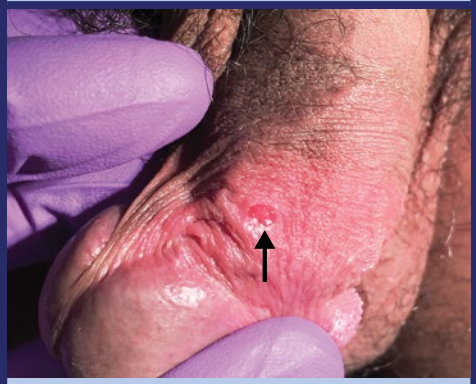
Single sharply-demarcated ulceration with rolled edges at the penile sulcus of a patient with primary syphilis.

Source: New York City Department of Health & Mental Hygiene, Sexual Health Clinics



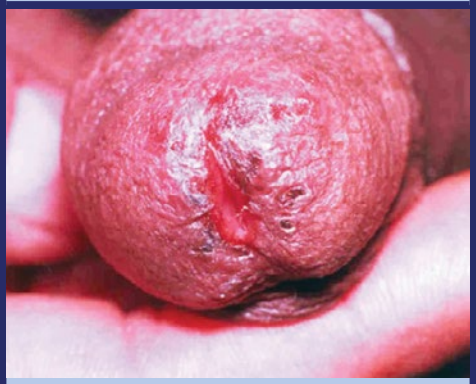
A single mildly crusted ulceration at the foreskin of a patient with primary syphilis which is associated with localized penile edema and right-sided lymphadenopathy.

Source: Public Health—Seattle & King County STD Clinic; National STD Curriculum https://www.std.uw.edu/go/pathogen-based/syphilis/core-concept/all.



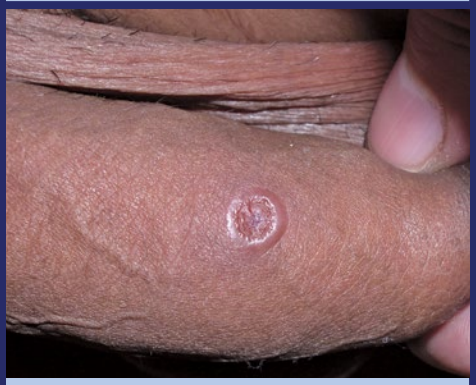
A single superficial erosion on the distal penile shaft which was dark field positive in a patient with primary syphilis.

Source: New York City Department of Health & Mental Hygiene, Sexual Health Clinics



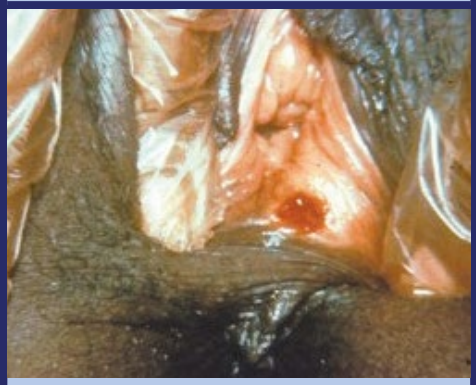
Crusted erosions at penile glans which were attributed to primary syphilis.

Source: Dr. Joseph Engelman, San Francisco City Clinic



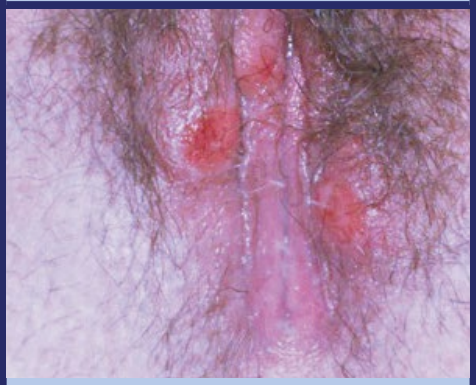
A healing ulceration which shows persistent rolled edge on the shaft of the penis in a patient with primary syphilis.

Source: New York City Department of Health & Mental Hygiene, Sexual Health Clinics



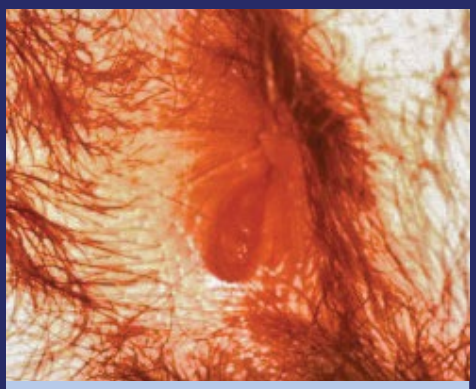
A syphilis chancre located on the posterior vaginal fourchette in a patient with primary syphilis.

Source: CDC/ NCHSTP/ Division of STD Prevention, STD Clinical Slides- Syphilis. https://www.cdc.gov/std/training/clinicalslides/slides-dl.htm



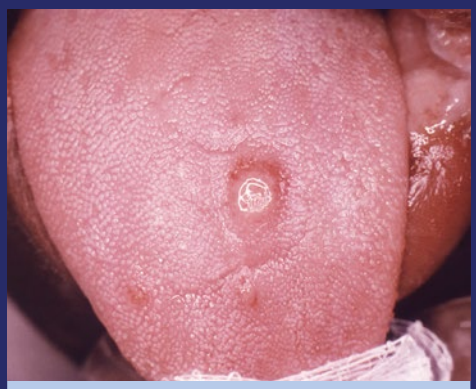
Bilateral vulvar chancres in a patient with primary syphilis.

Source: Dr. Joseph Engelman, San Francisco City Clinic



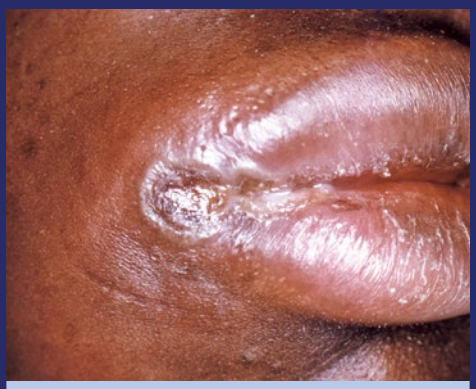
A perianal ulceration in a patient with primary syphilis.

Source: CDC/ NCHSTP/ Division of STD Prevention, STD Clinical Slides- Syphilis. https://www.cdc.gov/std/training/clinicalslides/slides-dl.htm



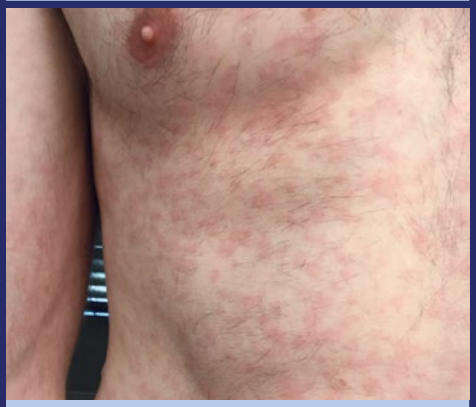
A circular ulceration on the surface of a tongue in a patient with primary syphilis.

Source: Division of STD Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention. www.cdc.gov/std/syphilis/images.htm



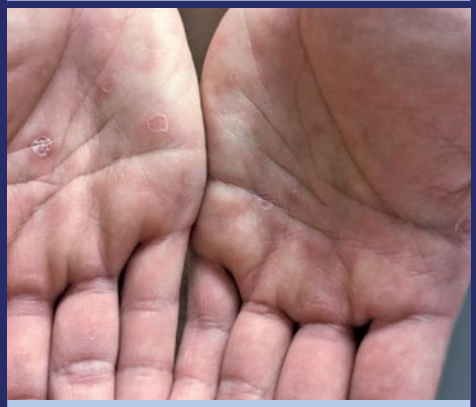
A sharp-edged circular ulceration at the right corner of the mouth in a patient with primary syphilis.

Source: Centers for Disease Control and Prevention, Public Health Image Library (Robert E. Sumpter); National STD Curriculum https://www.std.uw.edu/go/pathogen-based/syphilis/core-concept/all.



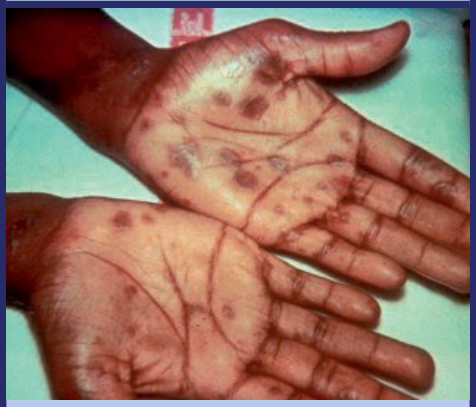
An erythematous maculopapular eruption on the trunk of a patient with secondary syphilis.

Source: Negusse Ocbamichael, PA; Public Health—Seattle & King County STD Clinic; National STD Curriculum https://www.std.uw.edu/go/pathogen-based/syphilis/core-concept/all.



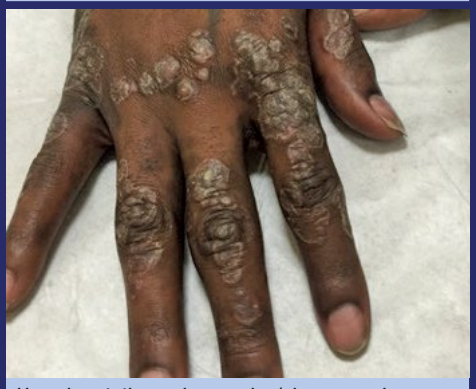
Somewhat faint erythematous macules seen on the palms of a patient with secondary syphilis.

Source: Negusse Ocbamichael, PA; Public Health—Seattle & King County STD Clinic; National STD Curriculum https://www.std.uw.edu/go/pathogen-based/syphilis/core-concept/all.



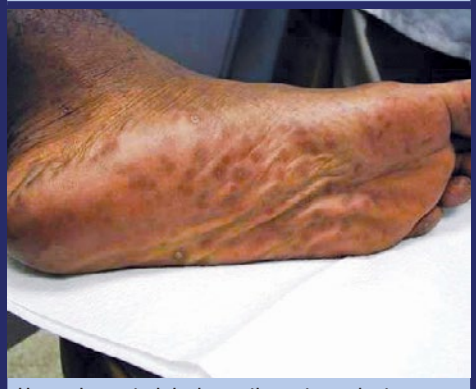
Multiple reddish-brown papulosquamous lesions on the palms of a patient with secondary syphilis.

Source: CDC/ NCHSTP/ Division of STD Prevention, STD Clinical Slides- Syphilis. https://www.cdc.gov/std/training/clinicalslides/slides-dl.htm



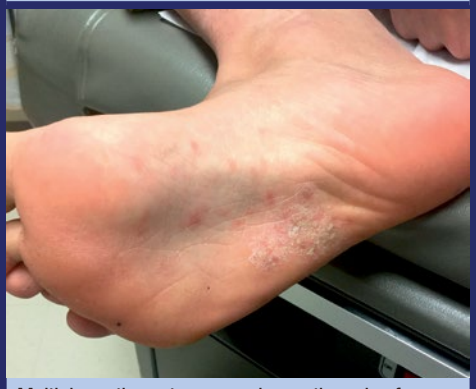
Hyperkeratotic, scaly macules/plaques and pustular lesions on the dorsal hand of a patient with secondary syphilis/Lues Maligna.

Source: Dr. Kimberly Workowski, Emory University



Hyperpigmented dusky erythematous plantar macules in a patient with secondary syphilis.

Source: Division of STD Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention. www.cdc.gov/std/syphilis/images.htm



Multiple erythematous macules on the sole of the foot with some associated desquamation and scaling in a patient with secondary syphilis.

Source: Negusse Ocbamichael, PA; Public Health—Seattle & King County STD Clinic; National STD Curriculum https://www.std.uw.edu/go/pathogen-based/syphilis/core-concept/all.

See pages 92–93 for additional photographic examples of dermatologic evidence of syphilis

Cover photos (top to bottom): Excerpt from the Natural History of Untreated Syphilis (Figure 1); rapid plasma reagin test card; palmar rash seen in a patient with secondary syphilis; injectable benzathine penicillin G.

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The **NYC STD Prevention Training Center** (NYC PTC) is a program of Columbia University Mailman School of Public Health. The NYC PTC is dedicated to increasing the sexual health knowledge and skills of healthcare professionals in the prevention, diagnosis, screening, management and treatment of sexually transmitted diseases. The NYC PTC offers classroom and web-based courses, hands-on training, clinical consultation and technical assistance to medical providers such as physicians, physician assistants, nurse practitioners, and nurses. The NYC PTC region includes New York, New Jersey, Ohio, Indiana, Michigan, Puerto Rico and the US Virgin Islands. The NYC PTC is one of eight regional training centers funded by the **Centers for Disease Control and Prevention** and is a member of the **National Network of STD Clinical Prevention Training Centers**.

The material presented in this publication is intended to serve as a source of clinical guidance in the diagnosis and management of syphilis. The information presented should not be construed as inflexible rules or standards. The 2015 Centers for Disease Control Sexually Transmitted Disease Treatment Guidelines served as the basis for this document. For a complete discussion of the evaluation and management of syphilis and other sexually transmitted infections, please refer to the current CDC STD Treatment Guidelines, which can be found at **https://www.cdc.gov/std/treatment**.

Clinical management for any given patient must consider a variety of case specifics and scenarios which may not be addressed in this document. Healthcare providers should consult with local infectious disease specialists for complex or confusing clinical scenarios. Consultations regarding the medical management of syphilis are available to providers in NYC (through the NYC Department of Health and Mental Hygiene) by calling: **347-396-7200** between 8:00 am and 4:00 pm, Monday to Friday.

Clinicians who are interested in obtaining clinical consultation regarding patient care related to sexually transmitted infections can also visit the STD Clinical Consultation Network (STD CCN) at **https://www.STDCCN.org**. The STD CCN is a free clinical consultation service provided by expert faculty of the **National Network of STD Clinical Prevention Training Centers**. Consultations can be submitted at **(https://www.nnptc.org).** Consultations can be submitted at **https://www.STDCCN.org**.

To download an electronic version (PDF) please visit www.nycptc.org. Please contact the NYC PTC with questions at **nycptc@cumc.columbia.edu**

Contributors

Primary Contributors & Full Reviewers

Thomas Cherneskie, MD, MPH
New York City Department of Health and Mental Hygiene

Laura Bachmann, MD, MPH
US Centers for Disease Control and Prevention

Susan Blank, MD, MPH
New York City Department of Health and Mental Hygiene, US Centers for Disease Control and Prevention

Gail Bolan, MD
US Centers for Disease Control and Prevention

Demetre C. Daskalakis, MD, MPH
New York City Department of Health and Mental Hygiene

Elsie Lee, MD, MPH
New York City Department of Health and Mental Hygiene

Natalie Neu, MD, MPH
Columbia University Medical Center, NYC STD Prevention Training Center

Section Reviewers & Other Contributors *(Listed in alphabetical order)*

Vanessa Arias-Martinez
New York City Department of Health and Mental Hygiene

Mary Ashmore, MD MPH
New York City Department of Health and Mental Hygiene

Michael Augenbraun, MD
State University of New York (SUNY) Downstate Medical Center, Kings County Hospital Center

Shelby Boyle
New York City Department of Health and Mental Hygiene

Kenneth Bromberg, MD
State University of New York (SUNY) Downstate Medical Center

Erica J. Hardy, MD
Women & Infants Hospital, Providence RI, Alpert Medical School of Brown University

Tarek Mikati, MD, MPH
New York City Department of Health and Mental Hygiene

Gowri Nagendra, MPH
Columbia University Medical Center, NYC STD Prevention Training Center

Diana Sanchez MPH PhD
New York City Department of Health and Mental Hygiene

Julia Schillinger, MD, MSc
New York City Department of Health and Mental Hygiene

Marguerite Urban, MD
University of Rochester Medical Center

John Winters, MD, MPH
New York City Department of Health and Mental Hygiene

Editors:

Margaret Millstone
New York City Department of Health and Mental Hygiene

Elizabeth Selkowe
New York City Department of Health and Mental Hygiene

Lise Millay Stevens, MA, Editor

Acronyms and Abbreviations

ART – Antiretroviral therapy

BSTD – Bureau of Sexually Transmitted Diseases

CDC – Centers for Disease Control and Prevention

CIA/CLIA – Chemiluminescence Immunoassay/Clinical Laboratory Improvement Amendments

CLIA – Clinical Laboratory Improvement Amendments

CMIA – Chemiluminescent microparticle immunoassay

CNS – Central nervous system

CSF – Cerebrospinal fluid

CSF-FTA – Cerebrospinal fluid- fluorescent treponemal antibody

CSF-FTA-ABS – Cerebrospinal fluid-fluorescent treponemal antibody absorption test

CSF-RPR – Cerebrospinal fluid-rapid plasma reagin

CSF-VDRL – Cerebrospinal fluid-Venereal Disease Research Laboratory

CT – Computed tomography

DFA – Direct fluorescent antibody

DIS – Disease Intervention Specialist

EIA – Enzyme immunoassay

EIA/CLIA – Enzyme immunoassay/Clinical Laboratory Improvement Amendments

FDA – US Food and Drug Administration

FTA-ABS – Fluorescent treponemal antibody absorption

GC NAAT – Gonorrhea nucleic acid amplification test

HIV – Human immunodeficiency virus

HSV1 – Herpes simplex virus type 1

HSV2 – Herpes simplex virus type 2

IM – Intramuscular

IV – Intravenous

MFI – Multiplex flow immunoassay

MIA/MBIA – Multiplex immunoassay/microbead immunoassay

MSM – Men who have sex with men

NAAT – Nucleic acid amplification testing

NNPTC – National Network of Prevention Training Centers

NYC – New York City

NYC DOHMH – New York City Department of Health and Mental Hygiene

NYS – New York State

PCR – Polymerase chain reaction

PEP – Post-exposure prophylaxis

PrEP – Pre-exposure prophylaxis

POC – Point-of-care

RPR – Rapid plasma reagin

STD – Sexually transmitted disease

STI – Sexually transmitted infection

TPPA – *Treponema pallidum* particle agglutination

VDRL – Venereal Disease Research Laboratory

WBC – White blood cell

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Introduction

Effective diagnosis, management, and prevention of syphilis requires a combination of clinical and public health activities. Prompt recognition of signs and symptoms of the disease, screening patients at risk to detect asymptomatic infection, accurate staging of infected patients, adequate treatment and follow-up, and fruitful risk-reduction counseling are all critical clinical components in the management of the individual patient. Public health considerations aimed at preventing ongoing transmission and controlling the burden of disease in the community include: identification of contacts of an infectious case so as to provide screening and post-exposure prophylaxis; optimization of existing disease surveillance systems (which rely, in part, on prompt reporting by healthcare providers of all newly-diagnosed infections) to track trends and distribution of disease; and the interview of persons diagnosed with infectious syphilis to identify emerging risk factors associated with syphilis acquisition in the community. These clinical and public health activities can be broken down into ten steps (See **Figure 1**). This monograph provides details about how to successfully perform each step of the process.

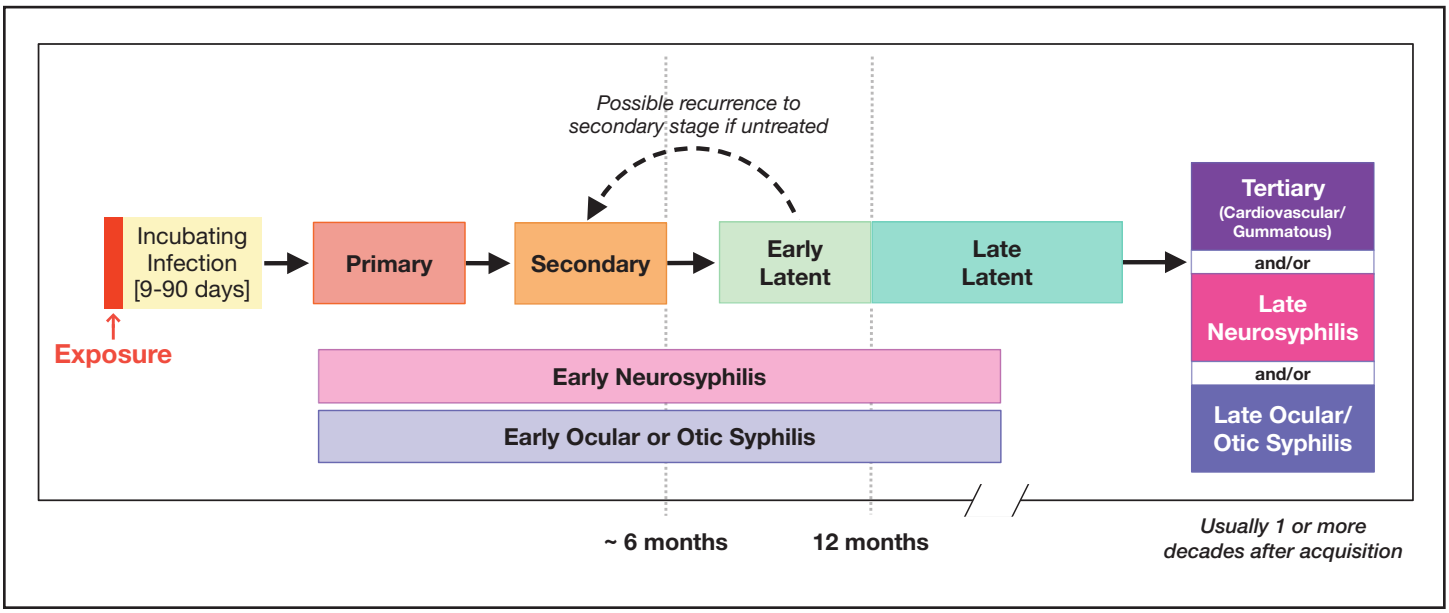
Figure 1. Ten Steps in the Diagnosis, Management, and Prevention of Syphilis

1. **Maximize asymptomatic case detection by screening all patients at risk and patients from at risk populations**
2. **Maintain a high index of suspicion for syphilis in at-risk patients presenting with anogenital ulcerations or other new onset dermatologic findings (eg, rash or warty lesions)**
3. **Carefully interpret available serologic results**
4. **Accurately stage any new infection—by utilizing serologic test results, exam findings, the presence of any current or recent signs/symptoms of syphilis, any history of recent exposure to a syphilis case, and medical history of past serologic testing and treatment**
5. **Provide stage-appropriate treatment**
6. **Rule out coexisting sexually transmitted infections, including HIV**
7. **Ensure referral and management of sexual and needle-sharing contacts**
8. **Promptly report newly diagnosed or treated cases of syphilis to the State/local health department**
9. **Monitor treated patients clinically and serologically to ensure adequate response to therapy and detect reinfection**
10. **Encourage behaviors that decrease the risk of syphilis reinfection and the acquisition of other sexually transmitted infections**

The Natural History of Syphilis and Overview of Signs and Symptoms

For a graphical summary of the natural history of syphilis, see **Figure 2**.

Figure 2. The Natural History of Untreated Syphilis



Transmission of syphilis is primarily through sexual contact or in utero, from mother-to-child. Sexual acquisition of the *Treponema pallidum* spirochete occurs following exposure of mucous membranes or microscopically-abraded skin during sex. The average **incubation period** of syphilis (ie, time from exposure to the development of initial signs or symptoms) is approximately 3 weeks, but can be as short as 10 days or as long as 90 days.[1–3] During the incubation period, serologic test results will remain negative and the patient is not considered to be infectious. Without post-exposure prophylaxis for syphilis, however, persons with incubating infection will go on to develop lesions of primary syphilis, a highly infectious stage of infection.

Following exposure, a localized infection occurs at the site of initial inoculation with proliferation and sensitization of lymphocytes and macrophages which results in the development of one or more **primary syphilis** skin lesions.[4] Classically, the primary syphilis lesion can begin as a macule progressing to a papule which then erodes to become the classic painless ulceration, ie, syphilis "chancre." Atypical lesions can frequently be seen, with one study reporting that of patients with primary syphilis only 42.7% had a "classic" single lesion. Multiple lesions occur more frequently than previous reported, especially in persons living with human immunodeficiency virus (HIV).[5,6] In addition, atypical primary syphilis lesions can be seen which mimic herpes simplex virus (HSV), chancroid, or other non-sexually transmitted skin infections.[5,7,8] Painless regional, often bilateral, lymphadenopathy can accompany the primary stage lesions. Even without treatment, the lesion(s) will heal spontaneously within 1 to 6 weeks, usually without scarring, after which the patient may enter a short asymptomatic period before the onset of signs or symptoms of secondary stage infection.[1,9]

In contrast to the localized findings of the primary stage, **secondary syphilis** presents as a disseminated, systemic form of infection. Within a few hours after inoculation, lymphatic and hematogenous spread of the spirochete occurs to most organ systems in the body. Since *T pallidum* best proliferates in lower temperatures, most clinical signs and symptoms present as skin and mucous membrane eruptions.[10] Dermatologic manifestations of secondary syphilis include: a variety of rashes classically involving the palms and soles; wart-like growths; mucous patches; and alopecia. Skin findings are often accompanied by generalized, non-tender lymphadenopathy and non-specific systemic symptoms such as fever, headache, muscle aches, and fatigue, as well as a variety of other less common manifestations.[11,12] A summary of the manifestations of secondary syphilis is presented in **Table 1**. Lesions of secondary syphilis generally occur 4 to 8 weeks after the appearance of the primary ulcer[2]; in some patients presenting with evidence of secondary syphilis, the primary lesion will still be present.[9,13]

Painless primary stage ulcerations, especially in the rectum or vagina, may go unnoticed by both patients and clinicians; thus, the initial presenting evidence of infection among men who have sex with men (MSM) and women may actually be signs or symptoms of secondary, and not primary syphilis. If untreated, manifestations of secondary syphilis usually resolve within a few weeks, but in some cases may take months.[14] After resolving, a relapse of secondary syphilis signs or symptoms can occur, especially during the first year of infection.[15] Therefore, a patient who acquired their infection within the previous 12 months is considered to be infectious, even if asymptomatic at the time of diagnosis.

The sometimes-subtle dermatologic findings noted above that can occur during early syphilis highlight the need to perform a thorough physical examination in any patient being screened for syphilis or being evaluated for reactive syphilis serologic results.

The localized host immune response leads to bacterial clearance from primary and secondary lesions which ultimately resolve but fails to completely eliminate the spirochetes systemically, resulting in ongoing asymptomatic/latent infection.[4,10,16] Although the patient is asymptomatic, organisms may reseed the bloodstream intermittently during the latent stage of infection, posing an ongoing risk for maternal-fetal transmission.[17]

During latency, no clinical manifestations of primary or secondary syphilis are evident, and usually the infection can only be detected by serologic screening. For the purposes of determining appropriate treatment, the degree of infectiousness, and the expected serologic response to therapy, latent syphilis is broken down into three stages: **early latent** (duration of infection of less than or equal to 1 year), **late latent** (duration of infection of more than 1 year), or **latent syphilis of unknown duration** (for which there is insufficient information to pinpoint the duration of infection).

Central nervous system (CNS), ocular and otic involvement can occur at any stage of infection and the patient may either remain asymptomatic or manifest a variety of neurologic/psychiatric, visual/ocular, or auditory/vestibular signs and symptoms. (See **Table B2.**) The presentation of symptomatic neurosyphilis can differ depending on whether it occurs early or late in the course of infection.

Early neurosyphilis usually occurs a few months to a few years after initial infection. It is rare during the primary stage of infection but has been reported in 1 to 2% of patients with secondary syphilis.[18] This highlights the need for careful neurologic examination in all patients diagnosed with syphilis—including those with primary and secondary syphilis—to rule out neurosyphilis, as the management and pharmacotherapy are different if there is evidence of ocular, otic, or neurosyphilis. Early neurosyphilis occurs as a result of acute inflammation of the meninges and associated vasculature and includes **acute syphilitic meningitis** (often with subtle headache and cranial nerve abnormalities) and **meningo-vascular syphilis**. Meningo-vascular syphilis typically presents as a stuttering stroke-like syndrome which can eventually progress to a cerebrovascular accident when the artery becomes occluded from inflammation.

Ocular and otic involvement can occur with or without other neurologic signs/symptoms or cerebrospinal fluid (CSF) abnormalities. Ocular neurosyphilis most often presents as posterior uveitis, or panuveitis, presenting with symptoms of blurred vision, vision loss, eye pain or eye redness.[19]

Late neurosyphilis usually presents one or more decades after the initial infection and is considered to be part of **tertiary syphilis**. This form of neurosyphilis is a result of chronic inflammation and includes **general paresis** and **tabes dorsalis,** which can present with a wide variety of neurologic symptoms.[2]

Before the advent of antibiotics effective against *Treponema pallidum*, the natural history of untreated latent syphilis in immunocompetent patients followed the rule of thirds: approximately one-third of patients sero-reverted to a nonreactive, nontreponemal syphilis serology with no further evidence of infection; one-third remained reactive by nontreponemal serology but remained free of signs, symptoms, or complications; the remaining third went on to develop evidence of **tertiary syphilis**, sometimes after decades of chronic, persistent, asymptomatic infection.

Tertiary syphilis which also occurs a decade or more after initial infection if left untreated, usually presents as:

- **Cardiovascular disease** – including aortic aneurysm, aortic valve insufficiency, coronary stenosis, or myocarditis

- **Late neurologic complications** – including general paresis, tabes dorsalis, and gummatous disease of the brain or spinal cord

- **Late benign syphilis** – presenting with gumma (progressive inflammatory granulomatous lesions) of skin, bone, viscera, and other soft tissues that leads to the destruction of the affected organs

Although tertiary syphilis is now rare in the United States, neurologic, ocular, and otic complications of untreated syphilis still occur and can ultimately lead to irreversible sequelae. In addition, untreated syphilis in pregnant women can have tragic consequences for a developing fetus when transmitted in utero. (See **Appendix D**.)

Syphilis infection confers no long-term immunity. A person who has been adequately treated for syphilis can potentially become reinfected multiple times over their sexually-active lifetime. Repeat infection follows the same course as the initial infection, potentially progressing through the clinical stages described above.

10 Key Steps in the Diagnosis, Management and Prevention of Syphilis

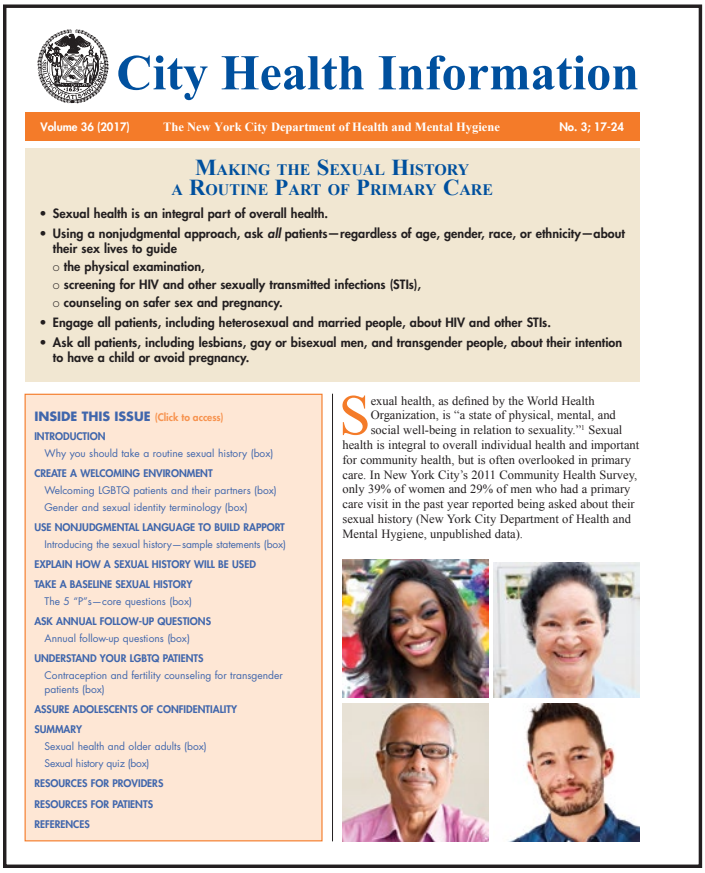
Step 1: Maximize Asymptomatic Case Detection by Screening Patients at Risk and Patients from At-risk Populations

Signs and symptoms of syphilis are transient and often go unrecognized by affected patients owing to mild or subclinical disease or the occurrence of occult lesions in the rectum or vagina; health care providers can also overlook signs and symptoms of syphilis as they may be non-specific and attributed to another diagnosis. This is the reason that syphilis is called the "great imitator." Since most patients diagnosed with the infection lack any signs or symptoms consistent with primary or secondary syphilis, asymptomatic screening remains a crucial means of early case detection and prompt treatment.[20–22]

As stated in the CDC's *2015 Sexually Transmitted Diseases Treatment Guidelines*,[23] obtaining a detailed sexual history is the key to understanding a patient's risk for infection and determining whether syphilis serologic screening is indicated.

> *In order to accurately assess an individual patient's risk for STIs, such as syphilis, clinical providers should be facile in obtaining a sexual and behavioral risk history. Respect, compassion, and a nonjudgmental attitude are essential. The use of open-ended questions and understandable, nonjudgmental normalizing language can help in building rapport.*
>
> *—Centers for Disease Control and Prevention, 2015* [23]

Important elements to include when taking a sexual history and suggestions regarding phrasing of questions are presented in **Figure 3**.



City Health Information

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MAKING THE SEXUAL HISTORY A ROUTINE PART OF PRIMARY CARE

- Sexual health is an integral part of overall health.
- Using a nonjudgmental approach, ask *all* patients—regardless of age, gender, race, or ethnicity—about their sex lives to guide
  - the physical examination,
  - screening for HIV and other sexually transmitted infections (STIs),
  - counseling on safer sex and pregnancy.
- Engage all patients, including heterosexual and married people, about HIV and other STIs.
- Ask all patients, including lesbians, gay or bisexual men, and transgender people, about their intention to have a child or avoid pregnancy.

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Sexual health, as defined by the World Health Organization, is "a state of physical, mental, and social well-being in relation to sexuality."[1] Sexual health is integral to overall individual health and important for community health, but is often overlooked in primary care. In New York City's 2011 Community Health Survey, only 39% of women and 29% of men who had a primary care visit in the past year reported being asked about their sexual history (New York City Department of Health and Mental Hygiene, unpublished data).

For additional information regarding making the sexual history a part of routine primary care, refer to the New York City Department of Health and Mental Hygiene's (NYC DOHMH) **City Health Information. (https://www1.nyc. gov/assets/doh/downloads/pdf/chi/chi-36-3.pdf)** [24]

Figure 3. Taking a Sexual History

How to Take a Sexual and Risk History[a]

General Approach

- Protect confidentiality—assure your patients that you will not share information with parents, partners or others about sexual behaviors or sexually transmitted infections (notable exceptions include sexual abuse or rape of a minor).
- Be sensitive, nonjudgmental, and direct.
- Use simple, age- and culturally-appropriate language.
- Avoid assumptions and generalizations regarding sexual practices.
- Encourage questions.
- Revisit the patient's sexual history at least annually.

What to Ask

"Sexual health is an important part of general health, so I always talk to all of my patients about it. I'd like to ask a few questions":

1. **Are you sexually active?** Use other terms to clarify "sex" and "sexual activity," if necessary.
2. **How many sexual partners have you had since last screened for STIs/HIV? Do you have sex with men, women, transgender partners, or any combination of these?**
3. **Do you have oral sex, vaginal sex, anal sex?** Information about the types of sex and partners helps guide which STIs to test for, and which sites to test.
4. **Have you ever had a sexually transmitted infection?** Previous or repeat infections may denote higher risk.
5. **Do you know your current HIV status?** Offer HIV testing routinely to all sexually active patients between the ages of 13 and 64 years. If the patient is living with HIV, confirm current treatment and degree of viral suppression.
6. **Do you use condoms? How often? For which types of sex?** Condoms protect against pregnancy and most STIs, including HIV. The consistency of condom use may differ by type of sex or sex partner.
7. **Are you currently taking HIV pre-exposure prophylaxis (PrEP)? Have you taken PrEP or PEP in the past?** If PrEP is indicated, assess patient's knowledge, questions, and concerns. If indicated, provide or refer for PrEP. Use of post-exposure prophylaxis (PEP) in the past is often a predictor of ongoing risk for HIV, and is an indication for considering PrEP.
8. **Have you been fully vaccinated for Human Papillomavirus (HPV), Hepatitis B?** Attempt to confirm documentation of completed series for Hepatitis B and HPV vaccines, as well as other sexually relevant vaccines such as Hepatitis A.
9. **Do you want to become pregnant (or father a child)?** If not, what kind of birth control method do you use?
10. **Have you ever had sex when you really didn't want to?** Health care providers must report suspected sexual abuse of minors to the NYS Central Registry for Child Abuse and Maltreatment at (800) 635-1522 or 311 (in New York City). Adult victims of rape should be referred to law enforcement and/or social services as needed: call the Sexual Assault Hotline at (800) 656-HOPE or 311 (in New York City).
11. **Are you ever frightened for your (or your children's) safety because of the anger of a partner or family member? Have you ever been injured by a partner or family member?** Victims of domestic and intimate partner violence can call the Domestic Violence Hotline at (800) 621-HOPE or 311 (in New York City).
12. **Do you have any questions for me about your sexual health?**

[a] Adapted from: New York City Department of Health and Mental Hygiene: Take Action—Stop the Spread. How to Take a Sexual History and Provide Brief Counseling. New York City STD/HIV Prevention Training Center **https://www.nycptc.org/x/Taking_a_Sexual_History.pdf**

Another approach for obtaining a sexual history can be found in the **CDC's Sexually Transmitted Diseases Treatment Guidelines**—The Five P's: Partners, Practices, Prevention of Pregnancy, Protection from STDs and Past History of STDs.

Providing Care to Adolescents

Providing sexual and reproductive health care to adolescents is fraught with concerns about confidentiality and parental consent. As a result, all states have created consent laws, giving adolescent minors the right to certain types of health services without parental consent, such as screening and treatment of STIs and reproductive health services.

Confidentiality to ensure the delivery of such care to adolescents is protected by myriad specific Public Health Laws and regulations. In New York State (NYS), adolescents' right to confidential sexual and reproductive health care is protected by New York public health laws (§2504; §2780, §2781 and §2786;[25–28] New York Social Service Laws 350 [1] [e];[29] 365-a [3] [d];[30] New York Codes, Rules and Regulations Title 18: 463.1, 463.6,[31] 505.13;[32] and the Code of Federal Regulations Title 42: 59.5 [a]).[33] For further information, consult the NYC DOHMH **publication** Sexual and Reproductive Health Care: Best Practices for Adolescents and Adults available at **www1.nyc.gov/assets/doh/downloads/pdf/ms/srh-clinical-guide.pdf**.

Adolescents in New York, and many other states, have a statutory right to confidential sexual and reproductive health care. They should be afforded confidential care except if the provider suspects physical, sexual or emotional abuse (which is required to be reported), or if the adolescent may be at risk of harm to self or others.

Discussing confidentiality issues with an adolescent prior to care is important and may be supplemented by a confidentiality statement posted in the waiting room or given to patients. Maintaining confidentiality regarding sexual and reproductive health services during the billing process, however, presents a challenge. Most insurance companies send letters or other notifications explaining benefits used or covered (explanation of benefits—EOB forms) to policy holders,[34] which are usually parents, guardians, or other adult caregivers. Although such statements may list general categories of services rendered such as "preventive services," parents or guardians may question the adolescent about the medical care received without the parents' knowledge. In addition, if laboratory services are provided, billing statements and results may be sent to the policy holder's address.

Providers can use strategies to maintain the confidentiality of adolescents' sexual health services, for example, by informing patients that they can request the EOB to be sent to a different address. In addition, providers can find ways to cover the costs of services (eg, grant funding, clinic funding or referral to local free sexual health services) to avoid having to bill the patient's insurance.

For additional sexual and reproductive health care guidelines and resources which address adolescents and young adult patient populations, see:

https://nationalcoalitionforsexualhealth.org/tools/for-healthcare-providers/compendium-of-sexual-reproductive-health-resources-for-healthcare-providers

The American Academy of Pediatrics also provides guidance and provider resources regarding adolescent sexual health, which is available at:
https://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/adolescent-sexual-health/Pages/default.aspx

Syphilis Screening Recommendations

The recommendations listed in **Table 1** are specifically targeted to the New York City (NYC) populations. Public health laws on syphilis screening during pregnancy can vary from state to state; providers should confirm specific state recommendations with their local or state health departments.

Table 1. Recommendations for Asymptomatic Serologic Screening for Syphilis by Population

Patient Population	Screening Recommendations
MSM	• At least annually if sexually active [23] • More frequent screening (eg, every 3 months) for persons with ongoing risk of infection/re-infection since last screened, see table footnote a (below). [23,35,36]
Patients Taking PrEP for HIV Prevention	• At PrEP initiation[37] • Every 6 months for all patients on PrEP; every 3 months for MSM at high risk, see table footnote a (below).[38]
Persons Living with HIV	• At initial HIV evaluation[39] • At least annually if sexually active[23] • More frequently (eg, every 3 months) for persons with ongoing risk of infection/re-infection since last screened, see table footnote a (below).[23,35]
Transgender Women and Men	• Because of the diversity of transgender persons (gender affirming surgical procedures, hormone use, gender of sexual partners, sexual practices), clinicians should make an individualized assessment of STI/HIV-related risk and offer screening for asymptomatic infection as appropriate[23]
Non-pregnant Women (Cis-gender) and Non-MSM Men	• No national recommendation for routine screening in the general population • Screening at least annually is recommended in sexually active persons who are at increased risk for infection, see table footnote b (below).[35]
Women Who Have Sex with Women	• No national screening recommendations; consider following the recommendations listed for non-pregnant women (see above)
Pregnant Women	• At the first prenatal medical encounter[23, 40-42] Syphilis screening at the time of initial pregnancy diagnosis should be considered, especially when access to prenatal care is not optimal or if there is any risk of loss to follow-up after referral for prenatal care[23] • At delivery (including live births, stillbirths, or terminations)[40–42] • At the time of a fetal death (after 20 weeks' gestation)[23] • Per CDC recommendations, pregnant patients who are at high risk for syphilis or live in areas of high syphilis morbidity, see table footnote b (below), such as NYC, should be rescreened early in the third trimester (at approximately 28 weeks' gestation) and at delivery[23] Given the increasing prevalence of syphilis in NYC, the NYC DOHMH also recommends the following for pregnant patients[41]: • Assessment of sexual risk for syphilis and other STIs at each prenatal visit • Serologic re-screening if patient reports: – A recent bacterial STI diagnosis – A new sexual partner – Sex with an MSM partner or transgender woman Though not a part of any formal national recommendations, syphilis screening of new sexual partners of sexually-active pregnant patients could help to prevent or identify unrecognized maternal infection
Neonates	• All neonates at delivery[40–42]

(Table continues on the following page)

Table 1. Recommendations for Asymptomatic Serologic Screening for Syphilis by Population *(continued)*

[a] Among MSM, transgender women with male partners, and persons with HIV, more frequent screening (eg, every 3 months) should be considered in patients who report any of the following for self or partner[38]:

- Multiple or anonymous sex partners
- A recent bacterial STI (eg, diagnosed at the previous visit or since last STI screening)
- Use of recreational substances, including methamphetamine (especially if used during sex)
- Participation in sex parties or sex in other high-risk venues
- Participation in any type of transactional sex (eg, commercial sex work, exchange of sex for drugs or services)

[b] In addition to MSM and persons with HIV, populations at increased risk of syphilis based on the current epidemiology in the US include the following[35,36]:

- Young adult men (younger than 29 years of age)
- Members of certain racial or ethnic groups (Black, Native Hawaiian/Other Pacific Islander, Hispanic/Latinx, and American Indian/Alaska Native)
- Persons reporting transactional sex (eg, commercial sex work, exchange of sex for drugs or services)
- Persons in correctional institutions
- Residents of specific geographic areas (eg, metropolitan areas such as NYC, southern and western US states)[22] For the most up-to-date CDC STD Surveillance data, visit **www.cdc.gov/std/stats**.

Abbreviations: HIV, human immunodeficiency virus; MSM, Men who have sex with men; NYC DOHMH, New York City Department of Health and Mental Hygiene; PrEP, Pre-exposure prophylaxis for the prevention of HIV; STI, sexually transmitted infection.

[23] Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines, 2015

[36] US Preventive Services Task Force. Screening for Syphilis Infection in Nonpregnant Adults and Adolescents. US Preventive Services Task Force Recommendation Statement. *JAMA*. 2016;315: 2321-2327.

[35] Cantor AG, Pappas M, Daeges M, Nelson HD. Screening for syphilis: updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2016;315(21):2328-2337.

[39] HIV Clinical Resource. NYS Department of Health AIDS Institute

[42] Mandated by some state public health laws including NYS Law Article 23, §2308

[40] N.Y. Comp Codes R. and Regs. Tit 10, § 69-2.2)

[41] NYC DOHMH Health Alert #14, Syphilis is increasing among women of child-bearing age in New York City, 2016

[37] Preexposure prophylaxis for the prevention of HIV infection in the United States– 2017 update, CDC (**www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2017.pdf**)

[38] PrEP for HIV Prevention, NYS Department of Health, **www.hivguidelines.org/prep-for-prevention/**

Note: The CDC recommends maternal testing for any stillbirth after more than 20 weeks gestation, though NYS Public Health Law mandates testing for any stillbirth after more than 22 weeks gestation.23,42

Diagnostic testing is also warranted in patients presenting with signs or symptoms suggestive of primary, secondary, tertiary, ocular, otologic, or neurosyphilis; this should include patients with unusual genital lesions, warts or other new onset dermatologic findings which could be consistent with syphilis.

Serologic testing for syphilis should also be performed (along with presumptive treatment) in patients reporting sexual or needle-sharing contact with a known syphilis case.

Screening for syphilis should be considered any time HIV screening is ordered, given the common risk factors and overlapping prevalence of the two infections.

Step 2: Maintain a High Index of Suspicion for Syphilis in At-risk Patients Presenting with Ano-genital Ulcerations or Other New Onset Dermatologic Findings

Primary Syphilis: Anogenital Ulcer or Lesions

(See pages ii–iii for photographic examples)

When evaluating a patient presenting with an anogenital ulcer or lesion, a variety of sexually transmitted etiologies must be considered, including: herpes simplex virus types 1 and 2; *T pallidum* (syphilis); *Haemophilus ducreyi* (the cause of chancroid); *Chlamydia trachomatis* L1, L2 and L3 serovars (which are associated with lymphogranuloma venereum, ie, LGV); and *Klebsiella granulomatis* (originally classified as *Calymmatobacterium granulomatis*), which is responsible for granuloma inguinale (also known as donovanosis). Chancroid and granuloma inguinale are seen rarely in the United States, and HSV and syphilis account for the majority of sexually transmitted cases of genital ulcer disease, although the frequency of each of these conditions can differ by geographic area and patient population.[22,23,43]

See **Table 2** for a comparison of the classic presentation for each of the most common sexually transmitted infectious causes of genital ulcer disease.

The classic syphilis chancre is a single, sharply-demarcated, firmly indurated, painless, clean-based ulceration ranging in size from 1cm to 2cm in diameter. Although the presence of these classic characteristics simultaneously is highly predictive of primary syphilis, they occur together in only one-third of all primary chancres.[20,44] The single most specific characteristic for primary syphilis is ulcer induration.[44]

Atypical primary syphilis lesions occur more frequently than previously recognized and include: ulcerations that are non-indurated or irregularly bordered; painful primary lesions (especially in the anal area or if secondarily infected with other skin or rectal organisms).[5,44,45] Multiple ulcerations have been reported in up to 40% of primary syphilis cases, a finding that appears to occur more commonly in persons with HIV, though studies exploring the effect of HIV viral suppression on these findings are lacking.[6] Given the occurrence of non-classic-appearing or atypical primary lesions, even if an anogenital skin lesion(s) seems more consistent with another etiology (eg, herpes simplex virus, chancroid, Behcet's disease, fixed drug eruption, or superinfected traumatic lesion)[46,47], syphilis should still be considered, especially in patients with increased risk for STIs. Also, the presence of one STI at the site of a genital lesion does not exclude a coexisting infection in the same lesion. In a case series, two or more pathogens have been detected in over 20% of genital ulcers.[43]

Primary syphilis ulcers/lesions are seen most commonly at the penis in men; in women, primary lesions are seen most often on the labia, fourchette, and, to a lesser extent, on the cervix.[9] Anorectal and oral primary lesions may also occur, depending on the site of exposure.[9] Regional lymphadenopathy usually accompanies the primary lesion(s), but can be a subtle presentation.

One of the key public health goals regarding STIs is to prevent ongoing transmission through prompt presumptive treatment of suspected cases (decreasing the duration of infectiousness for any given case). This is especially true of primary syphilis, which is a highly infectious stage of syphilis. Therefore, all sexually active adults or adolescents who present with anogenital lesion(s) should be tested for syphilis. Healthcare providers evaluating sexually active adults or adolescents presenting with genital lesion(s) who are also at increased risk for syphilis (eg, MSM) should consider providing presumptive treatment for syphilis at the time of the initial visit, rather than awaiting laboratory results. In such a circumstance, any risk of overtreatment in the presenting patient is offset by the need to protect the health of the community.

Lesion-Based Diagnostic Testing in Primary Syphilis

Serologic testing may be negative during early primary syphilis and lesion-based testing may be the only means of confirming the diagnosis. In many cases, it may take 1 to 4 weeks after the appearance of the primary lesions for nontreponemal and treponemal antibodies to develop.[48]

Treponemal tests may be slightly more sensitive at the primary stage compared with the nontreponemal tests, but neither a negative treponemal test nor a negative nontreponemal test rules out primary syphilis. Follow-up testing may be needed to confirm or completely rule out syphilis as the etiology of the genital lesion(s).[49,50] Although there is only limited availability in most clinical settings, direct lesion-based testing of suspicious ulcers or moist papules can be used to confirm a diagnosis of primary or secondary syphilis.

Lesion-based testing includes:

- ***T pallidum*** **polymerase chain reaction (PCR) testing of lesion exudate:** Although there are no US Food and Drug Administration (FDA) approved commercially-available assays, PCR testing may be available through individual reference laboratories that have undertaken the necessary Clinical Laboratory Improvement Amendments (CLIA) validation requirements. Clinicians providing care to high-risk patient populations (such as MSM) could attempt to locate a reference laboratory that offers *T pallidum* PCR testing to aid in the diagnosis of primary syphilis in patients presenting with ano-genital lesions.

- **Dark field microscopy of lesion exudate:** Although not widely available, dark field microscopy testing is still performed in some STI specialty clinics such as the NYC DOHMH Sexual Health Clinics. Patients in NYC can be referred to one of the NYC DOHMH **Sexual Health Clinics** by contacting **347-396-7200**. Clinicians can consult with their local or state health department to determine availability in other areas of the US.

- **Direct fluorescent antibody testing (DFA) of lesion exudate:** DFA testing utilizes fluorescein-labeled treponeme-specific antibody but is currently unavailable in any laboratories in the US.

Table 2. Clinical Features of Anogenital Ulcers[46,51–56]

Diagnosis (Causative Agent)	Incubation Period	Dermatologic Characteristics		Associated signs and symptoms
		Initial Lesion	Ulceration(s)	
Syphilis (*T pallidum*)	About 3 weeks (9–90 days)	Papule(s)	Well-demarcated, painless, round-oval, indurated ulceration(s) with a smooth, nonpurulent, relatively nonvascular base; more commonly solitary. Atypical lesions can be common.	Bilateral, firm, nontender lymphadenopathy
Herpes *(Herpes simplex virus)*	2–12 days	Multiple vesicles, papules, or pustules	Multiple erosions or superficial ulcerations with an erythematous, nonvascular base; ulcers are often tender (especially during primary outbreak) and may coalesce	During primary outbreak, systemic symptoms are common (eg, fever, headache, myalgias, and fatigue). Bilateral tender, nonfluctuant lymphadenopathy can be seen during primary infection
Lymphogranuloma venereum -LGV **(*C trachomatis*, serovars *L1, L2, L3*)**	3 days–6 weeks	Usually small, solitary papule, pustule, or vesicle	Elevated, round-oval ulceration of variable depth and tenderness. Note: Although LGV can present as an ano-genital ulceration, the more common presentation over recent years has been symptoms of proctitis caused by rectal LGV.	Associated with unilateral, tender lymphadenopathy which may suppurate and rupture to form draining sinuses or fistulae. Lymphangitis and local or regional genital edema can also be seen.
Chancroid (*H ducreyi*)	1–14 days	Multiple papules or pustules	Multiple, very tender, soft, excavated ulcerations with a purulent, vascular or friable base, irregular borders and ragged, undermined edges	Painful inguinal adenopathy seen in half of cases[55]; Suppurative adenopathy or buboes seen in up to 40% of cases[56]
Granuloma inguinale, aka Donovanosis **(*K granulomatis*)**	1 week–6 months	Firm papule or subcutaneous nodule	Multiple presentations: • Solitary or multiple **painless**, elevated, firm fleshy, beefy red, friable ulcers of variable depth • Deep necrotic foul-smelling ulcerations • Verrucous ulcers or growths with raised irregular edges • Sclerotic lesions with extensive fibrosis	Adenopathy is uncommon, but when present, may develop into non-tender pseudobuboes.

Secondary Syphilis: Disseminated Mucocutaneous Eruptions and Other Manifestations

(See pages iii, 92–93 for photographic examples)

The rash of secondary syphilis can be nonspecific in appearance and present as a macular, papular, annular, or pustular eruption, and can be either generalized or localized. Skin lesions are usually nonpruritic and are scattered across the trunk, extremities, or anogenital areas. Discrete, oval, sometimes scaly lesions can be seen on the palms of the hands and soles of the feet in more than half of cases.[11] Exam findings of secondary syphilis may be difficult to distinguish from other common dermatologic conditions such as pityriasis rosea, varicella zoster, tinea versicolor, drug eruption, viral exanthema, acute HIV infection, and, in the case of annular syphilitic lesions, erythema annulare centrifugum, granuloma annulare, or sarcoidosis. Secondary syphilis rashes are often misdiagnosed because sexual histories are not performed and, as a result, STI risk is not recognized and syphilis is not considered in the differential diagnosis.

The primary lesion may still be present at the onset of symptoms or signs of secondary syphilis, a finding that is more commonly seen in persons with HIV.[6,9,13] Patients with concurrent findings of primary and secondary syphilis should be staged and treated for secondary stage infection.

Secondary syphilis should be considered in any patients at risk for infection who present with a new-onset rash (generalized or localized), especially when associated with systemic complaints such as fever, headache, muscle aches, fatigue, and generalized lymphadenopathy. Given the considerable overlap between symptoms of secondary syphilis and acute HIV infection, as well as shared risk factors, both diseases should be considered and ruled out. Since condyloma lata, seen in secondary syphilis, may not be easily distinguished from condyloma acuminata (caused by human papillomavirus infection), syphilis serologic testing should be performed when diagnosing or treating any new anogenital wart.

Other less common manifestations of secondary syphilis include: mucous patches and patchy alopecia; syphilitic meningitis; meningovascular syphilis; ocular or otic syphilis; clinical symptoms and signs of renal, hepatic, gastric involvement (rare); and necrotic skin lesions associated with lues maligna (commonly seen decades ago but uncommon in the 21st century). **Table 3** summarizes the diverse clinical manifestations of secondary syphilis.

Of note, since the signs of secondary syphilis occur as a result of disseminated infection, the occurrence of anal lesions in patients denying anal-receptive sex, or oral lesions in patients denying oral sex, may indicated the presence of secondary syphilis. To avoid overlooking manifestations of secondary syphilis, patients presenting with reactive syphilis serologic testing should have a complete examination of the skin and mucous membranes, including the oral cavity, genitals, and anus, regardless of the types of sexual contact reported by the patient. Also, all patients with signs of secondary syphilis must have a careful neurologic examination. Identification of neurologic, ocular, or otic involvement in a patient diagnosed with syphilis would require intravenous treatment with aqueous crystalline penicillin G rather than intramuscular benzathine penicillin G.

Serologic tests should be reactive once the patient exhibits signs of secondary syphilis and will often have relatively high nontreponemal titers (eg, 1:32 or higher), although the level of the titer alone should not be used to rule in or rule out any specific stage of infection.[1,10,48]

Table 3. Summary of the Signs and Symptoms of Secondary Syphilis[9–12, 57–62]

Organ System	Clinical Findings
Skin and Mucous Membranes	• Rash or other skin lesions with varied appearance frequently on palms/soles – Macular/papular/maculopapular – Annular – Psoriasiform – Necrotic (rare) • Condyloma lata: moist, gray-white, wart-like growths appearing in warm moist areas such as the perineum and the anus • Patchy alopecia, often with a moth-eaten appearance • Mucous patches: flat, silver-gray discrete macules, plaques or erosions involving the mouth, tongue, or ano-genital mucosa • Split- or fissured-papules at the angles of the mouth and nasolabial folds (rare)
Systemic	• Lymphadenopathy • Systemic symptoms including: malaise, fever, and other nonspecific constitutional symptoms
Gastrointestinal	• Gastric syphilis • Hepatitis (usually subclinical)
Renal	• Glomerulonephritis • Nephrotic syndrome
Musculoskeletal	• Arthritis • Periostitis
Neurologic	• Signs/symptoms of meningitis (eg, subtle headache) • Cranial nerve (CN) dysfunction (especially 6th, 7th, 8th CN) • Meningovascular syphilis with stuttering stroke symptoms
Ocular/Otic	• Symptoms of anterior, posterior, or panuveitis; other manifestations include episcleritis, vitritis, retinitis, papillitis, interstitial keratitis, acute retinal necrosis, and retinal detachment • Symptoms of otologic syphilis (eg, hearing loss, tinnitus, vertigo)

Step 3: Carefully Interpret Available Serologic Results

Serologic testing for syphilis includes a variety of assays that fall into 2 general categories—nontreponemal assays and treponemal (or treponeme-specific) assays. **Table 4** summarizes the performance characteristics and clinical utility of these two types of serologic tests.

Table 4. Comparison of Nontreponemal and Treponeme-specific Serologic Testing

	Nontreponemal	Treponeme-specific
Assay	• RPR (Rapid Plasma Reagin) • VDRL (Venereal Disease Research Laboratory)	• FTA-ABS (Fluorescent Treponemal Antibody Absorption) • TPPA (*T Pallidum* Particle Agglutination) • EIA (*T Pallidum* Enzyme Immunoassay) • CIA/CLIA (Chemiluminescence Immunoassay) • MIA/MBIA (Multiplex/Microbead Immunoassay) • CMIA (Chemiluminescence Microparticle Immunoassay) • MFI (Multiplex Flow Immunoassay) • Immunoblot • Rapid point-of-care treponemal assays
Antibody Detected	Antibody to cardiolipin-cholesterol-lecithin antigen	Antibody to recombinant treponemal antigen
Type of Result Useful in Patient Management	Qualitative (reactive vs. nonreactive) **AND** quantitative (titer) results	Qualitative results
Test Difficulty and Cost	Performed manually with visual interpretation; therefore, can be more labor and time intensive and subjective than treponeme-specific testing	Immunoassays can be automated, resulting in cost-savings for large volume laboratories and have more objective results
Test Sensitivity **(False-negative Results)**	**May have limited sensitivity during:** • Early infection • Infection with high titers, ie, prozone phenomenon (if the sera is run undiluted or not diluted out to a titer of at least 1:16) • Long-standing untreated infection after prolonged latency	• May be falsely nonreactive in very early infection, but can seroconvert sooner than nontreponemal assays • Are not subject to false-negative results due to prozone phenomenon, which is seen with nontreponemal tests. • Persistent reactivity even after long-standing disease latency can result in identification of untreated syphilis cases for whom the RPR has become nonreactive

Continued on following page

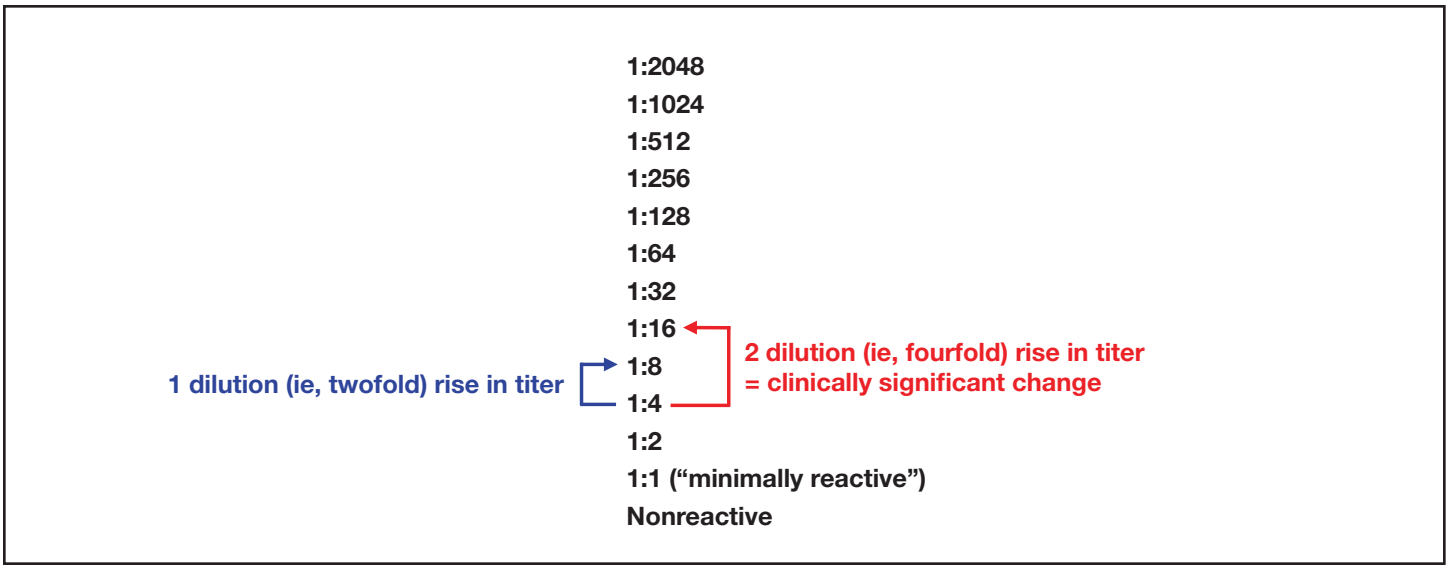
Table 4. Comparison of Nontreponemal and Treponeme-specific Serologic Testing *(continued)*

	Nontreponemal	Treponeme-specific
Test Specificity **(False-positive results)**	**Both nontreponemal and treponeme-specific serologic tests have imperfect specificity**	
	• Lower specificity than treponemal testing, therefore any reactive nontreponemal test must be confirmed by a treponeme-specific test to confirm a diagnosis of syphilis • False-positive results can be caused by other infections or chronic inflammatory conditions (See **TABLE 8**)	• False-positive results from cross-reacting nontreponemal serum antibodies (eg, other treponemal diseases such as Yaws, Pinta, Bejel and other spirochete infections such as Lyme) are rare • Superior specificity • Traditionally used to confirm a reactive nontreponemal result • More recently used as the initial screening test in high volume labs (reverse sequence algorithm) but if screening low risk populations may have more false-positive results
Association With Disease Activity	• Quantitative results usually correlate with disease activity: – Titers generally decline following treatment and rise with reinfection – Testing can revert to nonreactive after successful treatment • Testing may revert to nonreactive **even without** treatment after prolonged latency	• Results not associated with disease activity – Long-lasting reactivity usually seen despite curative therapy – Can't distinguish current active (untreated) syphilis from previously treated infection • May be able to detect long-standing untreated infection even when nontreponemal reactivity has waned due to prolonged latency
Clinical Uses	• Initial test used as part of the traditional sequence syphilis screening algorithm (See **Figure 5**) • Used to monitor serologic response to therapy • Used to detect reinfection in patients with a history of previous treatment (eg, a rise in RPR titer sustained > 2 weeks)	• Initial test used as part of the reverse sequence syphilis screening algorithm (See **Figure 6**) • Used to confirm a reactive nontreponemal result as part of the traditional sequence syphilis screening algorithm • May detect infection in situations where nontreponemal test is nonreactive (eg, very early primary infection or old untreated latent infection)

Nontreponemal Assays

Nontreponemal assays such, as the rapid plasma reagin (RPR) and venereal disease research laboratory (VDRL), detect nonspecific antibodies produced in response to presence of antigenic particles, including cardiolipin, which are released by host tissue in the setting of certain acute and chronic conditions including syphilis.[17, 48] Although highly sensitive for the detection of syphilis, the RPR and VDRL have limited specificity, and when reactive, require confirmation with a treponeme-specific assay.

Figure 4. Example of Quantitative Nontreponemal Titers That Indicate a Clinically-significant Change



Both qualitative and quantitative nontreponemal testing can be performed. Quantitative testing involves serial dilution of serum specimens to determine the amount of nontreponemal antibody present. Each dilution in nontreponemal titer represents a 2-fold change; therefore, a rise or fall in RPR/VDRL titer by 2-dilutions represents a 4-fold change. When comparing quantitative nontreponemal results over time in a patient previously treated for syphilis, a 2-dilution (or 4-fold) rise or fall in RPR/VDRL titer represents a clinically significant change. (See **Figure 4**).

Quantitative results (ie, RPR titers) usually correlate with disease activity, rising in early infection and declining over time, even without treatment. Following adequate therapy, nontreponemal titers can revert to nonreactive status especially if treatment is early in the course of infection. Nevertheless, some adequately treated patients will have persistently reactive or "serofast" nontreponemal test results. Serofast reactivity is estimated to occur in 15% to 20% of early syphilis cases and 35% of patients treated for late latent infection.[63,64]

The RPR and VDRL, both nontreponemal serologic tests, are equally reliable in the diagnosis of syphilis. Nevertheless, comparing quantitative results (ie, titers) over time between RPR and VDRL is difficult because they use different testing methods; in general, RPR titers are often slightly higher than VDRL titers for a given specimen. Sequential testing over time to monitor response to treatment or to screen for reinfection is best done using the same nontreponemal assay (RPR or VDRL) in the same laboratory.

Nontreponemal testing is used as the initial step in the traditional syphilis screening algorithm, see **FIGURE 5**.

Note: Since RPR testing is the most common form of nontreponemal testing used in clinical practice in the US, the remainder of this document will use the terms "nontreponemal serologic testing" and "RPR" interchangeably.

Treponeme-Specific Assays

Treponeme-specific testing includes assays such as the fluorescent treponemal antibody (FTA), the *T pallidum* particle agglutination (TPPA), and the chemiluminescence immunoassay (CIA). Unlike nontreponemal tests, which decline or become nonreactive after successful treatment, treponeme-specific tests usually remain reactive for life in patients with syphilis, even when they have received adequate therapy. The exception is a patient who is treated very early in the course of infection.[65] Therefore, treponemal tests cannot be used to differentiate active, untreated syphilis from previously treated infection or to evaluate previously treated patients for possible reinfection.

Although quantitative treponemal test results are some-

times included in the laboratory report, they do not correlate well with disease activity and should not be ordered or used to determine syphilis staging, assess post-treatment serologic response or screen for reinfection.

Treponeme-specific testing is used as the initial step in the reverse sequence syphilis screening algorithm, (See **Figure 6**).

Rapid Point-of-Care Testing for Syphilis

Historically, the qualitative RPR has been the only commercially-available, rapid point-of-care (POC) serologic test for syphilis. Recently, multiple treponeme-specific POC tests have been developed and there are Clinical Laboratory Improvement Amendment (CLIA)-waived tests that have attained US Food and Drug Administration (FDA) approval. The utility of these tests in the diagnosis of syphilis is limited to patients with no history of previously treated infection, since treponemal tests tend to remain positive even after treatment. Therefore, these tests cannot be used to screen for reinfection among patients with a history of syphilis.

In practice, the prevalence of syphilis in the population tested significantly affects the utility of these rapid treponemal tests—the positive predictive value for syphilis infection is significantly lower in patient populations with a low prevalence; in populations with a high prevalence, there is an increased likelihood that a positive treponemal result is due to persistent serofast reactivity from a previously treated infection. Also, despite demonstrating robust performance characteristics during the development phase, data on the field use of POC assays in various clinical and nonclinical settings are limited and additional evaluation of test reliability and accuracy is ongoing.

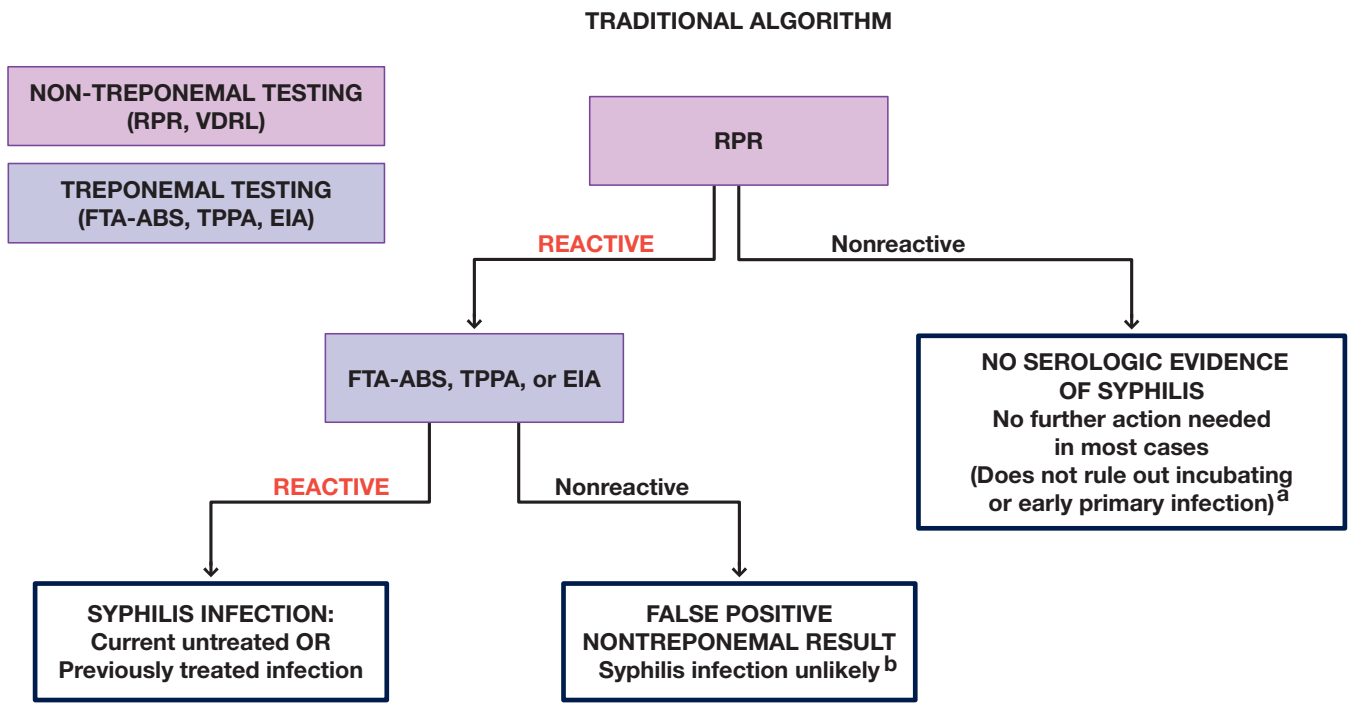
Serologic Testing Algorithms

To maximize the sensitivity and specificity of the serologic diagnosis of syphilis, the results of both nontreponemal and treponeme-specific testing must be taken into account along with patient information such as any current or recent signs/symptoms of syphilis, history of syphilis exposure and any previous serologic results or treatment.

Laboratories use one of two testing algorithms, which incorporate nontreponemal and treponeme-specific assays—the traditional algorithm or the reverse sequence algorithm discussed below.

Traditional Syphilis Screening Algorithm (See **Figure 5.**) The traditional algorithm utilizes a nontreponemal test (eg, RPR) as the initial screening test with reactive specimens undergoing confirmatory testing with a treponeme-specific assay (such as the FTA-ABS, TPPA or EIA).

Figure 5. Traditional Syphilis Screening Algorithm[66]



[a] Does not rule out incubating or early primary infection.

- **In a patient who reports an exposure,** in the past 90 days, to a sexual (or needle-sharing) partner newly diagnosed with syphilis, providers should offer presumptive treatment (See **Step 7**). If presumptive treatment is not administered, repeat serologic testing should be performed in 1 month and 3 months to rule out seroconversion following the recent exposure.
- **In a patient presenting with a skin lesion** on physical examination which is suspicious for primary syphilis, providers should consider presumptive treatment even in the face of nonreactive serologic results; lesion-based testing could also be performed if available. If presumptive treatment is not administered, repeat serologic testing should be performed in 2–4 weeks to assess for syphilis seroconversion and rule out primary infection. In a patient presumptively treated for primary syphilis whose initial syphilis serology is negative, repeat serologic testing can be performed 2–4 weeks following the initial nonreactive result. Such retesting may detect early seroconversion and if reactive can confirm the syphilis diagnosis as well as establish a baseline titer useful in post-treatment follow-up.

[b] In a patient with no history of syphilis treatment, an isolated reactive RPR could represent partial/early seroconversion. If the patient reports a recent exposure to a syphilis case, presents with a skin lesion suspicious for primary syphilis, has a high nontreponemal test titer (eg, >1:8), or is at increased risk for syphilis, repeat testing in 2–4 weeks might reveal further seroconversion (including reactive treponeme-specific testing). If a patient is at high risk for syphilis and there is a significant risk of loss to follow-up, presumptive treatment could also be considered.

See **TABLE 5** for additional details regarding interpretation of algorithm endpoints and further management.

Reverse-Sequence Syphilis Screening Algorithm (See **Figure 6**.)

With the increased availability of automated treponeme-specific immunoassays, many clinical laboratories have begun to use a reverse-sequence testing algorithm that utilizes a treponeme-specific immunoassay, such as the enzyme-linked immunosorbent assay (EIA) or chemiluminescent immunoassay (CIA), for initial screening. Specimens that are reactive by treponemal testing then undergo reflex qualitative RPR testing and if reactive, quantitative RPR testing (ie, titering).

A positive result by the reverse-sequence algorithm can occur in persons with untreated or inadequately treated syphilis, those with successful treatment in the past, and those with false-positive results, which can occur in patient populations with a low likelihood of infection.[23]

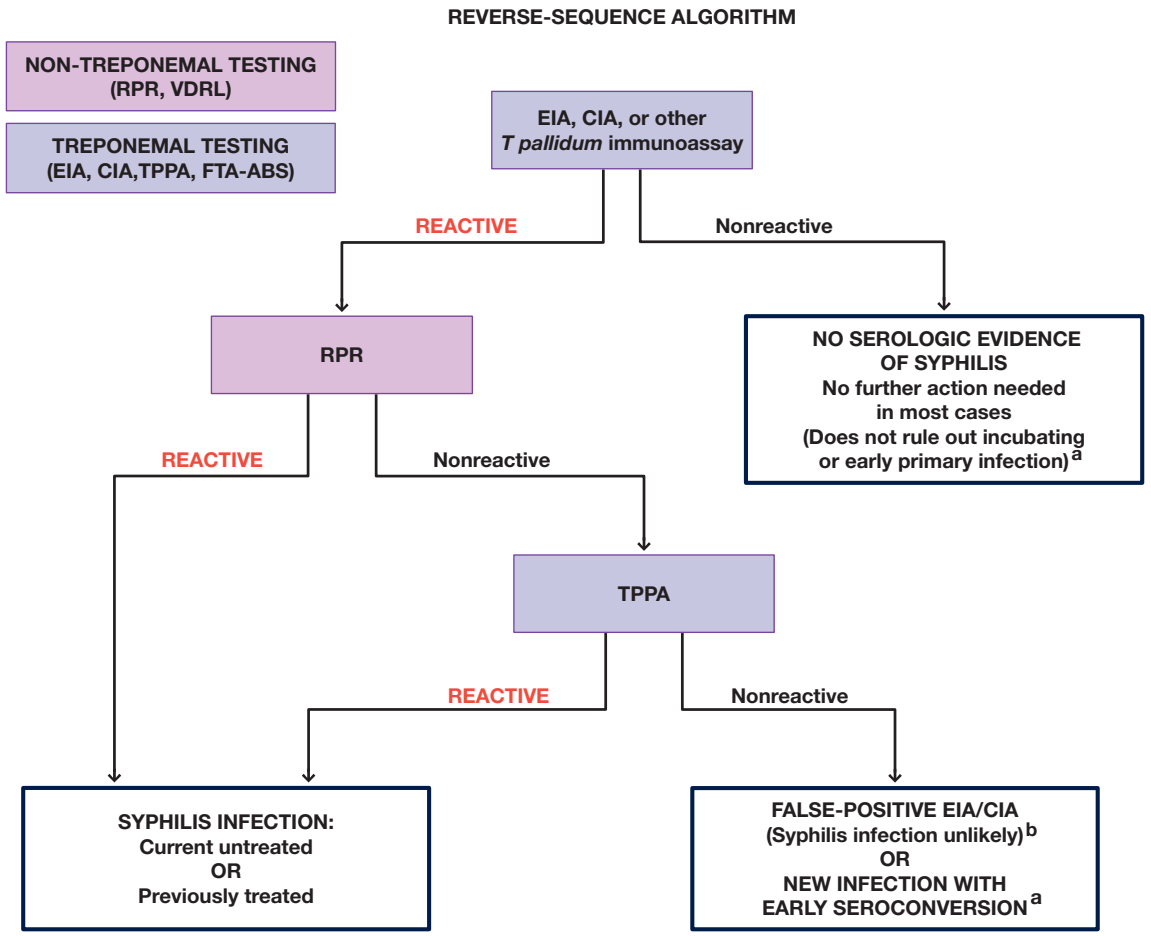
Reverse-sequence testing poses 3 challenges: (1) a higher likelihood of a positive result in patients with a history of treated syphilis; (2) the occurrence of a positive treponemal result with a negative nontreponemal result, which requires a second treponeme-specific test (eg, TPPA) and can be difficult to clinically interpret (eg, positive CIA/EIA with a nonreactive RPR and a reactive TPPA); and (3) a higher likelihood of a false-positive result for some immunoassays in low-prevalence populations (eg, positive CIA/EIA with a nonreactive RPR and a negative TPPA).

The reverse-sequence screening algorithm has the advantage of detecting a few more incubating and primary syphilis cases and cases of long-standing, untreated latent infection that would be missed by the traditional sequence algorithm because of a loss of RPR reactivity.

Table 5 and **Table 6** review the possible interpretations and suggested management of each serologic scenario seen with either the traditional or reverse-sequence testing algorithms. Clinicians should consult with their laboratory to confirm the testing algorithm used and refer to the corresponding interpretation table. Clinical decision-making regarding individual patients should take into account: the specific patient risk history; previous treatment and testing information; any history of syphilis signs and symptoms; physical examination findings; partner information; and disease prevalence in the patient population. Providers should confer with local infectious disease or STI specialists for guidance on specific case management. The local health department can also be contacted to obtain additional information about (1) RPR titers or previously documented treatment that may be in the public health registry but not in the patient's current medical record, and (2) sex partner information, eg, any recent syphilis diagnoses in the patient's sexual contact(s).

For issues regarding discordant serologic results (eg, Reactive EIA, Nonreactive RPR, Reactive TPPA) when using the reverse sequence screening algorithm during pregnancy, see **Appendix C**.

Figure 6. Reverse-Sequence Syphilis Screening Algorithm[66]



[a] Does not rule out incubating or early primary infection.

- **In a patient who reports an exposure**, in the past 90 days, to a sexual (or needle-sharing) partner newly diagnosed with syphilis, providers should offer presumptive treatment (See **Step 7**). If presumptive treatment is not administered, repeat serologic testing should be performed in 1 month and 3 months to rule out seroconversion following the recent exposure.
- **In a patient presenting with a skin lesion** on physical examination which is suspicious for primary syphilis, providers should consider presumptive treatment even in the face of nonreactive serologic results; lesion-based testing could also be performed if available. If presumptive treatment is not administered, repeat serologic testing should be performed in 2–4 weeks to assess for syphilis seroconversion and rule out primary infection. In a patient presumptively treated for primary syphilis whose initial syphilis serology is negative, repeat serologic testing can be performed 2–4 weeks following the initial nonreactive result. Such retesting may detect early seroconversion and if reactive can confirm the syphilis diagnosis as well as establish a baseline titer useful in post-treatment follow-up.

[b] In a patient with no history of syphilis treatment, an isolated Reactive EIA/CIA could represent partial/early sero-conversion. If the patient reports a recent exposure to a syphilis case, presents with a skin lesion suspicious for primary syphilis, or is at increased risk for syphilis, repeat testing in 2–4 weeks might reveal further seroconversion (including a reactive RPR or TPPA). If a patient is at high risk for syphilis and there is a significant risk of loss to follow-up, presumptive treatment could also be considered.

See **TABLE 6** for additional details regarding interpretation of algorithm endpoints and further management.

Table 5. Interpretation of Serologic Results When Using the TRADITIONAL Syphilis Screening Algorithm

Step 1 Nontreponemal Test (eg, RPR)	Step 2 Treponemal Test (eg, EIA/CIA)	Evaluation and Further Management	Interpretation(s)
Reactive	**Reactive**	**If no documented history of treatment:** • Provide stage-appropriate treatment • Although usually part of reflex testing by the laboratory, ensure that a quantitative RPR result (ie, titer) was obtained	• Current untreated infection
		If there is documented history of treatment[a] and adequate posttreatment serologic response (See **Table 15**)**:** **1.** If RPR titer is low and stable, history and clinical exam are negative, and there is no known recent exposure to syphilis, then no further action needed	• Previously treated syphilis with persistent, ie, serofast, serologic reactivity
		2. If there is a sustained (> 2 weeks) 2-dilution (ie, 4-fold) or higher increase in RPR titer, consider re-infection or treatment failure	• Possible reinfection • Possible treatment failure
		3. If recent exposure or ulceration on exam consistent with primary syphilis, see below[b]	• Cannot rule out Incubating or early primary infection
Reactive	Nonreactive	**If history and clinical exam are negative and no known risk for recent exposure to syphilis:** No further action needed If RPR Titer > 1:8: Consider repeat testing (RPR and treponemal test) to rule out possible false-negative treponemal result[c]	• False-positive RPR screening test • False-negative treponemal test
		If recent exposure or new onset anogenital ulceration on exam, see below[b]	• Rule out false-negative treponemal test or confirm false-positive RPR screening test
Nonreactive	Not performed	**If history and clinical exam are negative and no known risk for recent exposure to syphilis:** No further action needed.	• No laboratory evidence of syphilis infection
		If recent exposure or new onset anogenital ulceration on exam, see below[b]	• Incubating infection • Very early primary infection
		If signs/symptoms of possible secondary syphilis: Ask laboratory to perform quantitative RPR testing (ie, serial dilutions) to rule out prozone[d]	• Rule out new infection with prozone reaction[d]

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(Table 5 continued)

Adapted from: Association of Public Health Laboratories. Suggested Reporting Language for Syphilis Serology Testing, Silver Spring, MD; 2015. **https://www.aphl.org/aboutAPHL/publications/Documents/ID_Suggested_Syphilis_Reporting_Lang_122015.pdf**[66] and CDC Sexually Transmitted Diseases Treatment Guidelines, 2015. **MMWR Recomm Rep** 2015;64(3); 34-51.[23] **https://www.cdc.gov/mmwr/preview/mmwrhtml/rr6403a1.htm**

California Department of Public Health (CDPH) Sexually Transmitted Diseases (STD) Control Branch; California STD Controllers Association; California Prevention Training Center (CAPTC). Use of Treponemal Immunoassays for Screening and Diagnosis of Syphilis Guidance for Medical Providers and Laboratories in California, February 2016. **https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/UseofTreponemalImmunoassays_Syphilis.pdf**[67]

[a] For patients reporting a history of treatment that is not documented in the current medical record, clinical providers can contact the local/state health department to access previous testing and treatment information. All positive syphilis test results, diagnoses and treatment reported to the local or state health department are maintained in a syphilis registry for that jurisdiction.

[b] Presumptive treatment should be provided for patients who: (1) report a sexual (or needle-sharing) contact in the past 90 days with a partner newly diagnosed with syphilis (See **Step 7**); or (2) present with a skin lesion suspicious for primary syphilis on physical examination. Lesion-based testing could also be performed if available. Even in the case of a patient presumptively treated for incubating (due to known exposure) or primary infection whose initial syphilis serology is negative, repeat serologic testing should be performed 2-4 weeks following the initial nonreactive result. Such retesting may detect early seroconversion and if reactive can confirm the syphilis diagnosis as well as establish a baseline titer useful in post-treatment follow-up.

[c] Since false-positive RPRs are usually seen with a lower titer, a false-negative treponemal result should be considered if RPR titer is > 1:8 or if the patient is at high risk for infection. Repeat testing should include RPR and treponemal test; consider also testing with an alternate treponemal assay.[48,50]

[d] A prozone reaction can result in a false-negative RPR, in an undiluted serum specimen, when nontreponemal antibody levels are excessively high. (See **Figure 7**.)

Abbreviations: CIA, chemiluminescence immunoassay; EIA, enzyme immunoassay; RPR, rapid plasma reagin

Table 6. Interpretation of Serologic Results Using a REVERSE SEQUENCE Syphilis Screening Algorithm

Step 1	Step 2	Step 3	Evaluation and Management	Interpretation
Screening Treponemal Test (eg, EIA/CIA)	**Nontreponemal Test (eg, RPR)**	**Supplemental Treponemal Test (eg, TPPA)**		
Reactive	**Reactive**	Not performed	**<u>If no documented history of treatment:</u>** Provide stage-appropriate treatment; ensure that a quantitative RPR was obtained	• Current untreated infection
			<u>If there is documented history of treatment[a] and adequate post-treatment serologic response</u> (See Table 15): 1. If RPR titer is low and stable, history and clinical exam are negative, and patient denies any recent symptoms or known exposure to syphilis, no further action needed 2. If sustained (> 2 weeks) ≥ 2-dilution (4-fold) increase in RPR titer, consider re-infection (especially if ongoing risk of STI) or treatment failure 3. If recent exposure or ulceration on exam consistent with primary syphilis, see below[b]	• Adequately treated syphilis with persistent (ie, serofast) serologic reactivity • Possible re-infection • Possible treatment failure • Cannot rule out Incubating or early primary infection
Reactive	Nonreactive	**Reactive**	**<u>If no documented history of treatment:</u>** Provide stage-appropriate treatment and repeat testing to rule out early seroconversion	• Long-standing, untreated latent infection (with loss of nontreponemal reactivity)
			<u>If there is documented history of treatment[a] and adequate post-treatment serologic response</u> (**See Table 15**): · Likely represents serofast serology · If clinical exam is negative and no known recent symptoms or known exposure to syphilis, no further action needed	• History of syphilis with persistent posttreatment serologic reactivity
			<u>If recent exposure or ulceration on exam consistent with primary syphilis:</u> See below[b]	• Incubating infection • Early primary syphilis
			<u>If signs/symptoms of possible secondary syphilis:</u> Ask laboratory to perform quantitative RPR testing (with serial dilutions) to rule out prozone[c]	• Rule out new infection with prozone reaction[c]

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Table 6. Interpretation of Serologic Results Using a REVERSE SEQUENCE Syphilis Screening Algorithm *(cont.)*

Step 1	Step 2	Step 3	Evaluation and Management	Interpretation
Screening Treponemal Test (eg, EIA/CIA)	**Nontreponemal Test (eg, RPR)**	**Supplemental Treponemal Test (eg, TPPA)**		
Reactive	Nonreactive	Nonreactive	**If clinical exam is negative and no known risk for recent exposure to syphilis:** Likely represents false-positive EIA/CIA, no further action needed in low risk populations. If at increased risk for infection, consider repeating RPR and treponemal test in 2-4 weeks	• False-positive screening EIA/CIA (if patient is low risk) • Incubating infection
			If recent exposure or new onset anogenital ulceration on exam: See below [b]	• Incubating infection • Early primary syphilis
Nonreactive	Not performed	Not performed	**If clinical exam is negative and no known recent exposure to syphilis:** No further action needed.	• No laboratory evidence of syphilis infection
			If recent exposure or new onset anogenital ulceration on exam: See below[b]	• Incubating infection • Very early primary syphilis

Adapted from: *Use of Treponemal Immunoassays for Screening and Diagnosis of Syphilis*, California Department of Public Health Sexually Transmitted Diseases Control Branch, 2/2016;[67] Association of Public Health Laboratories. Suggested Reporting Language for Syphilis Serology Testing, Silver Spring, MD; 2015;[66] Sexually Transmitted Diseases Treatment Guidelines 2015. *MMWR Recomm Rep* 2015;[23]

California Department of Public Health (CDPH) Sexually Transmitted Diseases (STD) Control Branch; California STD Controllers Association; California Prevention Training Center (CAPTC). Use of Treponemal Immunoassays for Screening and Diagnosis of Syphilis. Guidance for Medical Providers and Laboratories in California, February 2016. **https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/UseofTreponemalImmunoassays_Syphilis.pdf** [67]

[a] For patients reporting a history of treatment that is not documented in the current medical record, clinical providers can contact the local/state health department to access previous testing and treatment information. All positive syphilis test results, diagnoses and treatment reported to the local or state health department are maintained in a syphilis registry for that jurisdiction.

[b] Presumptive treatment should be provided for patients who: (1) report a sexual (or needle-sharing) contact in the past 90 days with a partner newly diagnosed with syphilis (See **Step 7**); or (2) present with a skin lesion suspicious for primary syphilis on physical examination. Lesion-based testing could also be performed if available. Even in the case of a patient presumptively treated for incubating (due to known exposure) or primary infection whose initial syphilis serology is negative, repeat serologic testing should be performed 2-4 weeks following the initial nonreactive result. Such retesting may detect early seroconversion and if reactive can confirm the syphilis diagnosis as well as establish a baseline titer useful in post-treatment follow-up.

[c] A prozone reaction can result in a false-negative RPR, in an undiluted serum specimen, when nontreponemal antibody levels are excessively high. (See **Figure 7**.)

Abbreviations: CIA, chemiluminescence immunoassay; EIA, enzyme immunoassay; RPR, rapid plasma reagin

False-Negative Serologic Results

Certain clinical scenarios can cause false-negative serologic results, these include the following:

Possible Incubating Infection

The incubation—or "window" period—for syphilis can be as long as 90 days, during which time all serologic testing can be nonreactive. Therefore, patients at significant risk for incubating syphilis, such as those reporting an exposure to a known syphilis case within the preceding 90 days, should be offered presumptive treatment despite the lack of serologic or exam evidence of infection.[23]

Early Primary Infection

Serologic tests for syphilis can have limited sensitivity during early primary syphilis.[35] Seroconversion may take as long as a few weeks after the appearance of a primary syphilis lesion.[17,48] Therefore, nonreactive serologic results in a patient presenting with a suspicious anogenital skin lesion does not rule out primary syphilis and presumptive treatment should be strongly considered.

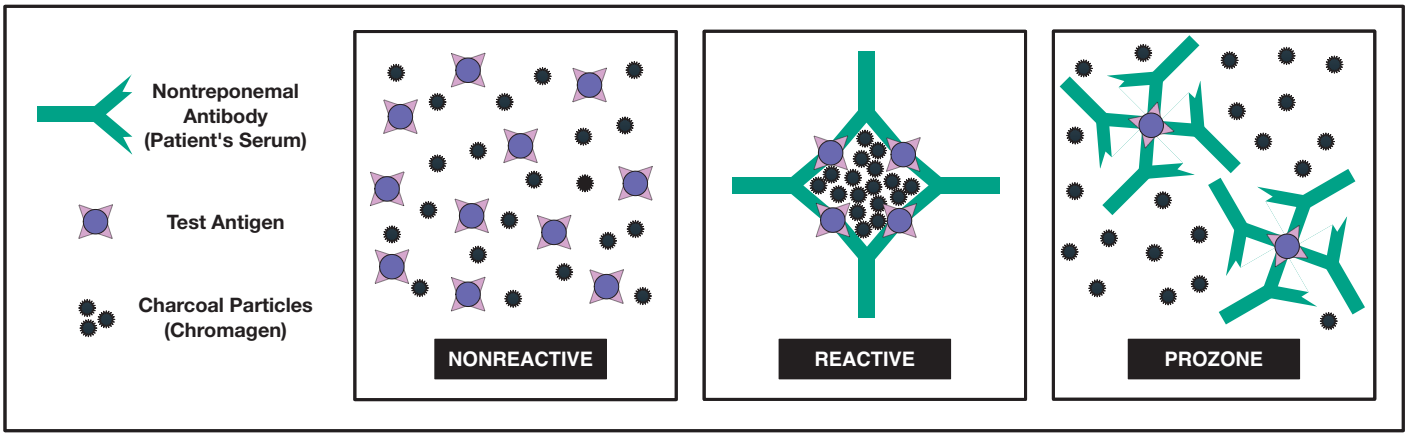
Some treponemal assays (particularly the TPPA) may be more sensitive than nontreponemal tests in diagnosing early primary syphilis[35,68–70]; therefore, inconsistent serologic results (eg, reactive EIA/TPPA and nonreactive RPR) may indicate early treponemal sero-conversion.

In patients treated presumptively for primary syphilis whose initial syphilis serology was negative, reactive results on repeat testing in 2 to 4 weeks would be consistent with delayed seroconversion associated with the treated infection. Nevertheless, if such a patient reported reexposure to an untreated partner diagnosed with syphilis, retreatment should be offered.

Patients With Possible Longstanding, Untreated Infection

Even without treatment, nontreponemal reactivity can wane in longstanding infection. Up to 30% of patients diagnosed with late syphilis will have nonreactive, nontreponemal testing despite a lack of treatment.[48,63,71] When using the reverse sequence syphilis screening algorithm, reactive treponemal testing (eg, reactive EIA and TPPA) with a nonreactive RPR could indicate a longstanding, untreated infection.

Figure 7. The Mechanism Underlying Nontreponemal Syphilis Serologic Assays



False-Negative Nontreponemal Testing Due to Prozone Reaction

The **prozone phenomenon** occurs when excessive amounts of nontreponemal antibody in the serum of an infected patient block the usual antigen-antibody reaction, resulting in a false-negative, nontreponemal result in an undiluted serum specimen. The prozone phenomenon has been reported in 1% to 2% of patients with secondary syphilis and occurs more commonly in patients with high nontreponemal test titers.[72–75]

RPR testing involves mixing a small amount of the patient's serum with commercially prepared test antigen, which also includes charcoal particles. If the patient's serum contains nontreponemal antibody, it will couple with the test antigen to form lattice-like cells with charcoal particles trapped inside.[49] Macroscopically, this will appear as clumping or agglutination of the charcoal particles. If a patient has excessive amounts of serum antibody, all the available test antigen can become saturated, which can interfere with the lattice formation and produce a false-negative RPR. (See **Figure 7**.) Treponeme-specific tests are not susceptible to the prozone phenomenon and, when reactive, might serve as a clue to syphilis infection under these circumstances.

If a prozone reaction is suspected (eg, a nonreactive nontreponemal result despite suspicious exam findings, especially those of secondary syphilis), the provider should contact the laboratory to request that quantitative RPR testing (with titered/serial dilution) be performed to rule out a prozone. Dilution of the patient's serum will decrease the concentration of nontreponemal antibody, effectively eliminating any prozone interference.

False Positive Serologic Results

Nontreponemal Testing

False-positive, nontreponemal testing has been reported in 1% to 2% of the general US population, most commonly in patients with certain underlying acute and chronic conditions. (See **Table 8**.)[48,76,77] Up to 90% of false-positive, nontreponemal results have a titer of less than 1:8.[1,48,50]

Treponemal Testing

False-positive treponemal test results occur in fewer than 1% of healthy individuals[78] and most often during pregnancy, with advanced age, and in patients with connective tissue and autoimmune disorders, type-1 diabetes mellitus, Lyme disease, certain viral infections (including herpes simplex virus), infectious mononucleosis, leprosy, and endemic treponematoses (such as yaws, pinta and bejel).[79–84] Nevertheless, in patients with a reactive syphilis serology, the presence of one of these conditions does not preclude a concomitant syphilis infection.

Table 8. Causes of False-Positive, Nontreponemal Syphilis Serology[48,49,76,85]

Spirochaete Infections	• Leptospirosis • Lyme disease • Pinta • Rat-bite fever • Relapsing fever • Yaws
Other Infections	• Bacterial Endocarditis • Brucellosis • Chancroid • Cytomegalovirus • Herpes simplex virus • HIV seroconversion illness • HIV/AIDS • Infectious mononucleosis (EBV) • Kala-azar (visceral leishmaniasis) • Lepromatous leprosy • Lymphogranuloma venereum • Malaria • Measles • Mumps • Pneumonia (pneumococcal, mycoplasma) • Rickettsial disease • Toxoplasmosis • Tropical spastic paraparesis (HTLV-1) • Trypanosomiasis • Tuberculosis • Varicella-zoster virus • Viral hepatitis

Physiologic	• Older age • Pregnancy
Autoimmune Disorders	• Autoimmune hemolytic anemia • Autoimmune thyroiditis (Hashimoto's disease) • Primary biliary cirrhosis • Idiopathic thrombocytopenic purpura • Immunoglobulin abnormalities • Rheumatoid arthritis • Systemic lupus erythematosus • Ulcerative colitis
Other Conditions	• Dysproteinemias • Hepatic cirrhosis • Intravenous drug use • Lymphoproliferative disorders • Malignancy • Malnutrition • Some vaccinations

Abbreviation: AIDS, acquired immune deficiency syndrome; EBV, Epstein-Barr virus; HIV, human immunodeficiency virus; HTLV-1, human T-lymphotropic virus type 1.

Interpretation of Serologic Results in Patients Previously Treated for Syphilis

Interpreting a reactive syphilis serology and determining the need for possible treatment can be particularly challenging in patients with a history of previously treated syphilis and residual serofast serologic results.

Figure 8 outlines a general approach to patients found to have confirmed reactive serologic results who report a history of syphilis treatment. Diagnostic and treatment decisions in specific clinical situations should consider the following:

- The stage of previous infection
- The treatment received and the degree of documentation
- The serologic response following treatment
- Any significant, and sustained (> 2 week), increase in RPR titer as compared with the lowest post-treatment serofast titer
- Recent risk and exposure history
- Any recent symptoms suggestive of primary or secondary syphilis
- Exam findings at the time of evaluation
- Prevalence of syphilis in the patient population

Optimal case management may require clinicians to consult with their local department of health (for previous testing and treatment information and information regarding recent infection in patient's contacts) or local infectious disease specialists for guidance regarding diagnosis and treatment. See **Appendix F** for a list of provider resources.

Licensed health care professionals can obtain current and historical syphilis test results and treatment information regarding patients residing in NYC by accessing the New York City Confidential Syphilis Serologic and Treatment Registry, a repository of positive syphilis test results and treatment information reported to the NYC DOHMH.

For additional information on accessing the NYC Confidential Syphilis Serologic and Treatment Registry, see **Step 8**.

Other jurisdictions in NYS and throughout the United States have similar confidential serologic and treatment registries that can be accessed by health care providers through their respective local or State departments of health.

Persistent Serologic Reactivity Following Syphilis Treatment

Following treatment, **nontreponemal test** titers usually decline, commonly seroreverting to nonreactive status—especially if treated early in the infection.[86] Based on one large cohort study, 72% of those treated for primary syphilis and 56% of those treated for secondary syphilis seroreverted to a nonreactive RPR or VDRL assay after 2 to 3 years.[65] Some adequately treated patients will have persistently reactive or "serofast" nontreponemal test results, few of whom benefit from additional treatment.[87] Serofast nontreponemal results, are generally, but not always, seen at a low test titer (eg, < 1:8).[2,88]

There are limited data regarding serological response to therapy for patients with latent infections, though titer changes appear to be gradual and a serofast (persistently reactive) nontreponemal result following treatment seems to occur more frequently for longstanding latent infections than it does for those treated during the primary or secondary stages.[14]

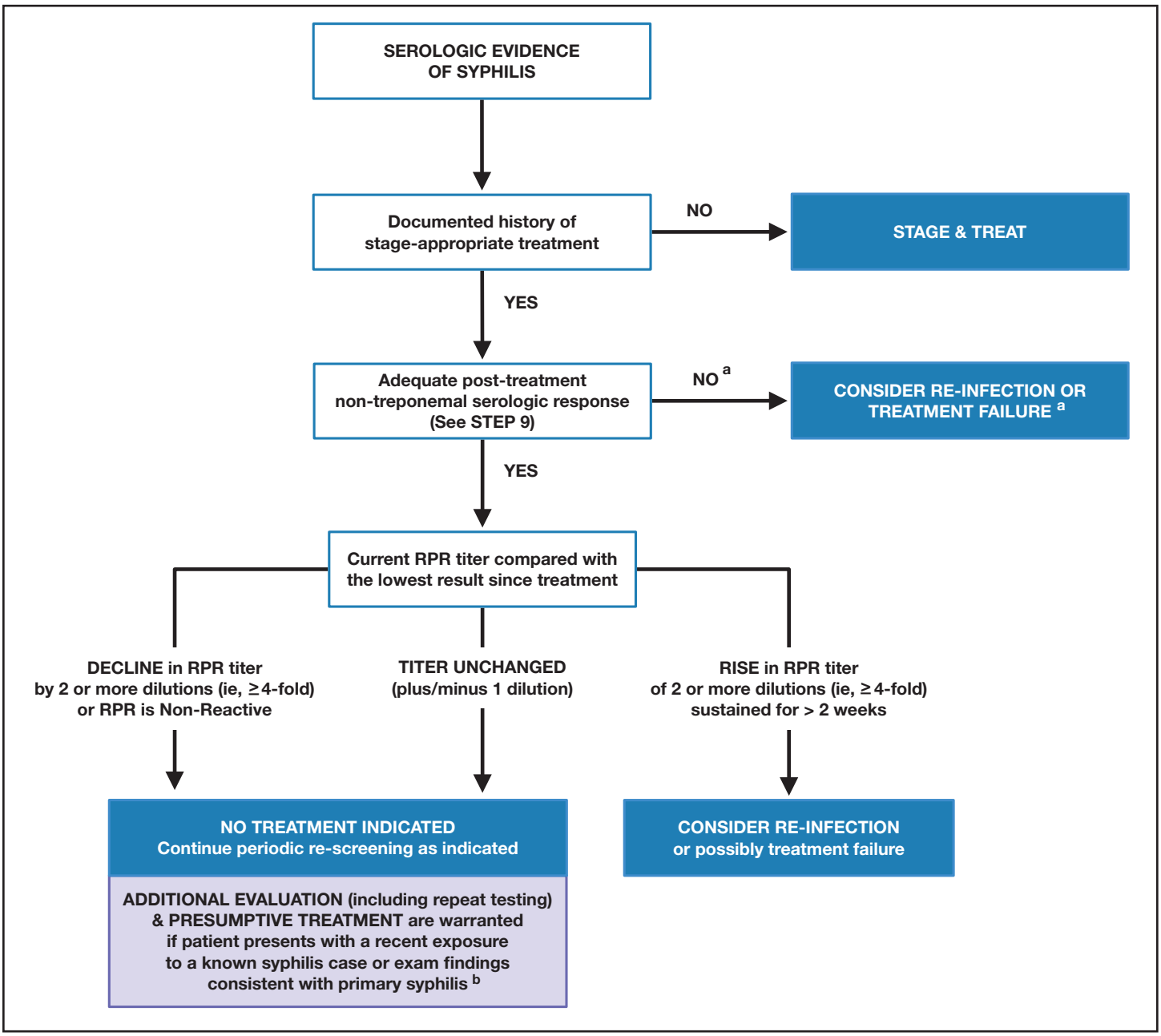
See **Step 9** for further discussion of persistent serologic reactivity in patients previously treated for syphilis.

Unlike the RPR, **treponeme-specific tests** generally remain reactive for life, even in successfully treated patients, especially if treatment occurs after the primary stage.[89,90]

Identifying Re-Infection

In a patient previously treated for syphilis, a sustained (> 2 weeks) increase of 2 or more dilutions (ie, ³ 4-fold increase) in RPR/VDRL titer (eg, from 1:4 to 1:16) on subsequent follow-up or rescreening could indicate: (1) reinfection, (2) treatment failure due to unrecognized neurosyphilis, or (3) yet to be determined host factors. For further discussion of posttreatment serologic monitoring, patient follow-up, persistent serologic reactivity and evaluation of treatment failure, see **Step 9**.

Figure 8. Steps in Evaluating Reactive Syphilis Serologic Results in a Patient With a History of Previous Treatment



[a] If recently treated, insufficient time may have elapsed to expect a complete serologic response. Continued monitoring is indicated in such cases, although a patient with a sustained 2-dilution (ie, 4-fold) titer rise since treatment would necessitate evaluation for possible re-infection or treatment failure.

[b] Serologic testing should always be performed at the time of treatment; if the patient is in the early stages of infection seroconversion (or an increase in nontreponemal titer) may have occurred since the day of last testing. If the titer remains serologically low/negative on day of treatment, consider retesting 2-4 weeks after treatment for possible seroconversion/titer rise to confirm diagnosis.

Step 4: Accurately Stage Infection in Patients with Confirmed Disease

Once it is determined that a patient is infected with syphilis based on medical history, physical examination and serologic results, the stage of disease must be determined. Accurate staging of any newly-diagnosed syphilis infection is necessary to:

- Select the appropriate treatment regimen
- Monitor the serologic response to treatment
- Determine the risk of late complications
- Guide partner management
- Ensure accurate case reporting and assessment of disease trends within the community (via local public health surveillance systems)

Among patients diagnosed with syphilis, the patient history and physical exam can help determine the stage of infection. For patients reporting a history of signs or symptoms consistent with syphilis that have since resolved or contact with a partner who was diagnosed with syphilis, the timing of these findings may help in determining the stage and duration of disease. All patients with reactive syphilis serologic results should undergo a thorough physical examination (including oral, vaginal and anal surfaces) to rule out the presence of any primary or secondary lesions, or evidence of tertiary disease.

Table 9 summarizes the diagnostic criteria for each stage of syphilis. **Figure 9** provides a decision tree that outlines a general approach to syphilis staging. Clinical diagnostic criteria differ to some extent from surveillance case definitions which are used for case reporting and epidemiologic analyses. For a comparison between diagnostic criteria and current CDC surveillance case definitions, see **Step 8**.

Table 9. Syphilis Clinical Staging Criteria in Adults[23]

STAGE	DIAGNOSTIC CRITERIA
Incubating Infection	**Exposure to an infectious case of syphilis in the previous 90 days** *AND* **No exam findings of syphilis** *AND* **No serologic or other laboratory evidence of syphilis**
Primary	**Exam findings consistent with primary syphilis at the time of treatment:** • Presence of a classic syphilitic chancre (ie, a single, painless, rubbery or indurated anogenital or oral ulcer) • Presence of multiple or atypical anogenital primary lesions • *Primary lesions can sometimes be confirmed with dark field or T pallidum PCR testing* **+/- Serologic evidence of infection (or reinfection):** Reactive syphilis serologic results support the diagnosis, but may be absent in early primary syphilis
Secondary	**Laboratory evidence of syphilis infection (or re-infection)**, eg, serologic or lesion-based testing *AND* **Exam findings consistent with secondary syphilis at the time of treatment**, for example: • Mucocutaneous eruptions (localized or generalized), including palmar or plantar rashes • Condyloma lata (moist, flat, whitish-gray, wart-like papules or plaques) • Mucous patches (membranous lesions of tongue, buccal mucosa, lips) • Generalized lymphadenopathy, malaise, fever, other nonspecific constitutional symptoms • Patchy alopecia

Continued on following page

Table 9. Syphilis Clinical Staging Criteria in Adults[23] *(continued)*

STAGE	DIAGNOSTIC CRITERIA
Early Latent	**Serologic evidence of syphilis infection (or reinfection)** *AND* **No exam findings of primary, secondary or tertiary syphilis at the time of treatment** *AND* **Any of the following:** • Documented seroconversion within the past 12 months (ie, a currently reactive syphilis serology with nonreactive results documented within the past 12 months) • A sustained rise (> 2 weeks) in nontreponemal test titer of 2 or more dilutions (ie, ≥ 4-fold rise) within the past 12 months[a] • Unequivocal symptoms of primary or secondary syphilis within the past 12 months[b] • Sexual or needle-sharing contact with a person diagnosed with an infectious stage of syphilis (ie, primary, secondary or early latent) during the past 12 months[c] • Only possible exposure has been within the previous 12 months, eg, a patient who reports that their first sexual contact occurred within the last 12 months[b]
Late Latent	**Serologic evidence of infection (or re-infection)** *AND* **No exam findings of primary, secondary, or tertiary syphilis at the time of treatment** *AND* **None of the criteria for early latent syphilis are met** *AND* **Evidence suggests that the infection was acquired greater than 12 months prior to diagnosis**
Latent of Unknown Duration	**Serologic evidence of infection (or re-infection)** *AND* **No exam findings of primary, secondary, or tertiary syphilis at the time of treatment** *AND* **None of the criteria for early latent are met** *AND* **Available information is insufficient to determine the duration of infection**
Tertiary	**Clinical manifestations of late syphilis** including: • Cardiovascular disease (eg, aortitis, coronary vessel disease) • Gummatous disease of the skin or other organs • Late neurologic complications (eg, tabes dorsalis, or general paresis) *AND* **Laboratory evidence of infection** by serologic, CSF, or direct pathology testing
Neurosyphilis	See **Appendix B**; can occur along with primary, secondary, or latent infection

[a] A sustained rise in nontreponemal test titers in a patient with a history of adequate treatment in the past may represent either reinfection or treatment failure (persistent infection). If a patient is at little or no risk of reinfection, further evaluation and management for possible treatment failure needs to be considered. (See **Step 9**.)

[b] Even the most seemingly reliable sexual history can be susceptible to recall bias or imprecise definitions of "sexual contact." Therefore, caution should be used in relying upon the sexual history for staging purposes. Similarly, a patient report of resolved signs or symptoms which sound consistent with primary or secondary syphilis could erroneously point toward a diagnosis of early latent infection and result in under treatment if the findings reported by the patient, in actuality, had a non-syphilitic etiology.

[c] For patients found to have latent infection, who also report having had sexual contact with a partner diagnosed with syphilis in the past 12 months, many do not have specific information regarding their partner's stage of infection. This information may be available through the local health department as part of case reporting and follow-up activities.

Abbreviations: CSF, cerebrospinal fluid; PCR, polymerase chain reaction.

Staging Latent Infection

Patients with reactive syphilis serologic results and who lack evidence of primary, secondary or tertiary syphilis at the time of treatment are staged as **latent syphilis**. Serologic reactivity is usually the only evidence of infection at the time of presentation. To guide the length of treatment and determine the necessary partner management, latent infection is divided into three clinical stages: (1) **early latent syphilis**, (2) **late latent syphilis**, and (3) **latent syphilis of unknown duration**—based on the length of time the infection is thought to have been present.

1. **Early Latent Syphilis:**
   Patients who have evidence suggesting their *infection was acquired within the past 12 months*, see **Table 9** for specific criteria.

2. **Late Latent Syphilis:**
   Patients who have evidence suggesting their *infection was acquired more than 12 months ago*; for example:
   - Patients with serologic evidence of syphilis infection (or reinfection) who were not treated at that time (eg, if they were lost to follow-up) and are ultimately brought to treatment more than 12 months after the initial serologic abnormalities were identified
   - Patients with serologic evidence of syphilis who report being treated more than 12 months earlier but, as part of the current evaluation, retreatment is recommended due to insufficient proof of past treatment or possible inadequate treatment at the time of initial diagnosis
   - Patients with serologic evidence of syphilis who reliably deny any sexual contact in the past 12 months

3. **Latent Syphilis of Unknown Duration:**
   Patients for whom there is insufficient information to determine the duration of infection, ie, patients with serologic evidence of syphilis infection (or re-infection) who deny:
   - any history of signs or symptoms of primary or secondary syphilis
   - any known exposures to partners with syphilis
   - any past serologic testing or treatment for syphilis in the past 12 months

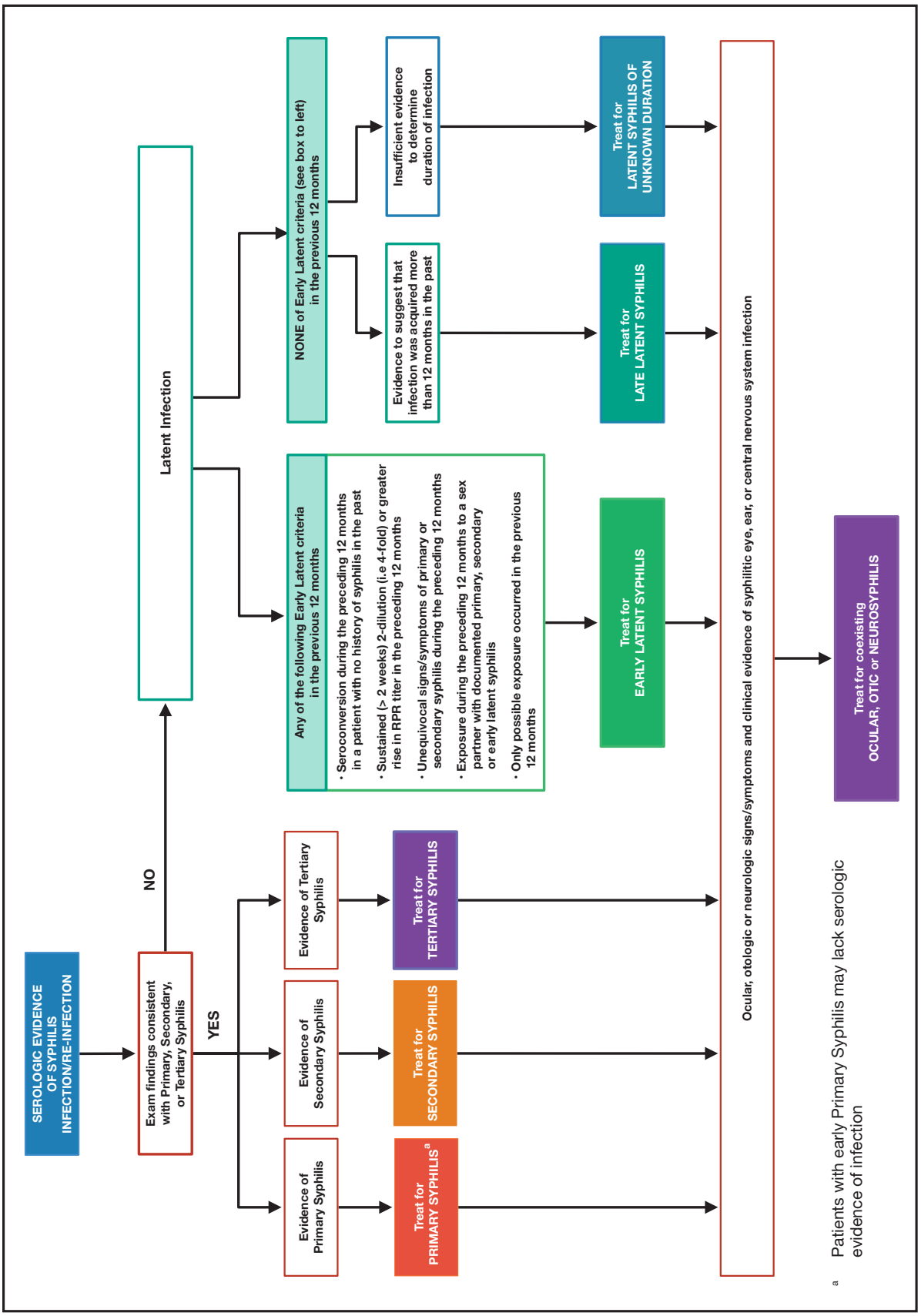
The importance of differentiating early latent syphilis from late latent syphilis and latent syphilis of unknown duration is that the recommended treatment and appropriate partner management differ for each of these latent stages. Persons with *late latent infection* and *latent infection of unknown duration* require a longer course of therapy and patients with *early latent infection* are more likely to be infectious to their pre-treatment contacts. (See **Table 10** and **Table 14**.)

Ruling Out Co-existing Ocular, Otic or Neurosyphilis

Neurologic, ocular, or otic involvement can occur and overlap with any stage of syphilis infection. Therefore, all patients diagnosed with syphilis, irrespective of stage of infection, should be asked about neurologic ophthalmologic, auditory, or vestibular symptoms.

A brief neurologic examination (See **Appendix B**, **Table B1**) should also be performed in all patients diagnosed with syphilis regardless of the presence or absence of ocular, otic, or neurologic symptoms. Individuals with serologic evidence of syphilis and signs or symptoms consistent with ocular, otic, or neurosyphilis require prompt follow-up for cerebrospinal fluid (CSF) testing, and in the case of ocular or otic findings, a slit lamp ophthalmologic examination or evaluation by an otolaryngologist/audiologist.[23] In addition, patients presenting in emergency departments, urgent care settings, and neurology, ophthalmology, and audiology clinics with evidence of neurologic, ocular or otic disease suggestive of syphilis should have appropriate testing for syphilis. For a more detailed discussion of ocular, otic and neurosyphilis including common signs and symptoms, indications for CSF testing, and recommended evaluation and management, see **Appendix B**.

Figure 9. Clinical Staging of Adult and Adolescent Patients With Serologic Evidence of Syphilis Infection/Reinfection



Step 5: Provide Stage-appropriate Pharmacotherapy

Management of untreated syphilis in adults and adolescents must be based on the clinical stage of infection **at the time of treatment**. Late latent syphilis or syphilis of unknown duration and tertiary syphilis require a longer course of treatment. (See **Table 10**.)

Treatment of Syphilis During Pregnancy
Intramuscular, long-acting benzathine penicillin G (or aqueous crystalline penicillin G, in cases of ocular, otic or neurosyphilis) remains the **only** regimen with documented efficacy against syphilis during pregnancy and for the prevention of congenital syphilis; pregnant patients who are penicillin-allergic should be referred for desensitization and treated with the CDC-recommended penicillin regimen.[23] See **Appendix C** for details regarding the management of syphilis during pregnancy.

Table 10. Treatment Recommendations for Syphilis in Non-Pregnant Adults by Syphilis Stage

Stage of Infection	CDC 2015 Recommended Treatment Regimen
Incubating Infection **Primary** **Secondary** **Early Latent**	Benzathine penicillin G 2.4 million units as a single intramuscular injection **Alternatives Regimens** (for *nonpregnant patients* with a documented penicillin allergy) • Oral doxycycline 100mg twice daily for 14 days *OR* • Oral tetracycline 500mg 4 times each day for 14 days
Late Latent or Latent of Unknown Duration	Benzathine penicillin G 7.2 million units total, administered as 3 separate doses of 2.4 million units intramuscularly, each at 1-week intervals [a] **Alternative Regimens** (for *nonpregnant patients* with a documented penicillin allergy) Note: Close serologic follow-up is critical, especially in patients living with HIV • Oral doxycycline 100mg twice daily for 28 days *OR* • Oral tetracycline 500mg 4 times daily for 28 days
Neurosyphilis or Ocular/Otic Syphilis	Aqueous crystalline penicillin G 18–24 million units per day, administered as 3–4 million units intravenously every 4 hours, or by continuous infusion, for 10–14 days **Alternative Regimen** • Procaine penicillin G 2.4 million units intramuscularly once daily for 10–14 days *PLUS* • Probenecid 500mg orally 4 times daily for 10–14 days
Tertiary	Tertiary syphilis should be managed in consultation with an infectious disease specialist. Testing for HIV infection and CSF examination should be performed before therapy is initiated.

[a] The optimal management of patients being treated for late latent syphilis or latent syphilis of unknown duration who miss scheduled doses of benzathine penicillin G therapy remains unclear. As noted in the 2015 CDC STD Treatment Guidelines: "Clinical experience suggests that an interval of 10–14 days between doses of benzathine penicillin **might be acceptable** before restarting the sequence of injections (ie, if dose 1 is given on day 0, dose 2 is administered between days 10 and 14). Pharmacologic considerations suggest that an interval of 7-9 days between doses, if feasible, **might be more optimal.**"[23] Dosing flexibility is not acceptable in the treatment of syphilis during pregnancy; pregnant patients who miss any scheduled doses of Bicillin (ie, returned more than 7 days after the previous dose) must repeat the full course three injections.[23]

Abbreviations: IM intramuscular; IV = intravenous

There are specific issues to keep in mind regarding penicillin formulations when providing treatment for syphilis:

- Intramuscular, long-acting benzathine penicillin G (ie, Bicillin L-A®) is the treatment of choice for all stages of syphilis **except** for neurosyphilis, which requires a penicillin formulation, such as intravenous aqueous crystalline penicillin G, that reliably achieves adequate drug levels in the CNS. (See **Appendix B**.) Other nonpenicillin-based regimens should be used in nonpregnant patients **only** when penicillin is strictly contraindicated.
- Oral formulations of penicillin are **not** recommended for treatment of syphilis.
- In the United States, benzathine penicillin G is commercially available in 2 different formulations:
  - **Bicillin L-A® (long-acting, benzathine penicillin G)**: Recommended for treatment of syphilis
  - **Bicillin C-R® (a combination of benzathine penicillin G and short-acting procaine penicillin G)**: Bicillin C-R may not provide the prolonged therapeutic drug levels necessary for syphilis cure and should not be used for syphilis treatment.

Shortages of benzathine penicillin in the US have periodically occurred. During these periods of limited availability, priority should be given to the treatment of pregnant persons found to be infected or exposed to syphilis as there are no alternatives to prevent congenital infection. During national shortages, the CDC typically posts additional information online at **http://www.cdc.gov/std/treatment**.

For a discussion of the assessment of patients reporting a penicillin allergy refer to the current **CDC STD Treatment Guidelines** on the CDC Division of STD Prevention website.[23]

Patients should be advised to avoid all sexual contact (including oral sex) until after the completion of treatment and the resolution of all symptoms. Patients needing only a single dose of benzathine penicillin should abstain from sexual contact for 7 days after their injection and, if present, until all skin/mucous membrane lesions are healed. They should also be advised to avoid contact with any ongoing sexual partners until those partners seek medical evaluation for possible infection and receive post-exposure prophylaxis (See **Step 7**).

Limited data suggest that several alternatives to penicillin might be effective in nonpregnant, penicillin-allergic patients. **Table 11** provides information on the use of penicillin vs. nonpenicillin treatment regimens.

Table 11. Effectiveness of Penicillin vs. Nonpenicillin Adult Syphilis Treatment Regimens[23]

Syphilis Stage	Intramuscular Benzathine Penicillin G	Oral Doxycycline (or Tetracycline)	Parenteral Ceftriaxone*
Primary, or Secondary	✔	• Limited studies, but many years of successful use • Acceptable alternative when penicillin is contraindicated or unavailable due to supply shortage	Comparable to benzathine penicillin in several small studies, but requires daily intramuscular/intravenous dosing of 1-2g daily x 10-14 days [a]
Early Latent Late Latent, Latent of Unknown Duration	✔		• Not well studied • Optimal dose and duration of therapy has not been defined
Syphilis During Pregnancy	✔	**Contraindicated**	• Not well studied
Syphilis in Persons Living with HIV	✔	• Not well studied • Should be used only in conjunction with close serologic and clinical follow-up • If there is significant risk of poor adherence, patients should undergo penicillin desensitization and treatment with standard stage-appropriate CDC-recommended penicillin regimen	

✔ Efficacy of benzathine penicillin is supported by strong observational studies, and decades of experience in achieving clinical resolution of symptoms, eliminating sexual transmission and preventing late sequelae.

[a] Although allergic cross-reactivity is rare with third generation cephalosporins in patients with a history of penicillin allergy, the use of ceftriaxone is contraindicated in persons with a history of an IgE-mediated penicillin allergy (eg, anaphylaxis, Stevens-Johnson syndrome and toxic epidermal necrolysis).[23]

Alternative Nonpenicillin Treatment Regimens

Oral doxycycline or tetracycline are acceptable alternatives for the treatment of syphilis in *non-pregnant*, penicillin-allergic patients. Doxycycline is preferred over tetracycline due to less frequent dosing and fewer gastrointestinal side- effects, which might improve adherence.

Some clinicians may be reluctant to use intramuscular benzathine penicillin even when no medical/allergic contraindication exists due to concerns about patient discomfort or logistical burdens regarding drug storage and administration. However, ensuring adherence with 2 to 4 weeks of twice daily oral therapy may be difficult. Strict adherence with multi-dose, multi-day oral therapies in the treatment of STIs has been shown to occur in only a small proportion of patients, even when medication is provided free of charge at the time of diagnosis.[91] Directly observed therapy with intramuscular regimens such as benzathine penicillin G provides greater assurance of adequate treatment.

Some evidence suggests that azithromycin, as a single 2g oral dose, is effective in treating primary or secondary syphilis in certain patient populations. Nevertheless, it is not a first-line CDC-recommended therapy, or second-line alternative therapy, due to the emergence of resistance and instances of treatment failure.[23] The CDC also recommends against the use of azithromycin in MSM, persons with HIV, and pregnant women.[23] If azithromycin must be used for primary or secondary syphilis in non-pregnant, HIV-negative heterosexual persons, close clinical and serologic follow-up is extremely important.

If a nonpenicillin regimen must be used, providers should stress to the patient the importance of strict adherence and attempt to ensure close clinical and serologic follow-up. Penicillin desensitization is recommended for all patients with a known penicillin allergy for whom there is a concern about possible loss to follow-up or adherence to the dosing schedule required with oral regimens.

Jarisch-Herxheimer Reaction

Patients treated for syphilis should be warned about the possibility of a Jarisch-Herxheimer reaction as associated symptoms could be confused for an allergic reaction to medication. The Jarisch-Herxheimer reaction usually occurs within the first 24 hours (most often within 2 to 8 hours) after initiation of treatment for syphilis.[92,93] Symptoms include exacerbation of dermatologic findings of secondary syphilis (including the accentuation of skin lesions that were too subtle to recognize at the time of the initial evaluation), and the onset of systemic symptoms such as fever, malaise, myalgias, nausea, vomiting, and headache.

The reaction is thought to result from the release of endotoxins, lipoproteins, and cytokines from killed spirochetes and is seen most commonly among patients treated with benzathine penicillin for primary or secondary syphilis, those with higher baseline nontreponemal titers at the time of initiation of therapy, and patients with no previous history of syphilis treatment. Symptoms usually resolve within 24 hours and treatment is supportive, using antipyretics and analgesics.

During pregnancy, the Jarisch-Herxheimer reaction can be associated with fetal distress and preterm labor; the highest risk occurs during the first 48 hours after treatment.[94] Close monitoring in collaboration with the patient's obstetrician is warranted but should not prevent or delay treatment; such a delay in treatment could result in equally serious sequelae for the developing fetus. Women receiving treatment for syphilis at any time during pregnancy should be informed about the possibility of a Jarisch-Herxheimer reaction and be advised to seek obstetric attention after treatment if they notice any fever, contractions or decreased fetal movements.

Step 6: Rule Out Coexisting Sexually Transmitted Infections, Including HIV

Because the mode of transmission and risk factors for syphilis are common to a variety of STIs, patients diagnosed with syphilis should also be screened for other STIs such as HIV, gonorrhea, and chlamydia. Screening for gonorrhea and chlamydia among MSM should include urine or genital nucleic acid amplification testing (NAAT), and extragenital testing based on reported sites of exposure (eg, oropharyngeal and anorectal gonorrhea/chlamydia NAATs for patients reporting performing oral sex or receiving anal sex, respectively). For more information on extragenital testing for gonorrhea and chlamydia, see the National Coalition of STD Directors resource at: **http://www.ncsddc.org/resource/extragenital/**

Given the frequency of HIV coinfection in persons newly diagnosed with syphilis in certain geographic areas or communities such as NYC, patients being treated for syphilis (or evaluated as a contact) have an increased risk of either being HIV infected at the time of syphilis exposure or, if previously HIV negative, having been exposed to both syphilis and HIV when they acquired their syphilis infection. Syphilis surveillance data in both in the United States and in NYC demonstrate a high HIV coinfection rate. Of reported cases of primary and secondary syphilis in the US who knew their HIV status, 45.5% of cases among MSM were HIV positive.[22] Among cases of syphilis reported in NYC during 2017 who were interviewed by the DOHMH, 51% of MSM with primary or secondary syphilis who knew their HIV status reported living with HIV.[21]

A retrospective, population-level analysis of men diagnosed with primary or secondary syphilis in NYC showed that among MSM who lacked evidence of prior or concurrent HIV infection at the time of their syphilis diagnosis, 1 in 20 was diagnosed with HIV within the following year.[95] A similar study found that 1 in 15 HIV negative MSM diagnosed with rectal gonorrhea and/or chlamydia at one of the NYC Sexual Health Clinics was subsequently diagnosed with HIV within the following year.[96] Therefore, screening for HIV is particularly important in patients diagnosed with, or exposed to, syphilis.

Table 12 details routine screening recommendations for STIs other than syphilis; **Table 13** lists the recommended diagnostic testing for the most common STIs.

For patients not known to be living with HIV, HIV screening should be performed at the time of initial syphilis diagnosis. Patients being treated for syphilis who screen negative for HIV should be counseled about HIV prevention options such as HIV preexposure prophylaxis (PrEP). (See **Figure 11B**.) In geographic areas in which the prevalence of HIV is high, persons who have primary or secondary syphilis should be retested for HIV in 3 months if the first HIV test result was negative.

If a patient is found to be infected with HIV, they should be promptly linked to HIV primary care and initiated on antiretroviral therapy; for those already living with HIV, provider should assure active (re-)linkage to care.

STD SCREENING GUIDELINES

The recommendations in this document are based on the 2015 CDC Sexually Transmitted Diseases Treatment Guidelines and CDC's STD Screening Recommendations Referenced in Treatment Guidelines and Original Recommendation Sources" chart referenced here: **http://www.cdc.gov/std/tg2015/screening-recommendations.htm** unless otherwise noted. Please visit the CDC site for full references. State guidelines and laws may differ; please check with your state for applicable laws and guidelines. **Some patients may fall into more than one of the populations/risk categories listed; in such cases, the more rigorous screening recommendation should be followed.** Please visit **www.nycptc.org** for updates and additional STD resources and education. Abbreviations: MSM=men who have sex with men; WSW=women who have sex with women; MSW=men who have sex with women; CT=Chlamydia trachomatis; GC=Neisseria gonorrhea; RAI = Receptive Anal Intercourse; BV=Bacterial Vaginosis; HPV=Human Papillomavirus; HAV=Hepatitis A Virus; HBV=Hepatitis B Virus; HCV = Hepatitis C Virus; TOC = Test of cure; PID=Pelvic Inflammatory Disease.

NEW YORK CITY STD HIV PREVENTION TRAINING CENTER

	CHLAMYDIA[1,2]	GONORRHEA[3,4]	SYPHILIS	HERPES	HIV	TRICHOMONAS & BACTERIAL VAGINOSIS	CERVICAL CANCER	HEPATITIS B	HEPATITIS C
WOMEN	Test at least annually for sexually active women under 25 years of age and sexually active women aged 25 years and older if at increased risk[5] Retest approximately three months after treatment	Test at least annually for sexually active women under 25 years of age and sexually active women age 25 years and older if at increased risk[8] Retest 3 months after treatment		Consider type-specific HSV serologic testing for women presenting for an STI evaluation, especially if multiple sex partners	All women aged 13-64 years and all women who seek evaluation and treatment for STIs	**Trichomonas:** consider screening women if at high risk[11] or in high prevalence settings (e.g., STD clinics and correctional facilities) **Bacterial Vaginosis (BV):** no routine screening recommendation	Women 21-29 years of age every 3 years with cytology Women 30-65 years of age every 3 years with cytology or every 5 years with a combination of cytology and HPV testing	Women at increased risk	Women, men and pregnant women born between 1945-1965 and if other risk factors are present[12]
PREGNANT WOMEN	All pregnant women under 25 years of age Pregnant women, aged 25 years and older if at increased risk[5] Retest during 3rd trimester if under 25 years of age or at risk[6]	All pregnant women under 25 years of age and older women if at increased risk[9] Retest 3 months after treatment	All pregnant women at the first prenatal visit Retest early in 3rd trimester and at delivery if at high risk[10]	Evidence does not support routine HSV-2 serologic screening among asymptomatic pregnant women. However, type-specific serologic tests might be useful for identifying pregnant women at risk for HSV infection and guiding counseling regarding the risk for acquiring genital herpes during pregnancy	All pregnant women at first prenatal visit and at delivery if not previously tested or no prenatal care Retest in 3rd trimester if at high risk[10]	**Trichomonas:** Insufficient evidence for screening asymptomatic pregnant women; symptomatic pregnant women should be screened. For pregnant women with HIV infection, screening at first prenatal visit is recommended. **BV:** Insufficient evidence to recommend routine screening in asymptomatic pregnant women at high or low risk for preterm delivery	Screening at same intervals as non-pregnant women	Test for HBsAg at first prenatal visit of each pregnancy regardless of prior testing; retest at delivery if at high risk	

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STD SCREENING GUIDELINES *continued*

	CHLAMYDIA[1,2]	GONORRHEA[3,4]	SYPHILIS	HERPES	HIV	TRICHOMONAS & BACTERIAL VAGINOSIS	CERVICAL CANCER	HEPATITIS B	HEPATITIS C
MEN-MSW (Men Who have Sex with Women)	Consider screening young men in high prevalence clinical settings (adolescent and STD clinics and correctional facilities) or in populations with high burden of infection (e.g. MSM)			Consider type-specific HSV serologic testing for men presenting for an STI evaluation, especially if multiple sex partners	All men aged 13-64 years and all men who seek evaluation and treatment for STIs			Men at increased risk	Women, men and pregnant women born between 1945-1965 and if other risk factors are present[12] *continued*
MEN-MSM (Men Who have Sex with Men)	At least annually, test at each site of exposure (urethra, rectum) for sexually active MSM regardless of condom use or every 3-6 months if at increased risk[7]	At least annually for sexually active MSM test at each site of exposure (urethra, rectum, pharynx) regardless of condom use and every 3-6 months if at increased risk[7]	At least annually for sexually active MSM and every 3-6 months if at increased risk[7]	Consider type-specific serologic tests for HSV-2 if infection status is unknown in MSM with previously undiagnosed genital tract infection	At least annually for sexually active MSM if HIV-negative or unknown status and if patient or sex partner has had more than one sex partner since most recent HIV test			All MSM should be tested for HBsAg	MSM born between 1945-1965 and if other risk factors are present[12] Annual HCV testing in MSM with HIV infection
PERSONS with HIV	For sexually active individuals, screen at first HIV evaluation and at least annually thereafter. Test at each site of exposure. More frequent screening might be appropriate depending on individual risk behaviors and local epidemiology	For sexually active individuals, screen at first HIV evaluation, and at least annually thereafter. Test at each site of exposure. More frequent screening might be appropriate depending on individual risk behaviors and local epidemiology	For sexually active individuals, screen at first HIV evaluation, and at least annually thereafter	Consider type-specific HSV serologic testing for persons presenting for an STI evaluation, especially if multiple sex partners, persons with HIV infection, and MSM at increased risk for HIV acquisition		**Trichomonas:** sexually active women at entry to care and at least annually thereafter	Women should be screened within 1 year of sexual activity or initial HIV diagnosis using conventional or liquid-based cytology; testing should be repeated 6 months later	Test for HBsAg and anti-HBc and/or anti-HBs	Serologic testing at initial evaluation. Annual testing for HIV+ MSM

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STD SCREENING GUIDELINES *continued*

	GC/CT[13]	SYPHILIS[13]	HIV	HEPATITIS A[16]	HEPATITIS B	HEPATITIS C
PERSONS TAKING PrEP[13]	All patients starting PrEP - genital/urine NAAT; extragenital screening should be performed at each site of exposure for at-risk MSM/transgender women (rectal and pharyngeal NAAT) and cisgender women (rectal NAAT). Rescreening: At least every 6 months for all patients on PrEP; At least every 3 months for MSM at high risk[14]; More frequent rescreening could also be considered for other high-risk individuals	All patients starting PrEP Rescreening: At least every 6 months for all patients on PrEP; At least every 3 months for MSM at high risk[14]; More frequent rescreening could also be considered for other high-risk individuals	All patients starting PrEP- 4th generation antibody/antigen testing (recommended) or 3rd generation antibody-only testing (alternative) at PrEP initiation[15] Rescreening: Every 3 months- repeat 4th generation antibody/antigen testing (recommended) or 3rd generation antibody-only testing (alternative)[15]	MSM and other individuals at high risk of HAV infection[17] starting PrEP Rescreening: If a new elevation in serum liver enzymes is present (if not immune or status is unknown)	All patients starting PrEP Rescreening: If a new elevation in serum liver enzymes is present (if not immune or status is unknown)[16]	All patients starting PrEP Rescreening: Annually for persons using injection drugs and other persons with ongoing risk of HCV exposure; rescreening should be performed for patients with a new elevation in serum liver enzymes (if status is unknown)[16]

1 **NAAT testing** FDA approved for first catch urine or vaginal swab.

2 **Perform local validation study** for use of NAAT at anal and pharyngeal sites

3 **NAAT testing** FDA approved for first catch urine or vaginal swab.

4 **Perform local validation study** for use of NAAT at anal and pharyngeal sites

5 **Those who have a new sex partner**, more than one sex partner, a sex partner with concurrent partners, or a sex partner who has a sexually transmitted infection. Screening for Chlamydia and Gonorrhea: US Preventive Services Task Force Recommendation Statement. Annals of internal medicine. Sep 23 2014.

6 **Those with a new sex partner**, more than one sex partner, a sex partner with concurrent partners, or a sex partner who has a sexually transmitted infection. Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines, 2015.

7 **More frequent STD screening** (i.e., for syphilis, gonorrhea, and chlamydia) at 3–6-month intervals is indicated for MSM, including those with HIV infection if risk behaviors persist or if they or their sexual partners have multiple partners. Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines, 2015

8 **Those who have a new sex partner**, more than one sex partner, a sex partner with concurrent partners, or a sex partner who has an STI. Additional risk factors for gonorrhea include inconsistent condom use among persons who are not in mutually monogamous relationships; previous or coexisting sexually transmitted infections; and exchanging sex for money or drugs. Clinicians should consider the communities they serve and may opt to consult local public health authorities for guidance on identifying groups that are at increased risk. Screening for Chlamydia and Gonorrhea: US Preventive Services Task Force Recommendation Statement. Annals of internal medicine. Sep 23 2014.

9 **US Preventive Services Task Force**. Screening for syphilis infection in pregnancy: reaffirmation recommendation statement Annals of internal medicine. 5/19/2009 2009;150(10):705-709.

10 **Each state's guidelines and laws may differ**; please check with your State DOH for applicable laws and guidelines.

11 **Women with multiple sex partners**, exchanging sex for payment, illicit drug use, and a history of STDs

12 **Past or current injection drug use**, receipt of blood transfusion before 1992, long term hemodialysis, born to mother with Hep. C, intranasal drug use, receipt of an unregulated tattoo, and other percutaneous exposures. Moyer VA. Screening for hepatitis C virus infection in adults: US Preventive Services Task Force recommendation statement. Annals of internal medicine. Sep 3 2013;159(5):349-357

13 **Preexposure prophylaxis for the prevention of HIV infection** in the United States– 2017 update, CDC (**www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2017.pdf**)

14 **Individuals at high risk of acquiring STDs** include those who self-identify and/or who report any of the following for self or partner: multiple or anonymous sex partners, a bacterial STD diagnosed at a previous visit or since last STD screening, participation in sex parties or sex in other high-risk venues, participation in any type of transactional sex (e.g. commercial sex work), use of recreational substances during sex, PrEP for HIV Prevention, NYS Department of Health, **www.hivguidelines.org/prep-for-prevention/**

15 **The CDC does not recommend using oral fluid for rapid testing**; rapid testing is more sensitive when using a serum specimen rather than oral fluid. Testing should include HIV antibody/antigen testing and HIV RNA (Viral Load) testing if patient reports symptoms of acute HIV infection or possible HIV exposure (e.g. condomless anal/vaginal sex with an HIV-infected partner, injection drug use with shared injection equipment) in the previous 4 weeks or on the day of evaluation.

16 **PrEP for HIV Prevention**, NYS Department of Health, **www.hivguidelines.org/prep-for-prevention/**

17 **Patients who may benefit from Hepatitis A** serology include those: who have chronic liver disease or conditions that can lead to chronic liver disease (e.g., chronic HBV, chronic HCV, alcohol abuse, or genetic liver diseases); are travelers to countries with high or intermediate endemicity of infection; use illicit drugs (particularly injection drugs); live in a community identified by the local health department as experiencing an outbreak of HAV infection; have clotting-factor disorders; want to reduce their risk for HAV infection; are at occupational risk who are not otherwise required to receive HAV vaccination; are at risk of HAV-related morbidity or mortality. PrEP for HIV Prevention, NYS Department of Health, **www.hivguidelines.org/prep-for-prevention/**

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Table 13. NYC PTC Recommended Laboratory Diagnostics

This diagnostics summary is for educational purposes only. The individual clinician is in the best position to determine which tests are most appropriate. Adapted from the Spokane Washington Regional Health District's STD Toolkit

ETIOLOGIC AGENT	COMMON SYNDROMES	RAPID DIAGNOSTICS	DEFINITIVE DIAGNOSTICS
Chlamydia trachomatis	Non-gonoccocal urethritis (NGU), cervicitis, proctitis, PID	Urine leukocyte esterase can be helpful to look for presence of inflammation	**Nucleic Acid Amplification Tests (NAATs) cervical, urethral or vaginal swabs, or first catch urine** Local validation studies required for use of rectal or pharyngeal specimen testing
Neisseria gonorrheae	Urethritis, cervicitis, proctitis, PID	Gram stain for symptomatic men	**Nucleic Acid Amplification Tests (NAATs) -cervical, urethral or vaginal swabs or first catch urine)** Local validation studies required for use of rectal or pharyngeal specimen testing Cervical/intraurethral swab for culture if persistent or recurrent infection, or concern for resistance
Trichomonas vaginalis	Vaginitis, urethritis	Rapid antigen detection test, Saline wet prep	NAAT testing (vaginal, endocervical and urine in women)
Candida albicans, other Candida sp.	Vaginitis, balanitis	10% KOH prep; Gram stain	Culture if wet mount negative and signs or symptoms
Bacterial vaginosis, anaerobic bacteria	Malodorous vaginal discharge with or w/o pruritis	Saline wet prep- clue cells, whiff test (fishy odor with 10% KOH), and vaginal pH >4.5	Rapid tests- e.g., DNA probe and vaginal fluid sialidase activity
Herpes simplex virus (HSV)	Genital ulcer	Point of care HSV2 antibody tests- recent infection may have false negative	Type specific virologic tests: Ulcer- culture or PCR; Type specific serological tests: ELISA and Western blot (glycoprotein gG1/gG2 type-specific antibody test)
Treponema pallidum (syphilis)	Genital ulcer	Ulcer- darkfield microscopy; serological test; RPR, treponemal rapid EIA available reverse algorithm	Serological tests: RPR, VDRL, USR, ART, (nontreponemal tests); FTA-ABS, MHA-TP (treponemal tests); TPPA, darkfield is definitive if positive
Sarcoptes scabiei(scabies)	Dermatitis, ulcers	Mineral oil wet prep	Skin scraping of burrow is definitive
Phithirus pubis (pubic lice)	Dermatitis	Dry mount, observation of nits or lice	Detection of eggs, nits, or louse is definitive
Human Papillomavirus (HPV)	Genital warts (condylomata acuminate)	None; observation of lesions	Pap smear; HPV PCR
Salmonella sp., Shigella sp., Campylobacter sp.	Enteritis, proctocolitis	None	Stool culture; stool PCR
Entamoeba histolytica, Giardia lamblia	Enterocolitis	None	Wet prep or thrichrome stain of fresh or concentrated stool, giardia antigen test. Giardia PCR
Hepatitis virus: (A, B, C)	Hepatitis; elevated liver function enzymes	None; CLIA waived rapid HCV test (OraQuick HCV)	Serological test for specific antibody
HIV	Variable	Rapid HIV-1 Antibody Tests	HIV-1/HIV-2 antigen/antibody immunoassays and HIV differentiation assay (HIV1 vs HIV2 antibodies) and then HIV-1 NAT (for indeterminate or negative differentiation test). For patients with signs/symptoms of acute HIV, also send HIV RNA VL testing

Step 7: Ensure Referral and Management of Sexual and Needle-sharing Contacts

Given the relatively long incubation period for syphilis of up to 90 days, timely notification and prompt presumptive treatment (ie, postexposure prophylaxis) of sexual and needle-sharing contacts exposed to an infectious case of syphilis can effectively interrupt any ongoing transmission, thus preventing additional cases of infection in the community. Effective evaluation and treatment of exposed partners can also help to prevent reinfection of the treated case-patient.

The extent of partner management necessary is guided by the stage of infection in the case-patient. **Table 14** outlines the period of infectiousness of the case-patient and the appropriate management of exposed contacts.

Table 14. Infectiousness and Duration of Infectivity by Syphilis Stage

STAGE OF INFECTION	MAXIMUM PERIOD OF INFECTIOUSNESS * (Prior to symptom onset or first serologic evidence of infection/reinfection)	MANAGEMENT OF CONTACTS AT RISK FOR EXPOSURE
Incubating Infection	Persons being treated presumptively for incubating infection following a known exposure, who lack any exam or serologic evidence of syphilis, are **not** considered infectious—but will become infectious if left untreated. Therefore, contacts of persons treated for incubating infection are not at risk of exposure but may benefit from syphilis/STI screening.	N/A
Primary Syphilis	**3 months**	**Evaluation and presumptive treatment** of contacts exposed *within 3 months* prior to the onset of symptoms or signs in the case patient.
Secondary Syphilis	**6 months**	**Evaluation and presumptive treatment** of contacts exposed *within 6 months* prior to the onset of symptoms or signs in the case patient.
Early Latent Syphilis	**12 months** Since skin and mucous membrane lesions, which often go unrecognized by patients, occur predominately during the first year of infection, persons diagnosed with early latent syphilis are potentially infectious to contacts despite their lack of symptoms or exam findings at the time of treatment.[23]	**Evaluation and presumptive treatment** of contacts exposed *within 12 months* of first serologic evidence of infection or re-infection, in the case-patient.
Late Latent Syphilis	Persons diagnosed with late latent infection (ie, acquired > 1 year prior to treatment) are not considered to be infectious to current/recent sexual or needle-sharing contacts.	Long-term ongoing partners exposed to the case-patient more than 1 year ago may benefit from syphilis screening.
Latent Syphilis of Unknown Duration	If there is insufficient information to determine the duration of latent infection, the case-patient may have been infectious over the past year. Patients with latent syphilis of unknown duration who have high nontreponemal serologic titers (ie, > 1:32) have an increased likelihood of recent acquisition and of being infectious.[23]	**Evaluation and presumptive treatment** of contacts exposed *within 12 months* of first serologic evidence of infection, or re-infection in the case-patient.
Ocular, Otic, or Neurosyphilis	Central nervous system, ocular and otic infection are not sexually transmissible.	If the case-patient also meets the diagnostic criteria for primary, secondary, early latent, or latent of unknown duration, contacts should be managed as noted above.
Tertiary Syphilis	Not considered infectious.	

*** Any stage of syphilis during pregnancy is potentially infectious to the developing fetus.**

PARTNER NOTIFICATION

Notification and evaluation of exposed contacts serves to identify persons with unrecognized syphilis infection as well as those who might be incubating infection and would benefit from syphilis postexposure prophylaxis before becoming symptomatic or infectious.

Health care providers are not required to notify contacts directly, but they should counsel patients being treated for syphilis about the importance of partner management and advise them to instruct contacts to promptly seek medical care. In NYC, any persons exposed to syphilis who are 12 years or older can be referred to any of the NYC DOHMH Sexual Health Clinics for evaluation and treatment irrespective of immigration status, insurance coverage, or ability to pay. (For more information regarding NYC DOHMH Sexual Health Clinics, visit **nyc.gov/health/clinics**)

Health care providers can also assist in the partner notification process by endorsing partner notification services offered by the local health department. Many patients find it difficult to discuss their syphilis diagnosis with ongoing or previous partners and are relieved to discover that, in many cases, local health department staff can provide assistance. The NYC Department of Health prioritizes the following syphilis cases for case investigation and partner services: primary, secondary, early latent and high-titer late latent (or latent of unknown duration), as well as any possible case of syphilis in a woman (or transgender man) of childbearing age.

In NYC, and many other local health jurisdictions, when the health department is notified by a clinical provider of a newly diagnosed case of syphilis, or by a laboratory about a patient with a reactive syphilis serology, specially trained health department staff called Disease Intervention Specialists (DIS) will reach out to the provider and case-patient. The DIS will confirm that the patient received all recommended treatment, and that at-risk contacts were notified and encouraged to seek medical evaluation and treatment. If a case-patient has and shares information regarding exposed contacts, health department staff will conduct partner notification without revealing any information about the original case-patient or the type/timing of the exposure, thereby attempting to ensure the original case-patient's confidentiality.

EVALUATION OF PERSONS REPORTING A SYPHILIS EXPOSURE

The evaluation of persons reporting sexual or needle-sharing contact with someone diagnosed with syphilis should include:

- A medical history noting:
  - The timing of the exposure (including the last date of contact if known)
  - Any previous syphilis testing and treatment
  - The occurrence of any signs or symptoms of syphilis (currently or in the preceding 12 months)

- A thorough physical examination for clinical manifestations of syphilis

- Serologic screening for syphilis (utilizing a rapid point-of-care if available)
  - Given the persistent serologic reactivity seen in persons previously treated for syphilis, *quantitative* nontreponemal test titers are needed for comparison with previous posttreatment titers in order to assess for reinfection. Currently available rapid POC serologic testing consists of treponeme-specific tests or qualitative nontreponemal tests, making them unhelpful in evaluating persons with a history of syphilis treatment who report a new exposure.

TREATMENT OF PERSONS REPORTING A SYPHILIS EXPOSURE

If the exposed person is found to have exam evidence of syphilis or serologic evidence of infection/reinfection (by rapid POC serologic testing or recent reactive referral laboratory testing), their infection should be staged and stage-appropriate treatment should be provided. Since they have been identified as a case of syphilis *their* contacts should also be evaluated.

If the exam and rapid POC serologic testing are negative (or if rapid testing is not available or cannot be used due to previously treated syphilis), possible incubating infection must be assumed.

If the last sexual contact with the case-patient was within the past 90 days:
The CDC recommends presumptive treatment (even in the absence of clinical or serologic findings) of any persons exposed within the past 90 days (ie, the incubation/"window" period) to a case of primary, secondary, or early latent syphilis[23]—and possibly latent syphilis of unknown duration. In a person whose last potential exposure with the case patient was within the preceding 90 days, a nonreactive serology could indicate a false-negative result and be consistent with incubating infection. Standard of care is that providers should offer presumptive therapy (rather than awaiting serologic results) for persons exposed within the preceding 90 days.

Some patients who report sexual or needle-sharing contact with a person diagnosed with syphilis in the past 90 days may decline the offer of presumptive syphilis treatment, preferring to await laboratory results. Health care providers should strongly encourage presumptive treatment and counsel such patients about the following:

- A negative syphilis serology does not rule out infection that is in the incubation or window period, therefore presumptive treatment would still be recommended in the face of negative testing to prevent eventual progression to an infectious stage of syphilis, to reduce the risk of transmission and to avoid any symptomatic complications.
- While awaiting results of repeat testing, painless (but infectious) skin lesions may develop and can go unnoticed, especially if they occur in the rectum or vagina.
- If the patient declines presumptive treatment as a contact, follow-up serologies over the 90-day postexposure period would be needed to promptly detect seroconversion since the initial evaluation. If repeat testing becomes positive, transmission to partners may have already occurred.
- Subsequent seroconversion would result in a diagnosis of early syphilis and the need to notify and provide prophylactic treatment to any contacts since the initial evaluation.

If the last sexual contact with the case-patient was more than 90 days ago:
Patients whose last contact with an infectious syphilis case was more than 90 days ago who are found to be nonreactive serologically and are free of any signs or symptoms, can be considered to be uninfected. If follow-up is uncertain and point-of-care rapid serologic testing is unavailable (or cannot be performed due to previously treated syphilis), presumptive therapy at the time of initial evaluation is recommended rather than awaiting serologic results.

Step 8: Promptly Report Newly Diagnosed or Treated Cases of Syphilis to the State/Local Health Department

Public Health Codes (NYC Health Code §11.01; NYS Sanitary Code 10NYCRR 2.10,2.14)[97,98] mandate the reporting of all positive syphilis test results by laboratories, as well as the prompt reporting of any diagnosed cases by clinical providers (or their designees).

In cases of primary, secondary, and early latent syphilis, prompt reporting of cases allows for timely partner services and is critical in interrupting ongoing disease transmission. On average, persons who have been exposed to infectious syphilis will become infectious in approximately 3 weeks. If presumptive therapy (ie, post-exposure prophylaxis) can be provided before this time, incubating infection can be cleared without entering the infectious stage, and ongoing transmission can be prevented. Therefore, prompt reporting of cases can contribute significantly to disease prevention.

Case reporting also ensures that accurate staging and treatment information is added to the NYC Syphilis Registry. Licensed health care providers can access current and historical syphilis test results and treatment information in the New York City Syphilis Registry to inform the diagnosis and management of syphilis in their patients. For more information, see PDF at **https://www1.nyc.gov/assets/doh/downloads/pdf/std/syphilis-registry-check.pdf**

Aggregate information based on case reporting is also used to inform local or CDC resource allocation in the community.

Healthcare providers in NYC with questions about obtaining a syphilis registry check on one of their patients or reporting a case of syphilis can call **347-396-7201** for assistance.

It should be noted that surveillance case definitions, which are used for case reporting, differ to some extent from the clinical diagnostic criteria used for the purposes of treatment and patient management. See **Appendix E** for a comparison of Clinical Diagnostic Criteria and CDC Surveillance Case Definitions for Syphilis.

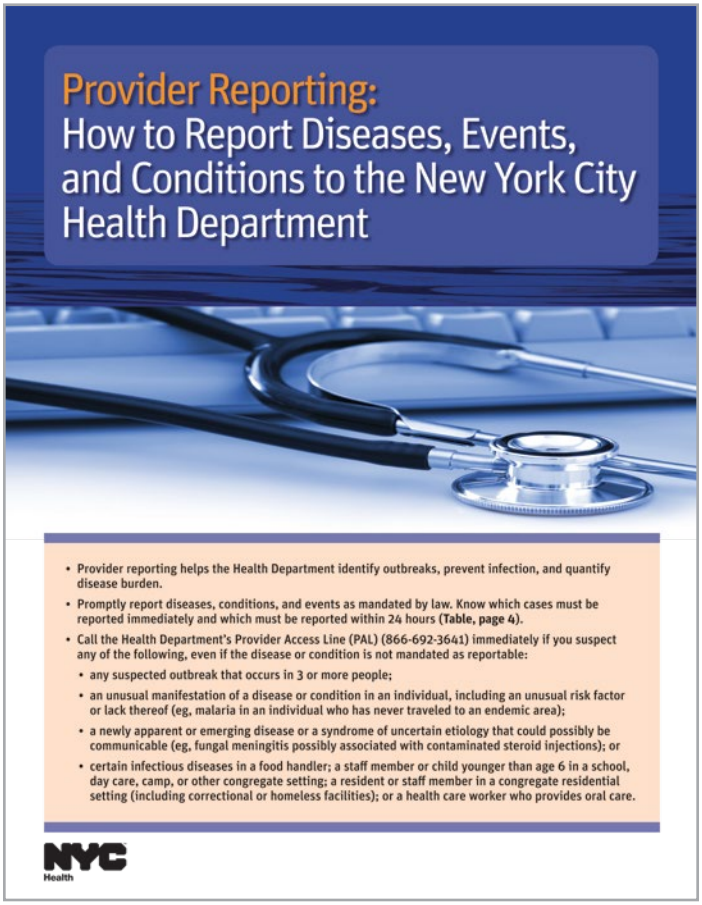

Figure 10 provides information regarding disease reporting in NYC. For information regarding reporting and partner services outside of NYC, healthcare providers can contact their respective state or local health departments or refer to their Department of Health websites (eg, information regarding disease reporting in New York State can be found at **https://www.health.ny.gov/professionals/reporting.htm)**

Figure 10. Case Reporting of Sexually Transmitted Infections by Healthcare Providers in NYC

How to Report a Case of a Sexually Transmitted Infection

New York City's Health Code Article 11 requires that certain diseases and conditions be reported to the Health Department immediately and others within 24 hours. In addition to all stages of Syphilis (including congenital), the following STIs are reportable to the NYC DOHMH: HIV/AIDS, chancroid, chlamydia, gonorrhea, granuloma inguinale, neonatal herpes (in infants aged ≤ 60 days), and lymphogranuloma venereum.

For a full and updated list of reportable diseases and conditions in NYC and additional information regarding case reporting, visit **www.nyc.gov/health/diseasereporting**

Cases should be reported within 24 hours:

- *Via Reporting Central*, which is accessible via NYCMED. Providers can register for an NYCMED account at **www.nyc.gov/nycmed**. For assistance with registration, e-mail nycmed@health.nyc.gov or call **888-NYCMED9 (888-692-6339)**.

  OR

- *By mail or fax* using the Universal Reporting Form (PDF) **https://www1.nyc.gov/site/doh/providers/reporting-and-services/notifiable-diseases-and-conditions-reporting-central.page**

Note: For certain diseases or conditions, such as measles or Invasive meningococcal disease providers should call the NYC Health Department's Provider Access Line (PAL) at 866-692-3641.

ABOUT THE PROVIDER ACCESS LINE: 866-692-3641

The Provider Access Line (PAL) is a 24/7 resource for case reporting and medical information (including syphilis serologic and treatment registry check).

Step 9: Monitor Treated Patients Clinically and Serologically to Ensure Adequate Response to Therapy and Detect Reinfection

Currently, there is no readily available test-of-cure for syphilis. CDC guidance for assessing adequacy of treatment is based on the resolution of clinical signs and symptoms, if present, and a 2-dilution (ie, 4-fold) or more decrease in the nontreponemal serologic titer within an appropriate time period (as compared with the baseline titer at the time of treatment). The appropriate time period for an expected titer decline is determined by the stage of infection and host factors. (See **Table 15.**)

Nontreponemal testing obtained at the time of treatment should be used to establish a baseline titer against which serologic response to treatment can be monitored. Results for specimens obtained more than 1 to 2 weeks prior to treatment may not represent an accurate baseline, especially in patients being treated for primary, secondary, or early latent syphilis whose titers may be actively rising. In such cases, repeat testing should be performed at the time of treatment.

The CDC recommends clinical and serologic re-assessment every 3 to 6 months for 12 to 24 months following treatment. (See **Table 14.**) More frequent retesting may be warranted in patients whose long-term follow-up is uncertain or if repeat infection is a concern. All patients treated for syphilis during pregnancy who are at high risk for reinfection or live in geographic areas with a high prevalence of syphilis, such as NYC, should receive close serologic follow-up until the time of delivery to detect and treat reinfection as early as possible, thereby more effectively preventing congenital infection.

Table 15. Recommended Follow-up of Treated Syphilis Cases[23]

STAGE OF INFECTION	HIV NEGATIVE	HIV INFECTED	EVIDENCE OF TREATMENT FAILURE OR POSSIBLE REINFECTION
	Follow up Serologies		
Primary and Secondary		3 months	• Persistence or recurrence of signs and symptoms • A sustained (more than 2 weeks) 2-dilution (ie, 4-fold) or more rise in nontreponemal titer following initiation of treatment (as compared with initial baseline or subsequent results) **POSSIBLY:** Failure of nontreponemal titer to decrease 2 dilutions (ie. 4-fold) by 6–12 months posttreatment[a]
	6 months	6 months	
		9 months	
	12 months	12 months	
		24 months	
Early Latent, Late Latent, and Latent Syphilis of Unknown Duration	6 months	6 months	• The development of signs and symptoms • A sustained (more than 2 weeks) 2-dilution (ie, 4-fold) or greater rise in nontreponemal titer following initiation of treatment (as compared with initial baseline or subsequent results) • In patients with an initial titer ≥ 1:32, failure of the nontreponemal titer to decrease at least 2 dilutions (4-fold) by 12–24 months posttreatment
	12 months	12 months	
		18 months	
	24 months	24 months	

[a] As noted in the 2015 CDC STD Treatment Guidelines, "Optimal management of persons who have less than a 2-dilution (ie, 4-fold) decline in nontreponemal test titer after treatment is unclear. At a minimum, these persons should receive additional clinical and serologic follow-up and be reevaluated for HIV infection. If additional follow-up cannot be ensured, retreatment is recommended. Because treatment failure might be the result of unrecognized CNS infection, clinical neurologic assessment and lumbar puncture with CSF examination can be considered in such situations."[23]

Definitive criteria for treatment failure vs cure have not been well established. However, there are steps clinicians can take to address the possibility of treatment failure among patients with recurrent signs/symptoms or those with nontreponemal titers which are rising or remain unchanged post-treatment. (See **Table 16.**)

Persistent Posttreatment Serologic Reactivity

Although not universal, nontreponemal serologic testing reverts to nonreactive status in most treated patients. Nevertheless, up to 20% of patients receiving the recommended therapy for primary or secondary syphilis will fail to demonstrate a 2-dilution decline in nontreponemal titers by 12 months post treatment.[86,99]

Even after an adequate serologic response to treatment (at least a 2-dilution titer decline, ie, a 4-fold decline) has been documented, patients should continue to be followed serologically either until nontreponemal testing becomes nonreactive or declines to a stable serofast titer (at least 12 to 24 months posttreatment). In patients with serofast serologies, the posttreatment serologic plateau will serve as the baseline against which future screening results are compared. Therefore, ensuring that the titer is at the end point of its decline following treatment is critical to establish a new baseline and allow for accurate serologic screening of possible reinfection in the future.

Rescreening

In geographic areas or populations with an increased prevalence of syphilis such as NYC, re-infection rates may be high.[100–102] Therefore, patients at continued risk of repeat infection should be re-screened periodically, at least annually and as frequently as every 3 to 6 months, depending on interval sexual history and patient risk factors. (See **Table 2**.)

Table 16. Evaluation and Management of Possible Treatment Failure

1. Rule Out Unrecognized HIV infection
Delayed serologic response to syphilis therapy can be seen in persons with HIV; therefore, re-screening for HIV should be performed if HIV testing was negative at time of syphilis treatment.
2. Consider Possible Reinfection
Assessment for possible reinfection: • Obtain an interim sexual/exposure history with special attention to individual and community factors: • Possible reexposure to an untreated ongoing partner • New exposure(s) to a known syphilis case • New-onset symptoms or signs of primary or secondary syphilis • Residence in a community or population with high prevalence of syphilis • Perform a thorough physical exam for evidence of primary or secondary syphilis
3. Question the Patient About Adherence to Oral Therapy
If an oral regimen was used due to penicillin allergy, referral for allergy testing and/or penicillin desensitization should be considered to allow for treatment with the CDC-recommended regimen of intramuscular benzathine penicillin.
4. Rule Out Unrecognized Neurosyphilis
Evaluation for possible neurosyphilis should include: • A medical history asking about any neurologic, ocular or otic symptoms • A careful neurologic exam • A lumbar puncture with CSF examination (including CSF-VDRL, CSF leukocyte count and CSF protein)a • Ophthalmologic or audiologic evaluation in patients with symptoms/signs of ocular or otic syphilis respectively If a diagnosis of ocular, otic or neurosyphilis is made, patient should be treated with the appropriate CDC-recommended penicillin-based regimen. (See **Appendix B, Table B6**.)
5. Provide Retreatment
If there is no evidence of syphilis reinfection or neurosyphilis, the patient should be retreated with benzathine penicillin G 2.4mU intramuscularly on a weekly basis for 3 weeks. If serologic titers fail to decline despite a normal CSF examination and re-treatment with the 3-week course of benzathine penicillin G, additional work-up or treatment is not generally recommended, although periodic (eg, annually or every 3–6 months depending on risk) repeat RPR titer checks may be warranted to screen for possible reinfection.

[a] In addition to possible treatment failure, other indications for lumbar puncture and CSF examination include[23]:

– Signs or symptoms of neurosyphilis (See **Appendix B, Table B2**)

– Manifestation of ocular or otic syphilis, even in the absence of other neurologic clinical findings

– Evidence of tertiary syphilis (eg, late-stage neurologic complications such as tabes or general paresis, or cardiovascular or gummatous disease)

Abbreviations: CDC, Centers for Disease Control and Prevention; CSF, cerebrospinal fluid; CSF-VDRL, cerebrospinal fluid Venereal Disease Research Laboratory.

Step 10: Encourage Behaviors That Decrease the Risk of Syphilis Reinfection and the Acquisition of Other Sexually Transmitted Infections

Patients recently diagnosed with syphilis or another STI, and those at ongoing risk of infection, should be engaged by the clinician in risk reduction counseling. Such counseling should attempt to address gaps in risk perception, identify specific risk behaviors that could be modified, assess barriers to behavior change and to health care access, address any complicating mental health or substance use issues, assess other co-occurring conditions such as housing stability, intimate partner violence, and other social determinants of health and assist in the development of a plan of action as well as providing any necessary referrals. Rather than using an approach which focuses solely on risk of disease or complications, many patients may be more responsive to messages framed by a positive goal of a healthy relationships and fulfilling sexual life for themselves and their partners.

Figure 11A compiles the key prevention messages that clinicians should convey to patients at risk for STIs, and those who may become pregnant.

Many risk behaviors that underlie the acquisition of syphilis are the same for HIV, and the presence of an STI such as syphilis has been shown to increase the risk of HIV acquisition. A recent retrospective population-level analysis of men diagnosed with primary or secondary syphilis in NYC showed that among MSM who lacked evidence of prior or concurrent HIV infection at the time of their syphilis diagnosis, 1 in 20 was diagnosed with HIV within the following year.[95] A similar study found that 1 in 15 MSM diagnosed with rectal gonorrhea or chlamydia at a NYC Sexual Health Clinic was subsequently diagnosed with HIV within the following year.[96] Therefore, a new STI diagnosis, such as syphilis, in an HIV-negative patient presents a key opportunity for discussing HIV prevention strategies such as PrEP. (See **Figure 11B**.)

Figure 11A. Key Counseling Messages for the Prevention of STIs and Pregnancy in At Risk Patients

Key Messages/Behaviors for Patients at Risk for Sexually Transmitted Infections and/or Pregnancy

- **Use Condoms As Often as Possible**
  Use condoms as often as possible, ideally every time you have sex. Condoms protect against HIV, other STIs and unintended pregnancy. Find a condom that works for you and your partners. Health experts recommend using condoms made of latex or synthetic nitrile. Add silicone or water-based lube, especially during anal sex. Either type of lube is safe with latex condoms.
- **Get Tested for HIV**
  An HIV test is the only way to know if you or a partner has HIV.
- **Get Checked for Other Sexually Transmitted Infections**
  - STIs can make it easier to get HIV or to pass it to others.
  - You may not know if you have an STI; most infections do not cause symptoms but, if undetected and left untreated, STIs can cause serious long-term complications.
  - If you are a man or transgender person who has sex with men, your medical provider should perform blood testing as well as testing of any parts of your body that you use during sex; a urine test may not be enough — you might need throat and anal tests as well.
  - Get tested at least annually; some people may need to get tested every 3 to 6 months. Talk to your provider to see what's best for you.
- **Talk to Your Partners about Testing**
  Ask your sexual partners about the last time they had an HIV or STI test; to be sure, get tested together.
- **Inform Your Sexual Contacts if You Are Diagnosed With an STI**
  If you are diagnosed or treated for an STI, it's important to tell your partners so they can be tested and treated as well. Informing partners can improve their health and decrease your risk of becoming reinfected. It's also important to make sure that you don't have sex until both you and your partners have completed treatment.
- **Support Yourself and/or Your Partners Living With HIV**
  Encourage partners living with HIV to get HIV care and take their medications every day so they can stay healthy and reduce their chance of passing HIV to others. People with HIV who maintain an undetectable viral load for at least six months do not transmit HIV through sex (Undetectable = Untransmittable).
- **Make Sure You Are Up-to-Date on Your Vaccinations**
  Some STIs can be prevented with a vaccine, including human papillomavirus (HPV), and hepatitis A and hepatitis B viruses. HPV can cause genital and anal warts, and cancers of the cervix, anus, throat, and parts of the vagina and penis. Hepatitis A and hepatitis B viruses can cause liver cancer.
- **Know About Emergency PEP (Post-exposure Prophylaxis)**
  HIV PEP is an emergency medication that can prevent HIV infection if started ideally within 36 hours, but not beyond 72 hours, after exposure. If you are not taking PrEP and think you were recently exposed to HIV, go immediately to your doctor or an emergency room and ask for PEP. You can also call the NYC PEP hotline at (844) 3-PEPNYC (844-373-7692) to get started on PEP right away. The hotline is available 24/7.
- **Know About PrEP (Pre-exposure Prophylaxis)**
  HIV PrEP is a daily pill that can you take to significantly reduce your risk of HIV infection, especially if you don't always use condoms.
- **Have a Strategy for Preventing Unintended Pregnancy**
  If you're worried about unintended pregnancy, there are many safe, effective and easy to use birth control options available to you. For more information, call 311 or visit **https://www1.nyc.gov/site/doh/health/health-topics/birth-control.page**
- **Avoid Alcohol and Drugs When You Have Sex**
  Drinking or getting high when you have sex can make it hard to remember to use condoms and contraception. For help to stop using, call **(888) NYC-WELL** (**888-692-9355**).
- **Use Clean Syringes**
  If you inject drugs, never share needles, cookers, cottons and/or drug solutions. Clean syringes are available for free all over NYC. For information on Syringe Exchange and Sterile Syringe Access Programs in NYC call 311 or visit **https://www1.nyc.gov/site/doh/health/health-topics/alcohol-and-drug-use-services.page**

Figure 11B. Preexposure Prophylaxis (PrEP) for the Prevention of HIV Infection

PrEP is the use of antiretroviral medication to prevent acquisition of HIV infection. It is used by HIV **uninfected** persons who are at high risk of being exposed to HIV through sexual contact or injection drug use.

PrEP should be considered as part of a **comprehensive prevention plan** that includes adherence and risk reduction counseling, HIV prevention education and provision of condoms.

PrEP is indicated for any patients currently diagnosed with syphilis (or treated in the past 6 months) if they are sexually active and not in a monogamous relationship with a recently tested HIV-negative partner.

PrEP Provider Resources

- **New York State Department of Health AIDS Institute Clinical Guidelines Program: PrEP for HIV Prevention https://www.hivguidelines.org/prep-for-prevention/**
- **CDC. PrEP for the Prevention of HIV Infection in the US—2017 Update: A Clinical Practice Guideline. https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2017.pdf**
- **CDC. PrEP for the Prevention of HIV Infection in the US—2017 Update: Clinical Providers' Supplement https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-provider-supplement-2017.pdf**
  The Clinical Providers' Supplement contains additional tools for clinicians providing PrEP, such as a patient/provider checklist, patient information sheets, provider information sheets, risk assessment, supplemental counseling information, billing codes, and practice quality measures.
- **NYC DOHMH, PrEP and PEP: Information for Medical Providers https://www1.nyc.gov/site/doh/providers/health-topics/prep-pep-information-for-medical-providers.page**

APPENDIX A: SYPHILIS IN HIV-INFECTED PERSONS

For the most part, diagnostic, treatment and follow-up recommendations regarding syphilis are the same for persons with and without HIV. **Table A1** outlines key HIV-related issues and recommendations regarding syphilis.

For a complete discussion of the clinical management of persons living with HIV refer to the New York State Department of Health (NYSDOH) AIDS Institute's *HIV Clinical Guidelines* (developed in collaboration between the NYS Department of Health AIDS Institute and the Johns Hopkins University School of Medicine, Division of Infectious Diseases), available at **https://www.hivguidelines.org/** [39]

Table A1. Key Aspects of Syphilis Diagnosis, Treatment, and Follow-Up in Persons with HIV

	Salient Aspects and Recommendations
Epidemiology and Screening	• A significant proportion of new primary and secondary syphilis cases occur among persons with HIV[103,104] Both national and NYC surveillance data show that the rate of HIV infection is nearly 50% among reported cases of primary and secondary syphilis in MSM with known HIV status.[22] • Among MSM diagnosed with primary or secondary syphilis in NYC who lacked evidence of prior or concurrent HIV infection at the time of their syphilis diagnosis, 1 in 20 was subsequently diagnosed with HIV within the following year.[95] • Syphilis screening among persons with HIV is recommended at the initial HIV evaluation and at least annually if sexually active.[23] More frequent screening (eg, every 3 months) for persons with ongoing risk of infection/reinfection since last screened may be beneficial.[23,35,105] • Syphilis screening of all pregnant patients, irrespective of their HIV status, at their first prenatal medical encounter is mandated by NYS Public Health Law.[42] • All patients believed to be HIV uninfected who are diagnosed with syphilis or evaluated as a contact exposed to syphilis, should be screened for HIV. In geographic areas in which the prevalence of HIV is high, persons who have primary or secondary syphilis should be retested for acute HIV in 3 months if the first HIV test result was negative.[23]
Syphilis-HIV Synergy	Syphilis infection has been shown to increase susceptibility to, acquisition of, and transmission of HIV. **HIV Transmission** Syphilis infection in persons with HIV increases the risk of viral transmission to HIV-uninfected persons.[106–111] **HIV Susceptibility and Acquisition** Syphilis infection among persons who are HIV uninfected increases the risk of HIV acquisition due to the following:[106–112] • Ulcerations caused by syphilis increase the risk of HIV acquisition[109,113,114] • The presence of an increased number of macrophages and CD4+ T-lymphocytes at the site of the syphilis ulcerations serve as target cells for HIV.[17]

Table A1. Key Aspects of Syphilis Diagnosis, Treatment, and Follow-Up in Persons with HIV (cont.)

	Salient Aspects and Recommendations
Symptomatic Presentation	• Persons with HIV more frequently present with multiple simultaneous primary ulcerations.[6,13] • Persons with HIV presenting with signs or symptoms of secondary syphilis are more likely to have evidence of a persistent primary lesion.[6,13,115] • Cases of unusual, severe, cutaneous manifestations of secondary syphilis, such as lues maligna (disseminated papulopustular or ulcero-nodular skin lesions), have been reported.[116–118] • Increases in the occurrence of ocular syphilis have been seen among persons with HIV.[119–124]
Serologic Testing for Syphilis	• For most persons with HIV, serologic tests are accurate and reliable for syphilis diagnosis and posttreatment follow-up.[23] • Although rare, unusual syphilis serology results have been observed among persons with HIV, including (1) false-negative results, (2) delayed appearance of seroreactivity, (3) high or fluctuating posttreatment, serofast, nontreponemal titers.[23,125,126]
Syphilis Treatment	• Current CDC-recommended first-line treatment regimens for syphilis apply equally to persons with and without HIV.[23] • Available data demonstrate that additional doses of benzathine penicillin G or other supplemental antibiotics for the treatment of primary, secondary, or early latent syphilis in persons with HIV do not result in enhanced efficacy.[86,127] • The use of antiretroviral therapy might improve clinical outcomes in persons with HIV infection and syphilis.[128–130]
Treatment of Syphilis in Patients with Penicillin Allergy	• Persons with HIV who have an allergy to penicillin should be managed according to the CDC Treatment Guidelines recommendations.[23] • The efficacy of alternative **nonpenicillin** regimens (eg, oral doxycycline or tetracycline) in persons with HIV infection has not been well studied, and these therapies should be used only in conjunction with close serologic and clinical follow-up.[23] • Patients with penicillin allergy whose adherence to therapy or follow-up cannot be ensured should be referred for penicillin desensitization and treated with the CDC-recommended benzathine penicillin G regimen.[23] • Azithromycin is not recommended for the treatment of syphilis in persons with HIV infection.[23] • Pregnant women with HIV who are penicillin-allergic should be desensitized and treated with the CDC-recommended penicillin-based regimen, since benzathine penicillin G is the only acceptable treatment during pregnancy. (See **Appendix C**.)
Post-treatment Follow-up	• Persons with HIV who are treated for syphilis should have more frequent and longer clinical and serologic follow-up.[23] – **Primary and Secondary Syphilis Follow-up:** Every 3 months for 1 year and once again 2 years posttreatment (ie, 3, 6, 9, 12, and 24 months following treatment). – **Early Latent Syphilis, Late Latent Syphilis, and Latent Syphilis of Unknown Duration Syphilis Follow-up:** Every 6 months for 2 years posttreatment (ie, 6, 12, 18, and 24 months following treatment).

Table A1. Key Aspects of Syphilis Diagnosis, Treatment, and Follow-Up in Persons with HIV (cont.)

	Salient Aspects and Recommendations
Serologic Response to Treatment	• Most persons with HIV have an appropriate clinical and serologic response to the recommended benzathine penicillin treatment regimen for primary and secondary syphilis.[23] • Conflicting data exist regarding delayed post-treatment syphilis serologic response among persons with HIV.[86,131–133] Although many studies have shown no difference in serologic response to therapy based on HIV status,[134–136] other authors have identified a higher risk of delayed serologic response or serologic treatment failure among patients with syphilis and HIV.[133,137–141] In addition, the use of antiretroviral therapy (ART) and the absence of immunosuppression appears to mitigate any poor serologic response in persons with HIV, though most studies done to evaluate serologic response to treatment have not analyzed the use of ART or viral load in the study design.[129,142] • Although long-term (eg, >1 year) comparative data are lacking, no treatment regimens for syphilis have been demonstrated to be more effective in preventing neurosyphilis in persons with HIV infection than the CDC-recommended syphilis regimens for persons without HIV infection.[86] • Patients with **negative HIV testing** at the time of syphilis treatment who demonstrate evidence of treatment failure (eg, persistent or recurrent signs/symptoms, or a sustained rise in nontreponemal titer), or a failure of expected decline in posttreatment titers, should be rescreened for HIV.[23]
Neurosyphilis and Indications for Cerebrospinal Fluid Examination	• Persons with HIV infection who have early syphilis might be at increased risk for neurologic complications;[143,144] Therefore, assessing for symptoms of neurologic involvement by patient history and neurologic exam remains important • Ocular syphilis has been reported more frequently among persons with HIV.[119–124,145,146] • All persons with HIV infection and syphilis should have a careful neurologic exam, even in the absence of neurologic or ophthalmic symptoms.[23] • Highly effective ART appears to mitigate the increased risk of neurosyphilis among persons with HIV.[129] ART has also been shown to facilitate the normalization of CSF results following neurosyphilis treatment.[128] • Neurosyphilis should be considered in the differential diagnosis of neurologic signs and symptoms in persons with HIV infection, irrespective of viral load or ART status. Persons with HIV and syphilis who have neurologic signs/symptoms should undergo immediate CSF examination.[23] • Patients with evidence of ocular/otic/tertiary syphilis or syphilis treatment failure should have CSF examination.[23] • In the absence of neurologic symptoms, routine CSF examination has not been associated with improved clinical outcomes and therefore is not recommended.[23] • Certain studies have demonstrated that among persons with HIV infection and syphilis, CSF abnormalities are associated with a low CD4 count (eg, ≤350 cells/mL) and/or a high RPR titer (eg, ≥1:32), but treatment of these laboratory abnormalities has not been shown to be of clinical benefit in patients without neurologic or ocular/otic symptoms.[129,130,147,148] • CSF abnormalities (eg, mononuclear pleocytosis and elevated protein levels) are common in persons with HIV infection, even in those without syphilis; this makes the interpretation of mild CSF abnormalities more difficult in patients with syphilis and HIV.[149,150] • Since CSF leukocyte count is usually elevated (>5 WBC/mm^3) in persons with HIV infection (especially those who are not on ART, have a CD4 count >200/uL, or detectable plasma HIV RNA) using a higher cutoff (>20 WBC/mm^3) might improve the specificity of neurosyphilis diagnosis.[23,151,152]

Table A1. Key Aspects of Syphilis Diagnosis, Treatment, and Follow-Up in Persons with HIV (cont.)

	Salient Aspects and Recommendations
Treatment and Follow-up of Neurosyphilis	• Several small observational studies in persons with HIV infection with neurosyphilis suggest that ceftriaxone 1-2 g IV daily for 10-14 days might be effective as an alternate regimen.[23,153–155] • Limited data suggest that post-treatment normalization of CSF parameters might occur more slowly in persons with HIV infection, especially those with more advanced immunosuppression.[128,129,147] Declining serologic RPR titers also may be a good predictor of CSF normalization.[128]

APPENDIX B: DIAGNOSIS AND MANAGEMENT OF NEUROSYPHILIS

Asymptomatic Neurosyphilis

Involvement of the CNS can occur at any stage of syphilis infection. Asymptomatic treponemal CNS invasion and CSF laboratory abnormalities are common in early stages of syphilis, often occurring concurrently with symptoms of primary or secondary syphilis.[1,149,156] The clinical significance of early asymptomatic infection and associated CSF findings is unclear, as most patients respond to standard stage-appropriate, non-neurosyphilis treatment regimens (eg, intramuscular benzathine penicillin G) without long-term complications.[17,68,86]

Symptomatic Neurosyphilis

Symptomatic neurosyphilis can be broadly divided into early syndromes (such as acute syphilitic meningitis and meningovascular disease) and late complications of untreated infection (such as general paresis and tabes dorsalis), which usually follow a long period of latency. Ocular and otologic involvement can occur during any stage of infection. **Table B2** outlines the clinical findings associated with each of these forms of neurosyphilis. Although it is helpful to conceptualize neurologic forms of syphilis as distinct syndromes, clinical presentations can straddle and blend these categories.

Identifying Ocular, Otic, or Neurosyphilis

All patients diagnosed with syphilis, irrespective of stage of infection, should be asked about neurologic complaints, including ophthalmologic and auditory issues. (See **Table B2**.) A brief neurologic examination should also be performed regardless of the presence or absence of neurologic symptoms. (See **Table B1**.) Individuals with serologic evidence of syphilis and signs or symptoms consistent with ocular, otic or neurosyphilis require prompt follow-up for lumbar puncture and cerebrospinal fluid (CSF) testing, and in the case of ocular or otic findings, a slit lamp ophthalmologic examination or evaluation by an otolaryngologist/audiologist.[23]

Table B1. Brief Neurologic Examination[157,158]

Brief Neurologic Exam

Mental Status Exam

Cranial nerve examination (Cranial Nerve)

- Visual acuity; visual fields[a] (II)
- Pupillary reaction to light & accommodation (II, III)
- Extraocular movement; rule out ptosis (III, IV, VI)
- Facial sensation; jaw movement (V)
- Facial muscle tone & control (VII)
- Gross hearing (VIII)
- Gag reflex; elevation of palate (IX, X)
- Shrugging of shoulders; turning of head (XI)
- Movement/protrusion of tongue (XII)

Nuchal Rigidity Testing

- Stiffness/pain with neck flexion
- Brudzinski's sign[b]
- Jolt accentuation maneuver[c]

Testing for any abnormalities in:

- **Motor function**
  - Muscle strength
  - Pronator drift
  - Fine motor control
- **Sensation**
  - Temperature or pain
  - Vibration or joint position sense
- **Deep tendon reflexes**
- **Coordination/balance**
  - Finger-to-nose testing
  - Romberg
  - Tandem heel-to-toe walking

[a] Fundoscopic exam could be helpful if available
[b] Brudzinski's sign: Reflex flexion of the patient's hips and knees after neck flexion by the examiner
[c] Worsening headache with rapid rotation of head from side to side

Table B2. Clinical Findings Associated with Neurosyphilis[1,47,68,159,180,181]

NEUROSYPHILIS SYNDROME		ONSET	POSSIBLE SYMPTOMS & CLINICAL FINDINGS (Exam findings are listed in bold)	
Asymptomatic Neurosyphilis		Soon after infected	None	
Acute Syphilitic Meningitis		Within 1st year *Can be seen during primary or secondary syphilis*	• Meningismus (headache, nuchal rigidity, photophobia) • Nausea, vomiting • Focal neurologic symptoms (vision changes, tinnitus, hearing loss, facial weakness or other cranial nerve symptoms) • Seizures	• Symptoms of increased intracranial pressure • **Nuchal rigidity (+ Kernig/Brudzinski signs)** • **Deafness (progressive or sudden)** • **Cranial nerve deficits (3rd, 6th, 7th, 8th CN)** • **Hemiplegia/Aphasia**
Meningo-vascular Neurosyphilis (Rare spinal cord involvement)		Months to years (average 7 years)	<u>Infarction-related focal neurologic symptoms</u> • **Paresthesias** • Seizures • **Hemiparesis, Hemiplegia** • **Aphasia** • **Hemianopsia (decreased vision or blindness in left or right half of visual field)**	<u>Pre-infarction symptoms</u> • Headache • Dizziness/vertigo • Stuttering stroke-like symptoms (weakness, **paresthesias**) • Psychiatric manifestations (mood, personality, or behavioral changes; irritability) • **Memory loss, slowed mentation & speech**
Ocular Syphilis[a]		Weeks to years	• Blurred vision • Eye pain (with eye movement or light) • Altered color perception (washed out colors) • Scotomas • New onset floaters • Excessive tearing • Blepharospasm (twitching of lid)	• **Redness of the eye** • **Decreased visual acuity, vision loss** • **Progressive concentric constriction of visual fields with normal visual acuity ("gun barrel sight")** • **Exam evidence of uveitis, retinitis**
Otic Syphilis[a]		Weeks to years	• Tinnitus; Vertigo; **Asymmetric hearing loss & deafness**	
Parenchymatous Neurosyphilis	**General Paresis** *(Syphilis Dementia)*	10–20 years	<u>**P.A.R.E.S.I.S.**</u> • **P**ersonality (emotional lability, paranoia, depression) • **A**ffect (lack of attention to personal appearance) • **Reflexes (hyperactive deep tendon reflexes)** • **Eye (pupillary abnormalities, Argyll Robertson pupils**[b]**)** • **Sensorium (illusions, delusions, megalomania, hallucinations)** • **I**ntellect (decreased recent/short-term memory, deficits in judgment, lack of insight) • **Speech (slurred)**	<u>Additional symptoms and signs</u> • Inappropriate social behavior • Seizures • Urinary or fecal incontinence • **Confusion; disorientation** • **Impaired handwriting** • **Flattening of facial lines** • **Loss of motor function; paralysis** • **Tremor of lips, tongue, face, fingers**
	Tabes Dorsalis	20–30 years	• Paresthesia in trunk and legs • Shooting/lightning pains (usually lower extremities) • Gastric/visceral crises (pain, nausea, vomiting) • Urinary or fecal incontinence • Impotence • **Progressive ataxia** • **Wide based gait with foot-slap** • **Cranial nerve disturbances (2nd, 3rd, 6th, 8th CN); ptosis; hearing loss, vestibular symptoms** • **Progressive concentric constriction of visual fields with normal visual acuity ("gun-barrel" sight)**	• **Argyll Robertson pupils**[b] • **Decreased deep tendon reflexes in lower extremities** • **Loss of position & vibratory sense in the lower extremities** • **Positive Romberg test** • **Abnormal heel-shin & finger-to-nose testing** • **Decreased muscle strength (late stages)** • **Charcot's joints** • **Traumatic ulcers on feet & lower extremities**

[a] Can be seen as an isolated finding or as part of another neurosyphilis syndrome.

[b] Pupillary abnormalities seen in neurosyphilis can include large, unequal pupils which are sluggishly reactive to light and accommodation. Over time, there can be progression to Argyll Robertson type pupils (seen more frequently in tabes than in paresis) which include the following characteristics: retinal sensitivity (ie, the eye is not blind); small, fixed pupils which do not react to strong light; normal convergence accommodation; limited ability of mydriatics (eg, atropine) to dilate the pupils; and lack of pupillary dilation to painful stimuli.[1]

Ocular Syphilis

Ocular involvement can occur at any stage of syphilis infection and most often presents with symptoms of posterior uveitis or panuveitis, which includes blurry vision, vision loss, or eye pain or redness.[19,121] Starting in late 2014, California and Washington states began to report clusters of syphilis cases with ocular involvement.[19] Subsequent case findings from January 2014 through December 2015 identified nearly 400 cases of suspected ocular syphilis in seven states and NYC. Most cases occurred in HIV-infected MSM, but a few cases also occurred among HIV-uninfected persons, including heterosexual men and women. Several cases resulted in serious sequelae, including blindness.[19] In response, the CDC released a clinical advisory that includes recommendations regarding screening and evaluation for ocular syphilis.[121] (See **Table B3**.)

Table B3. CDC Recommendations on Screening, Treatment and Reporting of Ocular Syphilis[121]

Screening for Ocular Syphilis
Clinicians should: • Screen for visual complaints in any patient at risk for syphilis (see **Figure B2** for list of possible symptoms); ocular syphilis can present with any of the following: – Uveitis (most commonly posterior or panuveitis) – Retinitis, retinal vasculitis, acute retinal necrosis – Retinal detachment – Optic neuritis – Iridocyclitis (inflammation of the iris and ciliary body) – Episcleritis (inflammation of the tissue between the conjunctiva and sclera) – Vitritis – Interstitial keratitis • Perform HIV screening for patients diagnosed with syphilis if their status is unknown or was previously HIV negative. • Perform a neurological exam (including cranial nerve testing) of any patient diagnosed with early syphilis, even those with no ocular or other neurologic symptoms.
Physical and Laboratory Examination
Any patient diagnosed with syphilis who reports ocular symptoms or has abnormal findings on ocular exam, even those lacking any other neurologic signs or symptoms, should receive: • An immediate ophthalmologic evaluation with slit-lamp examination *AND* • A CSF examination, including, at a minimum, CSF-VDRL, CSF leukocyte count, CSF protein[a]
Treatment of Ocular Syphilis Cases
Patients diagnosed with ocular syphilis should be managed in consultation with an ophthalmologist and treated with a CDC-recommended neurosyphilis regimen. (See **Table B6.**)
Case Reporting
Cases of ocular syphilis should be reported to the local or state health department within 24 hours of diagnosis.

[a] Up to 70% of patients with ocular syphilis will also have evidence of neurosyphilis on CSF testing. If CSF abnormalities are seen, post-treatment CSF follow-up may be indicated.[19]

Table B4: Diagnosing Neurosyphilis

Diagnosis of Neurosyphilis
A diagnosis of neurosyphilis usually relies on the following: • **Serum serologic evidence of syphilis**, eg, reactive treponeme-specific result alone or in combination with reactive nontreponemal result[a] *AND* • **Abnormal CSF Testing** – Reactive CSF-VDRL, or – Elevated CSF WBCs *or* Increased CSF Protein[b]

[a] Serum nontreponemal testing (eg, RPR) may be nonreactive in some cases of neurosyphilis, especially during late infection

[b] For patients with elevated CSF-WBC count or CSF protein but a nonreactive CSF-VDRL, additional CSF testing (eg, CSF-FTA) may assist in making a diagnosis of neurosyphilis. Although the CSF-FTA is less specific for neurosyphilis than the CSF-VDRL, it is highly sensitive. Therefore, neurosyphilis is highly unlikely when CSF-FTA testing is nonreactive, especially among persons with nonspecific neurologic signs or symptoms.[23,160]

Abbreviations: CIA, chemiluminescence immunoassay; CSF, cerebrospinal fluid; CSF-FTA, cerebrospinal fluid fluorescent treponemal antibody; CSF-RPR, cerebrospinal fluid-rapid plasma reagin; CSF-VDRL, cerebrospinal fluid- venereal disease research laboratory; EIA, enzyme immunoassay; RPR = rapid plasma reagin; WBC = white blood cell

Laboratory Diagnosis of Neurosyphilis

According to the CDC,[23] specific indications for CSF examination of adults diagnosed with syphilis include:

- Signs or symptoms of neurologic disease (See **Table B2**) including:
  - — Cranial nerve dysfunction (including auditory, visual or vestibular abnormalities)
  - — Symptoms or signs of meningitis or stroke
  - — Acute or chronic altered mental status
  - — Cognitive dysfunction
  - — Motor or sensory deficits (including loss of vibration sense)
- Manifestations of ocular or otic syphilis, even in the absence of other neurologic clinical findings
- Evidence of tertiary syphilis (eg, late stage neurologic, cardiovascular, or gummatous disease)
- Treatment failure, possibly including inadequate serologic response to therapy (See **Table 15**)

See **Table B5** for a summary of neurosyphilis diagnostic testing, including sensitivity, specificity, interpretation of CSF abnormalities. Results of CSF testing should be interpreted in consultation with an infectious disease or neurologic specialist.

Table B4 outlines the diagnostic criteria for neurosyphilis.

HIV screening should be performed in all patients being treated for syphilis, including those with ocular, otic, or neurosyphilis. If the patient is found to be infected with HIV, linkage to HIV primary care and prompt initiation of antiretroviral therapy should be encouraged. If the screening HIV test is negative, HIV prevention options—including pre-exposure prophylaxis—should be encouraged.

Several studies have shown that among persons with HIV and syphilis, cerebrospinal fluid (CSF) abnormalities consistent with neurosyphilis are associated with a CD4 count less than or equal to 350 cells/mL and/or a serum RPR titer higher than or equal to 1:32.[147,148,161] Nevertheless, routine CSF examination in persons with HIV and syphilis has not been associated with improved clinical outcomes in the absence of signs or symptoms of neurologic/ocular/otic disease, tertiary syphilis, or suspected treatment failure.[23]

Table B5. Laboratory Testing for Neurosyphilis

Test		Test Reliability and Limitations	Clinical Importance
Serum Testing	**Serum Nontreponemal Testing (RPR, VDRL)**	Can be nonreactive in patients with late neurosyphilis and late ocular syphilis	A nonreactive screening serum RPR (or a reactive EIA/CIA with a nonreactive reflex RPR as part of reverse-sequence screening) does not rule out a diagnosis of neurosyphilis
	Serum Treponeme-specific Testing (FTA-ABS, TPPA, EIA)	Reliably reactive in patients with neurosyphilis, even in late stage neurosyphilis	• In patients previously treated for syphilis, treponemal tests usually remain reactive for life • A nonreactive serum treponemal test generally rules out neurosyphilis
Cerebrospinal Fluid Testing	**CSF-VDRL**	• **High specificity** but **low sensitivity** • Can be **false-negative** in up to 70% of cases, especially in late neurosyphilis[162,163] • Can be **false-positive** if CSF specimen is contaminated with blood in a patient with high serum RPR titers[164]	• The CSF-VDRL is regarded as the gold standard for the diagnosis of neurosyphilis; a reactive result, in the absence of contaminating blood, confirms a neurosyphilis diagnosis • A nonreactive CSF-VDRL does **NOT** rule out neurosyphilis
	CSF-RPR	Unreliable performance as a diagnostic test for neurosyphilis	CSF-RPR testing should **NOT** be used in the evaluation of possible neurosyphilis
	CSF-FTA	• **High sensitivity** but **low specificity** • Passive transfer of serum IgG antitreponemal antibody across the blood-brain barrier may result in a **false-positive** CSF-FTA result, even in patients without CNS involvement[23] **Note:** Due to the significant frequency of false positive results, the CDC does not recommend the routine use of CSF-FTA testing.	• If performed, a nonreactive CSF-FTA result makes neurosyphilis highly unlikely, especially when presenting neurologic signs or symptoms are nonspecific • Nevertheless, since CSF-FTA test sensitivity does not reach 100%, the negative predictive value is dependent on the prevalence/likelihood of neurosyphilis in the test population; therefore, a nonreactive CFS-FTA result may **NOT** rule out neurosyphilis when clinical suspicion is high[165]
	Elevated Cerebrospinal Fluid White Blood Cell Count (> 5 WBCs/microL)	May have limited specificity in patients with HIV	• In patients with symptoms or signs of ocular or neurosyphilis, CSF leukocytosis is consistent with CNS infection • In persons with HIV and a mildly elevated CSF WBC count alone, it may be difficult to distinguish CSF leukocytosis from neurosyphilis from HIV-related CSF pleocytosis[a]
	Elevated CSF Protein (> 45mg/dL)	Less reliable in making a diagnosis of neurosyphilis in cases where the CSF-VDRL is nonreactive and CSF WBC count is normal	Caution should be used in making a diagnosis of neurosyphilis based only on elevated CSF protein

[a] Patients with HIV may have mild pleocytosis (> 5 WBC/mm^3) unrelated to neurosyphilis, especially those not on ART, those with a CD4 count >200ul or those with a detectable HIV viral load.[152] Whereas a CSF WBC count of > 20 WBCs/mm^3 suggests neurosyphilis, a CSF WBC count of 10-20mm^3 in persons with HIV and a nonreactive CSF-VDRL may require additional testing to confirm the diagnosis.

Abbreviations: ART, antiretroviral therapy; CIA, chemiluminescence immunoassay; CSF, cerebrospinal fluid; CSF-FTA, cerebrospinal fluid fluorescent treponemal antibody; CSF-RPR, cerebrospinal fluid-rapid plasma reagin; CSF-VDRL, cerebrospinal fluid- venereal disease research laboratory; EIA/CIA, enzyme immunoassay; FTA-ABS, fluorescent treponemal antibody absorption; RPR, rapid plasma reagin; TPPA, *T pallidum* passive particle agglutination; WBC, white blood cell.

Treatment of Neurosyphilis and Ocular Syphilis

The CDC recommended therapy for neurosyphilis consists of a 10- to 14-day course of intravenous penicillin (see **Table B6**). Of note, the duration of therapy for neurosyphilis is shorter than the course needed for adequate treatment of late latent syphilis or latent syphilis of unknown duration. Thus, an additional intramuscular dose of benzathine penicillin G 2.4 million units following the completion of the course of intravenous therapy can be considered to provide a total duration of therapy comparable to that used for late latent syphilis.[23]

Table B6. CDC-Recommended Regimens for the Treatment of Ocular, Otic and Neurosyphilis

First-line Therapy	Aqueous crystalline penicillin G 18–24 million units per day, administered as 3–4 million units intravenously every 4 hours, or by continuous infusion, for 10–14 days.
Alternate Regimen	**Use ONLY if follow-up and adherence with therapy can be ensured** Procaine penicillin G 2.4 million units, administered intramuscularly once daily for 10–14 days **PLUS** probenecid 500 mg orally 4 times daily for 10-14 days
Penicillin-Allergic Patients[a]	**Manage patient in consultation with an infectious disease specialist and/or a clinical allergist.** • Limited data suggest that ceftriaxone 2g daily either intramuscularly or intravenously for 10–14 days might be effective as an alternative treatment for persons with neurosyphilis.[23, 153-155] • Although cross-sensitivity between cephalosporins and penicillin can occur, the risk with third-generation cephalosporins (such as ceftriaxone) is thought to be negligible.[23] • If there are concerns about the safety of ceftriaxone in a particular patient, referral for penicillin allergy skin testing should be made when possible, especially in persons with HIV infection. If the penicillin allergy is confirmed (or allergy testing is unavailable), the patient should undergo desensitization and subsequent treatment with the recommended penicillin-based neurosyphilis regimen.[23]
Neurosyphilis During Pregnancy	**The only acceptable treatment in a pregnant patient is penicillin.** Pregnant patients in need of treatment for ocular, otic or neurosyphilis who have a known history of penicillin allergy should be referred for penicillin desensitization and subsequent treatment with the recommended penicillin-based neurosyphilis regimen (see First line Therapy, above).[a]
Ocular Syphilis	**Manage patient in consultation with an ophthalmologist.** Treatment should consist of a CDC-recommended neurosyphilis regimen, even if CSF examination is normal (see First-line Therapy above).
Otologic Syphilis	**Manage patient in consultation with an otolaryngologist or infectious disease specialist.** Many specialists recommend treating patients who have syphilis-related auditory disease with a neurosyphilis regimen, regardless of CSF results.

[a] For details regarding penicillin allergy assessment and desensitization, see the **2015 CDC STD Treatment Guidelines**.[23]

Abbreviations: CSF, cerebrospinal fluid.

POST-TREATMENT FOLLOW-UP

The CSF leukocyte count is a sensitive measure of response to treatment for neurosyphilis. The CDC recommends that patients treated for neurosyphilis who have an elevated CSF leukocyte count at the time of diagnosis should have a repeat CSF exam every 6 months until the cell count is normal.[23] Retreatment should be considered if CSF leukocyte cell count has not decreased after 6 months or if CSF leukocyte cell count or protein levels are not normal after 2 years.[23]

Post-treatment resolution of CSF-VDRL and CSF protein abnormalities may occur more slowly than CSF leukocyte cell counts and, in some patients, may persist indefinitely.[128,147] Therefore, normalization of CSF-VDRL and protein may be less important in assessing effectiveness of neurosyphilis therapy.

Some data suggest that serum serologic response (ie, an appropriate drop in serum nontreponemal test titers) following neurosyphilis treatment predicts normalization of CSF lab abnormalities in immunocompetent patients and those infected with HIV who are on antiretroviral therapy.[128]

Appendix C: Syphilis in Pregnancy

Maternal Screening for Syphilis

Mirroring overall trends in US syphilis incidence, rates of primary and secondary syphilis among women and rates of congenital syphilis have been increasing, with higher numbers of reported cases seen across all regions of the United States. US congenital syphilis rates have increased yearly since 2012, with a 44% increase nationally from 2016 to 2017.[22] In NYC, rates of primary and secondary syphilis among women increased 57% from 2015 to 2017.[21]

Congenital syphilis and its devastating complications are completely preventable. Prevention relies on early detection of unrecognized syphilis in the mother, detection of new infections throughout the pregnancy, and ensuring maternal treatment is administered at least 4 weeks prior to delivery. Given the gravity of the complications seen with congenital syphilis, there are clinical, public health, and regulatory systems in place to ensure that these preventive steps occur, including mandatory maternal and prenatal screening (see **Table C1**), and public health follow-up of reactive serologic results in women of childbearing age.

Vertical Transmission of Syphilis

Intrauterine transmission of syphilis from mother to child, and the frequency and severity of neonatal complications, depend on the stage of maternal infection and the timing of the new maternal infection during the pregnancy, specifically:

- The risk of congenital infection, premature delivery, stillbirth, and neonatal death is highest in mothers with primary or secondary syphilis.[166,167] Nevertheless, in utero transmission can occur at any stage of maternal infection, including early and late latent syphilis.
- The risk of in utero acquisition of syphilis, and the severity of fetal and neonatal sequelae, are both increased in women who become newly infected with syphilis during their pregnancy as compared with women with unrecognized, untreated syphilis who then become pregnant.[168-170] Therefore, providers should update patients' sexual histories at each prenatal medical visit. If a new or ongoing risk is identified (see **Table C1**), the patient should undergo serologic rescreening for syphilis while there is enough time to treat the mother prior to delivery and effectively prevent vertical transmission and neonatal complications.

When treating pregnant patients presenting with an anogenital ulceration, rash, or other exam finding consistent with syphilis, providers should take a thorough sexual and exposure history and repeat serologic syphilis screening, even if testing earlier during the pregnancy was negative.

Pregnancy should always be ruled out in all patients treated for syphilis who could be pregnant.

Table C1: Maternal and Neonatal Syphilis Serologic Screening Recommendations

Patient Population	Screening Recommendations
Pregnant Women	• At the first prenatal medical encounter[23,40–42] Syphilis screening at the time of **initial pregnancy diagnosis** should be considered, especially when access to prenatal care is not optimal or if there is any risk of loss to follow-up after referral for prenatal care[23] • At delivery (including live births, stillbirths, or terminations)[40–42] • At the time of a fetal death (after 20 weeks' gestation)[23] • Per CDC recommendations, pregnant patients who are at high risk for syphilis or live in areas of high syphilis morbidity (see table footnote a), such as NYC, should be rescreened early in the third trimester (at approximately 28 weeks' gestation) and at delivery[23] Given the increasing prevalence of syphilis in NYC, the NYC DOHMH also recommends the following for pregnant patients[41]: • Assessment of sexual risk for syphilis and other STIs at each prenatal visit • Serologic re-screening if patient reports: – A recent bacterial STI diagnosis – A new sexual partner – Sex with an MSM partner or transgender woman Though not a part of any formal national recommendations, syphilis screening of new sexual partners of sexually-active pregnant patients could help to prevent or identify unrecognized maternal infection
Neonates	• All neonates at delivery[40–42]

[a] In addition to MSM and persons with HIV, populations at increased risk of syphilis based on the current epidemiology in the US include the following[22,36]:

- Young adult men (younger than 29 years of age)
- Members of certain racial or ethnic groups (Black, Native Hawaiians/Other Pacific Islanders, Latinos, and American Indians/Alaska Natives)
- Persons reporting transactional sex (eg, commercial sex work, exchange of sex for drugs or services)
- Persons in correctional institutions
- Residents of specific geographic areas (eg, metropolitan areas such as NYC, southern and western US states)[22]
  For the most up-to-date CDC STD Surveillance data, visit www.cdc.gov/std/stats.

Abbreviations: HIV, human immunodeficiency virus; MSM, Men who have sex with men; NYC DOHMH, New York City Department of Health and Mental Hygiene; PrEP, Pre-exposure prophylaxis for the prevention of HIV; STI, sexually transmitted infection.

[23] Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines, 2015

[35] Cantor A, et al. Screening for Syphilis Infection in Nonpregnant Adults and Adolescents. US Preventive Services Task Force Recommendation Statement. *JAMA*. 2016;315: 2328-2337.

[36] US Preventive Services Task Force. Screening for Syphilis Infection in Nonpregnant Adults and Adolescents. US Preventive Services Task Force Recommendation Statement. *JAMA*. 2016;315:2312-2327.

[42] Mandated by some state public health laws including NYS Law Article 23, §2308

[40] N.Y. Comp Codes R. and Regs. Tit 10, § 69-2.2

[41] NYC DOHMH Health Alert #14, Syphilis is increasing among women of child-bearing age in New York City, 2016

Mothers With Reactive Serologic Results

Pregnant patients with reactive syphilis serologies should have current and past medical records reviewed. Information regarding past treatment and previous serologic results can also be requested from the local or state health department, which can also assist in obtaining serologic and treatment information from other states or jurisdictions. Seroreactive pregnant patients should be diagnosed, staged, and treated for syphilis if they lack clear documentation of stage-appropriate treatment in the past, or lack an appropriate serologic response to therapy (see **Step 9**). A rising, or persistently high posttreatment titer may indicate reinfection or treatment failure; retreatment should be considered in such cases.[23]

If maternal screening is performed using the reverse-sequence algorithm (EIA/CIA with reflex RPR) during pregnancy or at delivery and shows a positive treponeme-specific test result with a negative nontreponemal result (ie, reactive EIA, nonreactive RPR), distinguishing a false-positive result from an untreated infection can be challenging. The CDC recommends the following approach[23]:

If a treponemal test (eg, EIA or CIA) is used for antepartum syphilis screening, all positive EIA/CIA tests should be reflexed to a quantitative nontreponemal test (RPR or VDRL). If the nontreponemal test is negative, then the results are considered discrepant and a second treponemal test (TPPA preferred) should be performed, preferably on the same specimen. In most laboratories, the second treponemal test is performed as part of reflex testing.

If the second treponemal test is positive, *current or past syphilis infection can be confirmed.*

- ***For women with a history of adequately treated syphilis*** *who do not have ongoing risk, no further treatment is necessary.*
- ***Women without a history of treatment*** *should be staged and treated accordingly with a recommended penicillin regimen.*

If the second treponemal test is negative, *the positive EIA/CIA is more likely to represent a false-positive test result in low-risk women with no history of treated syphilis.*

- ***If the woman is at low risk for syphilis, lacks signs or symptoms of primary syphilis, has a partner with no clinical or serologic evidence of syphilis, and is likely to follow up,*** *repeat serologic testing within 4 weeks can be considered to determine whether the EIA/CIA remains positive or if the RPR/VDRL or the TPPA becomes positive. If both the RPR and TPPA remain negative, no further treatment is necessary.*
- ***If follow-up is not possible,*** *women without a history of treated syphilis should be treated according to the stage of syphilis.*

Table C2. Treatment Recommendations for Syphilis in Pregnant Patients by Syphilis Stage

Stage of Infection	CDC 2015 Recommended Treatment Regimen
Incubating Infection **Primary** **Secondary** **Early Latent**	Benzathine penicillin G 2.4 million units as a single intramuscular injection[a] *No alternatives exist for **pregnant patients** with a documented penicillin allergy.*[b]
Late Latent or Latent of Unknown Duration	Benzathine penicillin G 7.2 million units total, administered as 3 separate doses of 2.4 million units intramuscularly, each at 1-week intervals.[c] *No alternatives exist for **pregnant patients** with a documented penicillin allergy.*[b]
Neurosyphilis or Ocular/Otic Syphilis	Aqueous crystalline penicillin G 18–24 million units per day, administered as 3–4 million units intravenously every 4 hours, or by continuous infusion, for 10–14 days **Alternative Regimen** Procaine penicillin G 2.4 million units intramuscularly once daily for 10–14 days *PLUS* Probenecid 500mg orally 4 times daily for 10–14 days
Tertiary	Tertiary syphilis should be managed in consultation with an infectious disease specialist. Testing for HIV infection and CSF examination should be performed before therapy is initiated.

[a] Although the formal CDC recommendation for the treatment of primary, secondary, or early latent syphilis in pregnant patients is a single dose of benzathine penicillin G, some experts recommend a second dose of benzathine penicillin G (2.4 million units), administered 1 week after the initial dose.[23,171,172]

[b] Intramuscular, long-acting benzathine penicillin G (or aqueous crystalline penicillin G, in cases of ocular, otic or neurosyphilis) remains the only regimen with documented efficacy against syphilis during pregnancy and for the prevention of congenital syphilis; pregnant patients who are penicillin-allergic should be referred for desensitization and treated with the CDC-recommended penicillin regimen.[23]

[c] Dosing flexibility is not acceptable in the treatment of late latent syphilis or latent syphilis of unknown duration during pregnancy; pregnant patients who miss any scheduled doses of Bicillin (ie, return 8 or more days after the previous dose) must repeat the full course three injections.[23]

Treatment of Maternal Syphilis

Pregnant patients diagnosed with syphilis should be treated with a stage-specific penicillin regimen as outlined in the current CDC STD Treatment Guidelines[23] and summarized in **Table C2**.

Treatment for **late latent syphilis** or **latent syphilis of unknown duration** in a pregnant patient consists of benzathine penicillin G 2.4mU IM weekly for 3 weeks, with no more than 7 days between doses. If a pregnant patient misses a scheduled dose of benzathine penicillin (ie, presents 8 or more days after the previous injection), the full 7.2mU course should be repeated.

As is the case for non-pregnant persons diagnosed with syphilis, HIV screening is indicated in pregnant patients diagnosed with syphilis. Those who initially test negative for HIV may be at continued risk for HIV infection. Providers diagnosing syphilis in an HIV-uninfected woman should discuss the result with the patient and offer HIV PrEP, especially to women with male partners who are HIV-positive or who are at substantial risk for HIV infection (eg, men who inject drugs, MSM).[173]

A sonographic fetal evaluation should be performed in any patients diagnosed with syphilis in the second half of the pregnancy; however, this evaluation should not delay maternal treatment.[23] Sonographic evidence of fetal or placental infection are associated with increased risk of persistent congenital infection despite maternal treatment.[170]

Prompt presumptive treatment (irrespective of serologic test results) of pregnant patients who have been exposed to an infectious case of syphilis results in the clearance of any incubating maternal infection and dramatically reduces any risk of in utero transmission. Healthcare providers should not hesitate to provide post-exposure presumptive treatment to pregnant patients with a known exposure to sexual or needle-sharing partner recently diagnosed with syphilis.

Penicillin is the only CDC-recommended regimen for the treatment of syphilis during pregnancy and the prevention of congenital syphilis in the newborn.

Treatment of Penicillin-Allergic Women

Tetracyclines (including doxycycline) are contraindicated during pregnancy because of their harmful effects on tooth coloration and long-bone growth.[174] Erythromycin and azithromycin should not be used, because neither reliably cures maternal infection or effectively treats an infected fetus.[23,175] Data are insufficient to recommend ceftriaxone for the treatment of maternal infection and prevention of congenital syphilis.[23]

Pregnant patients being treated for syphilis with a known penicillin allergy should undergo desensitization in consultation with an allergy specialist and be treated with a CDC-recommended penicillin-based regimen as described in **Table C2**. For a review of penicillin allergy assessment and desensitization, see the 2015 CDC STD Treatment Guidelines[23] at **http://www.cdc.gov/std/tg2015**.

Risk of Jarisch-Herxheimer Reaction

Patients treated for syphilis during the second half of pregnancy are at risk for premature labor and/or fetal distress if the treatment precipitates a Jarisch-Herxheimer reaction (see **Step 5**). However, since any delay in maternal treatment can result in increased risk of fetal harm or miscarriage, concerns regarding a possible Jarisch-Herxheimer reaction **should not postpone prompt initiation of therapy**. Women receiving treatment during the latter half of the pregnancy should be advised to seek obstetric attention if they notice any fever, contractions, or decreased fetal movements.[23]

Posttreatment Follow-Up

Following treatment, nontreponemal serologic titers should be monitored closely throughout the remainder of the pregnancy to document response to treatment and to monitor for serologic evidence of reinfection.

Repeat screening should occur:

- At 28 to 32 weeks' gestation
- At delivery
- More frequent screening (eg, monthly) may be warranted in pregnant patients at increased risk for re-infection or in geographic areas with a high prevalence of syphilis (such as NYC). (See **Table C1**)

Because most women will deliver before their serologic response to treatment can be fully assessed, postpartum follow-up of mother and newborn are critical.[41] Neonatal evaluation and treatment for possible congenital syphilis is indicated if: (1) delivery occurs within 30 days of maternal treatment; (2) clinical signs of maternal infection are present at delivery; or (3) a rise of 2 or more dilutions (4-fold) are seen in maternal nontreponemal titers at delivery as compared with baseline titers at the time of treatment.

For information regarding additional routine serologic follow-up (eg, after delivery) in patients treated for syphilis, see **Step 9**.

Partner Management

A significant proportion of congenital syphilis cases are associated with a new maternal infection acquired during pregnancy (following negative serologic screening at the first prenatal visit or reinfection among women who received treatment early in the pregnancy).[176] Among partners from the 90 days prior to a maternal diagnosis of syphilis, negative serologic results cannot reliably rule out incubating infection. Ongoing contact with untreated partners poses a serious risk for maternal reinfection. Therefore, special attention should be paid to ensure that all sexual and needle-sharing contacts receive prompt presumptive therapy, irrespective of their serologic test results. For more details regarding partner notification and management, see **Step 7**.

APPENDIX D: PREVENTION, DIAGNOSIS, AND MANAGEMENT OF CONGENITAL SYPHILIS & SYPHILIS IN INFANTS AND CHILDREN

Serologic Screening in the Prevention and Detection of Congenital Infection

Congenital syphilis and its devastating complications can be completely prevented by timely screening during pregnancy and at delivery, and early detection and treatment of maternal infection. (See **Table C1** for recommendations regarding maternal and neonatal screening).

Evaluation of Neonates (Infants Less Than 30 Days Old) Born to Women With Reactive Syphilis Serologic Tests During Pregnancy

All neonates born to mothers who have reactive syphilis serologic results should be evaluated with a quantitative nontreponemal serologic test (eg, RPR). Testing should be performed on neonatal serum, because umbilical cord blood can become contaminated with maternal blood and yield a false-positive result, and Wharton's jelly within the umbilical cord can yield a false-negative result.[23] Serologic testing using a treponemal assay (ie, TPPA, FTA-ABS, EIA or CIA) on neonatal serum is not recommended because of the difficulty of interpreting the corresponding results.[23]

For all the complexities inherent in the interpretation of syphilis serologies in adults, the evaluation of a neonate born to a seroreactive mother is made even more challenging by the placental transfer of nontreponemal and treponeme-specific antibodies to the fetus. The CDC recommends a synthesis of the following clinical and laboratory information to assess the risk of congenital syphilis and determine the need for further evaluation and management:[23]

- Physical examination of both mother and child
- Pathologic evaluation and testing of the placenta and/or umbilical cord, as well as dark field or PCR testing of any suspicious neonatal lesions or abnormal newborn fluids, such as nasal discharge
- Serologic testing, including quantitative nontreponemal titers, of both the mother's and infant's serum at delivery
- Consideration of the timing and adequacy of any previous treatment administered to the mother (eg, treatment received prior to becoming pregnant, >4 weeks before delivery, or within the final 4 weeks of the pregnancy)
- Consideration of serologic response to any previous maternal syphilis therapy

Maternal Serologic Results

As noted in **Appendix C**, pregnant patients with reactive syphilis serologies should have current and past medical records reviewed. When necessary, information regarding past treatment and previous serologic titers can be requested from the local department of health, which can also assist in obtaining serologic and treatment information from other states or jurisdictions. Seroreactive women with no clear documentation of stage-appropriate syphilis treatment in the past or an appropriate posttreatment nontreponemal titer decline (See **Step 9**) should be diagnosed, staged, and treated for syphilis.

Mothers with well-documented treatment in the past who have rising or persistently high nontreponemal titers may have become reinfected or experienced treatment failure. Providers should strongly consider further evaluation and retreatment in such cases. (See **STEP 9**.)

Presentation of Congenital Infection in Neonates and Children Less Than 2 Years of Age

Although most infants infected in utero are asymptomatic at the time of delivery, infants and children younger than 2 years of age can present with a host of multi-organ system symptoms and clinical findings, the most common of which are listed in **Table D1**. Dermatologic manifestations of early congenital syphilis resemble those of secondary syphilis in adults, although the rash may be vesicular or bullous in infants.

Table D1. Manifestations of Congenital Syphilis in Infants Less Than 2 Years of Age[177,178]

Adverse Pregnancy Outcomes

- Stillbirth
- Prematurity
- Small for gestational age
- Nonimmune hydrops (eg, ascites, pleural, or pericardial effusion, skin edema)

Nose and Throat

- **Rhinitis/"Snuffles"**– thick or bloody nasal discharge
- Laryngitis with hoarseness or aphonic cry

Mucocutaneous

- Macular eruption
  - Dusky pink or copper-colored lesions, often with a fine silvery scale
  - Usually involves the back, perineum, extremities, palms, and soles; spares the anterior trunk
- Pemphigus syphiliticus
  - Bullous, crusting, or desquamatory eruption
  - Often prominent on palms and soles
- Paronychia
- Alopecia (especially of eyebrows)
- Mucous patches which can evolve into hemorrhagic fissures
  - Seen at the nares, lips, tongue, palate, anus and perineum
- Condyloma lata (perioral or perianal)

Hematologic

- Anemia
- Autoimmune hemolysis
- Thrombocytopenia

Gastro-intestinal

- Hepatomegaly
- Jaundice
- Pancreatitis
- Ileitis

Skeletal

Most infants with skeletal involvement are asymptomatic.

- Epiphysitis (usually of the radius, femur, humerus, and fibula)
- Metaphyseal osteochondritis
- Proximal tibial metaphyseal demineralization and destruction
- Diaphyseal periostitis
- Osteitis with alternating linear translucency and radiodensity ('celery stick' appearance on x-ray)
- Dactylitis (involving metacarpals, metatarsals, and proximal phalanges)
- Pseudoparalysis (due to painful bony lesions or fractures)

Central Nervous System

- Acute meningitis and hydrocephalus with meningismus, bulging fontanelles, or vomiting
- Cerebral infarction
- Chronic meningovascular disease
- Hypopituitarism
- Ocular abnormalities (eg, uveitis, chorioretinitis, glaucoma)
- Cranial nerve palsies

Other

- Generalized nontender lymphadenopathy (commonly involving epitrochlear nodes)
- Splenomegaly
- Nephrotic syndrome (+/- edema)
- Pneumonia alba (obliterative fibrosis)
- Myocarditis

Late Congenital Syphilis in Children > 2 Years of Age

A thorough examination of the child and a careful review of obstetric records, including maternal serologic results (along with information available through the state or local health department syphilis serologic and treatment registry), can assist in differentiating late congenital syphilis (acquired in utero) from syphilis resulting from child sexual abuse (acquired after delivery).

If child sexual abuse or neglect is suspected, the healthcare provider must report the case to child protective services; all US states and territories have laws that require this type of reporting. Although the exact requirements differ by state, if a provider has reasonable cause to suspect child abuse, a report must be made. Healthcare providers should contact their state or local child-protection service agency regarding child abuse reporting requirements in their states.[23]

Children with untreated late congenital syphilis (> 2 years of age) can present with a constellation of multi-organ signs and symptoms. The most common clinical manifestations are summarized in TABLE D2[177]:

Table D2. Manifestations of Congenital Syphilis in Children 2 Years of Age or Older[177,178]

Facial, dental, and skeletal malformations	**Neurologic complications**
• Frontal bossing • Saddle nose deformity • Rhagades • Anterior bowing of shins • Clutton's joints	• Intellectual disability • Hydrocephalus • Seizures • Cranial nerve palsies • Paresis
Dental Malfunctions	**Ocular**
• Hutchinson teeth • Mulberry molars	• Interstitial keratitis • Glaucoma • Corneal scaring • Optic atrophy
Hematologic	**Auditory**
• Hemoglobinuria	• Sensorineural hearing loss

Evaluation and Management of Congenital Syphilis and Syphilis in Infants and Children

A discussion of the evaluation, management, and follow-up of congenital syphilis and syphilis in older infants and children is beyond the scope of this monograph. For complete recommendations, see the 2015 CDC STD Treatment Guidelines at **https://www.cdc.gov/std/tg2015/congenital.htm**. Infants and children with serologic or exam evidence of syphilis should be managed in consultation with a pediatric infectious disease specialist.

Appendix E: A Comparison of Clinical Criteria in the Diagnosis of Syphilis in the Adult and Adolescent and Surveillance Case Definitions[179]

STAGE	Diagnostic Criteria for Clinical Case Management	CDC Surveillance Case Definitions for Case Reporting
Incubating Infection	**Exposure to an infectious case of syphilis in the previous 90 days** *AND* **No exam findings of syphilis** *AND* **No serologic or other laboratory evidence of syphilis**	**N/A**
Primary	**Exam findings consistent with primary syphilis at the time of treatment:** • Presence of a classic syphilitic chancre (ie, a single, painless, rubbery or indurated anogenital or oral ulcer) • Presence of multiple or atypical anogenital primary lesions • Primary lesions can sometimes be confirmed with positive dark field *or T pallidum* PCR testing **+/- Serologic evidence of infection (or reinfection):** Reactive syphilis serologic results support the diagnosis, but may be absent in early primary syphilis	**Syphilis, primary** The presence of one or more ulcerative lesions (eg, chancre), which might differ considerably in clinical appearance *AND* Laboratory criteria are met • Confirmatory Laboratory Criteria are met (**Confirmed case**) – Demonstration of *T pallidum* by darkfield microscopy in a clinical specimen not obtained from the oropharynx and not potentially contaminated by stool *OR* – Demonstration of *T pallidum* by polymerase chain reaction (PCR) or equivalent direct molecular methods in any clinical specimen *OR* • Supportive Laboratory Criteria are met (**Probable case**) – A reactive nontreponemal serologic test (RPR, VDRL, or equivalent method) *OR* – A reactive treponemal serologic test (TPPA, EIA, CIA, or equivalent method)

Continued on following page

Appendix E. A Comparison of Clinical Criteria in the Diagnosis of Syphilis in the Adult and Adolescent and Surveillance Case Definitions[179] *(continued)*

STAGE	Diagnostic Criteria for Clinical Case Management	CDC Surveillance Case Definitions for Case Reporting
Secondary	**Laboratory evidence of untreated infection/reinfection (serologic or lesion-based testing)** *AND* **Exam findings consistent with secondary syphilis at the time of treatment, for example:** • Mucocutaneous eruptions (localized or generalized), **including** palmar or plantar rashes • Condyloma lata (moist, flat, whitish-gray, wart-like papules or plaques) • Mucous patches (membranous lesions of tongue, buccal mucosa, lips) • Patchy alopecia • Generalized lymphadenopathy, malaise, fever, other nonspecific constitutional symptoms	**Syphilis, secondary** The presence of exam findings suggestive of secondary syphilis, eg, localized or diffuse mucocutaneous lesions (eg, rash—such as non-pruritic macular, maculopapular, papular, or pustular lesions), often with generalized lymphadenopathy; other signs including mucous patches, condyloma lata, and alopecia *AND* • Confirmatory Laboratory Criteria are met (**Confirmed case**) – Demonstration of T. pallidum by darkfield microscopy in a clinical specimen not obtained from the oropharynx and not potentially contaminated by stool *OR* – Demonstration of *T. pallidum* by polymerase chain reaction (PCR) or equivalent direct molecular methods in any clinical specimen. *OR* • Supportive Laboratory Criteria are met (**Probable case**) – A reactive nontreponemal serologic test (RPR, VDRL, or equivalent method) *AND* – A reactive treponemal serologic test (TPPA, EIA, CIA, or equivalent method)

Continued on following page

Appendix E. A Comparison of Clinical Criteria in the Diagnosis of Syphilis in the Adult and Adolescent and Surveillance Case Definitions[179] *(continued)*

STAGE	Diagnostic Criteria for Clinical Case Management	CDC Surveillance Case Definitions for Case Reporting
Early Latent (Case Reporting: Early Non-Primary Non-Secondary)	**Serologic evidence of untreated infection (or reinfection)** *AND* **No exam findings of primary, secondary, or tertiary syphilis at the time of treatment** *AND* **Any of the following:** • Documented seroconversion within the past 12 months (ie, a currently reactive syphilis serology with nonreactive results documented within the past 12 months) • A sustained rise in nontreponemal test titer for at least 2 weeks of 2 or more dilutions (ie, ≥4-fold rise) within the past 12 months • Unequivocal symptoms of primary or secondary syphilis in the past 12 months • Sexual or needle-sharing contact with a person diagnosed with an infectious stage of syphilis (ie, primary, secondary, or early latent) during the past 12 months • Only possible exposure has been within the previous 12 months, eg, a patient who reports that their first sexual contact occurred within the last 12 months	**Syphilis, early nonprimary nonsecondary (Probable case)** A person with no clinical signs or symptoms of primary or secondary syphilis who has: • One of the following: – No prior history of syphilis **AND** a current reactive nontreponemal test (eg, VDRL, RPR, or equivalent serologic methods) **AND** a current reactive treponemal test (eg, TPPA, EIA, CIA, or equivalent serologic methods) *OR* – A prior history of syphilis **AND** a current nontreponemal test titer demonstrating fourfold or greater increase from the last nontreponemal test titer (unless there is evidence that this increase was not sustained for >2 weeks) *AND* • Evidence of having acquired the infection within the previous 12 months based on *one or more of the following criteria*: – Documented seroconversion or fourfold or greater increase in titer of a nontreponemal test during the previous 12 months, unless there is evidence that this increase was not sustained for >2 weeks – Documented seroconversion of a treponemal test during the previous 12 months – A history of symptoms consistent with primary or secondary syphilis during the previous 12 months – A history of sexual exposure to a partner within the previous 12 months who had primary, secondary, or early nonprimary nonsecondary syphilis (documented independently as duration <12 months) – Only sexual contact (sexual debut) was within the previous 12 months

Continued on following page

Appendix E. A Comparison of Clinical Criteria in the Diagnosis of Syphilis in the Adult and Adolescent and Surveillance Case Definitions[179] *(continued)*

<table>
<tr><th>STAGE</th><th>Diagnostic Criteria
for Clinical Case Management</th><th>CDC Surveillance Case Definitions
for Case Reporting</th></tr>
<tr><td>Late Latent</td><td>Serologic evidence of infection (or re-infection)
AND No exam findings of primary, secondary, or tertiary syphilis at the time of treatment
AND None of the criteria for early latent are met
AND Evidence suggests that the infection was acquired greater than 12 months prior to diagnosis</td><td rowspan="2">Syphilis, unknown duration or late (Probable Case)
A person with no clinical signs or symptoms of primary or secondary syphilis who:
• Meets one of the following sets of criteria:
– No prior history of syphilis, and a current reactive nontreponemal test (eg, VDRL, RPR, or equivalent serologic methods), and a current reactive treponemal test (eg, TPPA, EIA, CIA, or equivalent serologic methods)
OR
– A prior history of syphilis, and a current nontreponemal test titer demonstrating fourfold or greater increase from the last nontreponemal test titer, unless there is evidence that this increase was not sustained for >2 weeks
OR
– Clinical signs or symptoms and laboratory results that meet the likely or verified criteria for neurologic, ocular, otic, or late syphilis manifestations (see below)
AND
• Who has no evidence of having acquired the disease within the preceding 12 months.
(See Syphilis, early nonprimary nonsecondary.)</td></tr>
<tr><td>Latent of Unknown Duration</td><td>Serologic evidence of infection (or re-infection)
AND No exam findings of primary, secondary, or tertiary syphilis at the time of treatment
AND None of the criteria for early latent are met
AND Available information is insufficient to determine the duration of infection</td></tr>
<tr><td>Tertiary</td><td>Clinical manifestations of late syphilis including:
• Cardiovascular (eg, aortitis, coronary vessel disease)
• Skin and other organ involvement (eg, gummatous lesions)
• Late neurologic (eg, tabes dorsalis, or general paresis)
AND
Laboratory evidence of infection by serologic, CSF, or direct pathology testing</td><td rowspan="2">For the purposes of syphilis case reporting, neurosyphilis, ocular syphilis, otic syphilis, and late/tertiary syphilis are not defined as a case in and of themselves. Cases should be reported according to stage of infection, as defined above (eg, primary syphilis; secondary syphilis; early nonprimary nonsecondary syphilis; or unknown duration or late syphilis) and any neurological, ocular, otic, or late syphilis manifestations should be noted in the case report data.
For definitions of Neurological, Ocular, Otic, or Late Syphilis manifestations, see below.</td></tr>
<tr><td>Neurosyphilis</td><td>See Appendix B; can occur along with primary, secondary, or latent infection</td></tr>
</table>

CDC Syphilis (*T pallidum*) 2018 Case Definitions **https://wwwn.cdc.gov/nndss/conditions/syphilis/case-definition/2018/**

Abbreviations: CIA, chemiluminescence immunoassay; CSF, cerebrospinal fluid; CSP, cerebrospinal fluid; EIA, enzyme immunoassay; PCR, polymerase chain reaction; RPR, rapid plasma reagin; TPPA, treponema pallidum particle agglutination; VDRL, Venereal Disease Research Laboratory.

Definitions of Neurological, Ocular, Otic, or Late Syphilis Manifestations

Neurological Manifestations

Possible Neurologic Manifestations:

A person with a reactive nontreponemal test (eg, VDRL, RPR, or equivalent serologic methods) and a reactive treponemal test (eg, TPPA, EIA, CIA or equivalent serologic methods)

AND

Clinical symptoms or signs that are consistent with neurosyphilis (eg, syphilitic meningitis, meningovascular syphilis, general paresis, including dementia, and tabes dorsalis) without other known causes for these clinical abnormalities

Likely Neurologic Manifestations:

A person with a reactive nontreponemal test (eg, VDRL, RPR, or equivalent serologic methods) and a reactive treponemal test (eg, TPPA, EIA, CIA or equivalent serologic methods)

AND *both of the following*:

- Clinical symptoms or signs that are consistent with neurosyphilis without other known causes for these clinical abnormalities

AND

- Elevated cerebrospinal fluid (CSF) protein (>50 mg/dL2) or leukocyte count (>5 white blood cells/cubic millimeter CSF) in the absence of other known causes of these abnormalities.

Verified Neurologic Manifestations:

A person with a reactive nontreponemal test (eg, VDRL, RPR, or equivalent serologic methods) and a reactive treponemal test (eg, TPPA, EIA, CIA or equivalent serologic methods)

AND *both of the following*:

- Clinical symptoms or signs that are consistent with neurosyphilis without other known causes for these clinical abnormalities

AND

- A reactive VDRL in CSF in the absence of grossly bloody contamination of the CSF.

Ocular Manifestations:

Possible Ocular Manifestations:

A person with a reactive nontreponemal test (eg, VDRL, RPR, or equivalent serologic methods) and a reactive treponemal test (eg, TPPA, EIA, CIA or equivalent serologic methods)

AND

Clinical symptoms or signs consistent with ocular syphilis* without other known causes for these clinical abnormalities.

Likely Ocular Manifestations:

A person with a reactive nontreponemal test (eg, VDRL, RPR, or equivalent serologic methods) and a reactive treponemal test (eg, TPPA, EIA, CIA or equivalent serologic methods)

AND *both of the following*:

- Clinical symptoms or signs consistent with ocular syphilis* without other known causes for these clinical abnormalities

AND

- Findings on exam by an ophthalmologist that are consistent with ocular syphilis* in the absence of other known causes for these abnormalities

Verified Ocular Manifestations:

A person with a reactive nontreponemal test (eg, VDRL, RPR, or equivalent serologic methods) and a reactive treponemal test (eg, TPPA, EIA, CIA or equivalent serologic methods)

AND *both of the following*:

- Clinical symptoms or signs consistent with ocular syphilis* without other known causes for these clinical abnormalities

AND

- Demonstration of *T pallidum* in aqueous or vitreous fluid by darkfield microscopy, or by polymerase chain reaction (PCR) or equivalent direct molecular methods.

* Ocular manifestations include symptoms/signs of posterior uveitis, panuveitis, anterior uveitis, optic neuropathy, and retinal vasculitis. (See **Appendix B**.)

Otic Manifestations:

Possible Otic Manifestations

A person with a reactive nontreponemal test (eg, VDRL, RPR, or equivalent serologic methods) and a reactive treponemal test (eg, TPPA, EIA, CIA or equivalent serologic methods) and clinical symptoms or signs consistent with otosyphilis† without other known causes for these clinical abnormalities.

Likely Otic Manifestations

A person with a reactive nontreponemal test (eg, VDRL, RPR, or equivalent serologic methods) and a reactive treponemal test (eg, TPPA, EIA, CIA or equivalent serologic methods)

AND *both of the following*:

- Clinical symptoms or signs consistent with otosyphilis† without other known causes for these clinical abnormalities

AND

- Findings on exam by an otolaryngologist that are consistent with otosyphilis† in the absence of other known causes for these abnormalities

Verified Otic Manifestations

A person with a reactive nontreponemal test (eg, VDRL, RPR, or equivalent serologic methods) and a reactive treponemal test (eg, TPPA, EIA, CIA or equivalent serologic methods)

AND *both of the following*:

- Clinical symptoms or signs consistent with otosyphilis† without other known causes for these clinical abnormalities

AND

- Demonstration of *T pallidum* in inner ear fluid by darkfield microscopy, or by polymerase chain reaction (PCR) or equivalent direct molecular detection methods.

† Manifestations of otic syphilis include sensorineural hearing loss, tinnitus, and vertigo

Late Clinical Manifestations

Likely Late Clinical Manifestations:

A person with a reactive nontreponemal test (eg, VDRL, RPR, or equivalent serologic methods) and a reactive treponemal test (eg, TPPA, EIA, CIA or equivalent serologic methods)

AND *either of the following*:

- Characteristic abnormalities or lesions of the cardiovascular system (eg, aortitis, coronary vessel disease), skin (eg, gummatous lesions), bone (eg, osteitis), or other tissue, in the absence of other known causes of these abnormalities

OR

- Clinical signs and symptoms consistent with late neurologic manifestations of syphilis (eg, general paresis, including dementia, or tabes dorsalis) in a case that meets the criteria for likely neurologic manifestations of syphilis (see above).

Verified Late Clinical Manifestations:

A person with a reactive nontreponemal test (eg, VDRL, RPR, or equivalent serologic methods) and a reactive treponemal test (eg, TPPA, EIA, CIA or equivalent serologic methods)

AND *either of the following*:

- Characteristic abnormalities or lesions of the cardiovascular system (eg, aortitis, coronary vessel disease), skin (eg, gummatous lesions), bone (eg, osteitis), or other tissue in the absence of other known causes of these abnormalities, in combination with either demonstration of *T pallidum* in late lesions by special stains or equivalent methods, or by polymerase chain reaction (PCR) or equivalent direct molecular methods, or demonstration of pathologic changes that are consistent with *T pallidum* infection on histologic examination of late lesions

OR

- Clinical signs and symptoms consistent with late neurologic manifestations of syphilis (eg, general paresis, including dementia, or tabes dorsalis) in a case that meets the criteria for verified neurologic manifestations of syphilis (see above).

APPENDIX F: CLINICAL PROVIDER RESOURCES

NYC DOHMH Sexually Transmitted Infection Resources

Visit **https://www1.nyc.gov/site/doh/providers/health-topics/stds.page**

for information on:

- NYC STD Health Alerts
- STD Case Reporting
- NYC Syphilis Serologic and Treatment Registry
- Expedited Partner Therapy for Chlamydia
- Extragenital Gonorrhea/Chlamydia Testing

Sexually Transmitted Infection Resources for Patients

Visit **https://www1.nyc.gov/site/doh/health/health-topics/sexually-transmitted-diseases.page**

for information regarding:

- Access to NYC DOHMH Sexual Health Clinics
- Sexually Transmitted Infection Fact Sheets for Patients

Regional and National STD Training Resources

- **NYC STD Prevention Training Center-** Visit **https://www.nycptc.org/**
- **National Network of STD Prevention Training Centers**- Visit **https://nnptc.org/**

NYC DOHMH Sexual and Reproductive Health Resources

Visit **https://www1.nyc.gov/site/doh/providers/health-topics/sexual-and-reproductive-health.page**

for resources on:

- Contraception
- Sexual and Reproductive Health in Adolescents
- Transgender Patient Care

HIV and AIDS Resources

Visit **https://www1.nyc.gov/site/doh/providers/health-topics/infectious-diseases.page**

for resources regarding:

- HIV Testing
- Reporting HIV and Partner Services
- Prescribing PrEP and PEP
- Services for People Living with HIV

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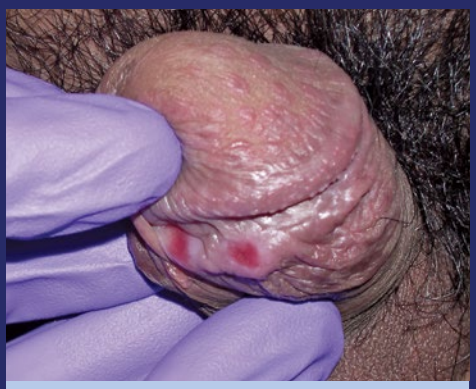
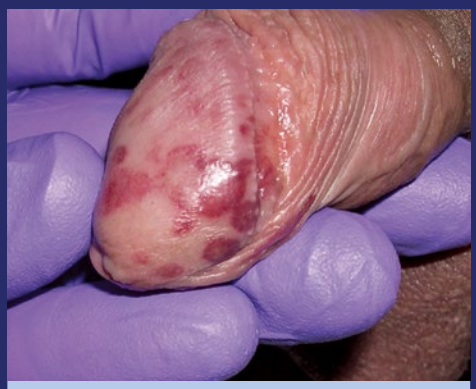
Notes

Notes



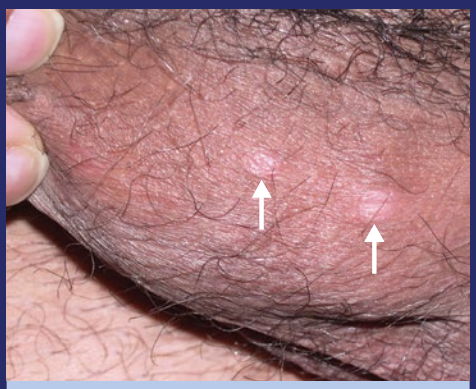
Multiple coalescing dusky erythematous macules with mild skin thickening in a case of secondary syphilis; note the two healing primary ulcerations which are still present.

Source: New York City Department of Health and Mental Hygiene, Sexual Health Clinic



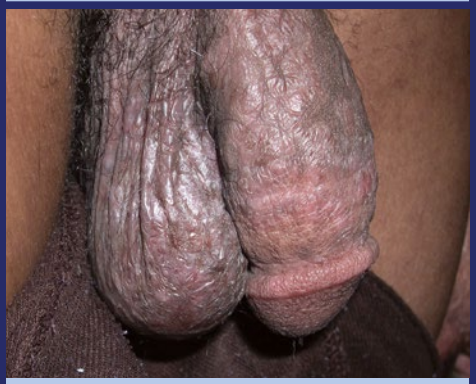
Multiple deeply erythematous macules, some of which have an annular appearance, on the glans and distal shaft of the penis in a patient with secondary syphilis.

Source: New York City Department of Health and Mental Hygiene, Sexual Health Clinic



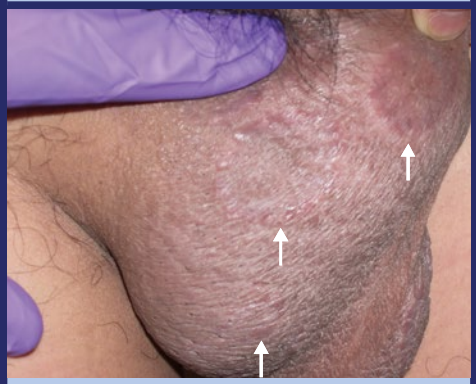
Multiple subtle mildly erythematous shiny macules seen on the scrotum of a patient with secondary syphilis.

Source: New York City Department of Health and Mental Hygiene, Sexual Health Clinic



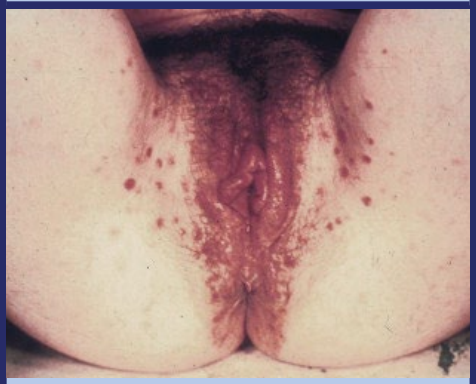
Multiple coalescing slightly erythematous macules/ patches and diffuse dermatitis causing mildly thickened, shiny skin surface in a patient with secondary syphilis.

Source: New York City Department of Health and Mental Hygiene, Sexual Health Clinicc



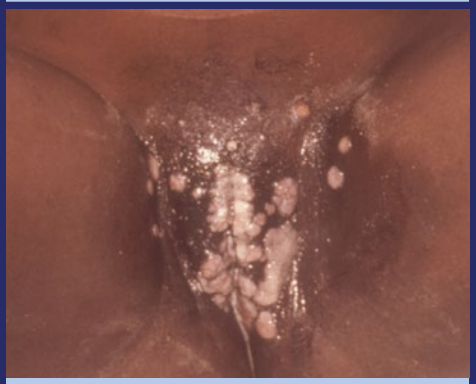
Multiple large circular patches, some of which have an annular appearance, on the scrotum of a patient diagnosed with secondary syphilis.

Source: New York City Department of Health and Mental Hygiene, Sexual Health Clinicc



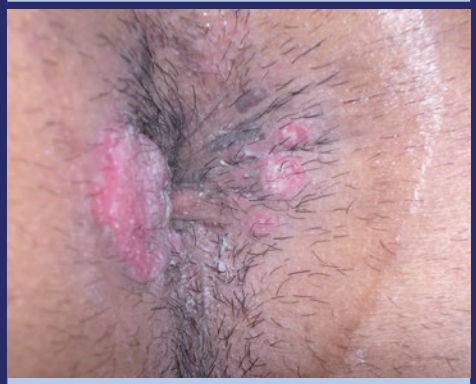
Multiple erythematous macules and papules on the labia, vulva, inner thighs, and perianal area in a patient with secondary syphilis.

Source: CDC/ NCHSTP/ Division of STD Prevention, STD Clinical Slides- Syphilis. https://www.cdc.gov/std/training/clinicalslides/slides-dl.htm



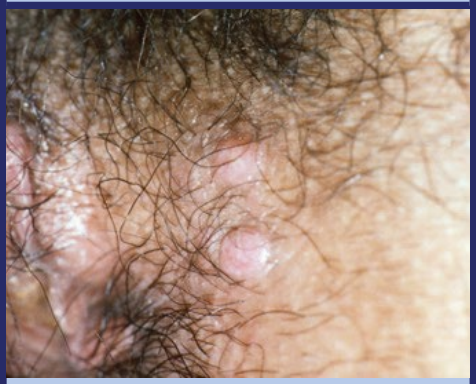
Multiple vulvar and intertriginous condylomata lata lesions in a patient with secondary syphilis.

Source: Centers for Disease Control and Prevention, Public Health Image Library (CDC/J.Pledger, 1976); National STD Curriculum https://www.std.uw.edu/go/pathogen-based/syphilis/core-concept/all.



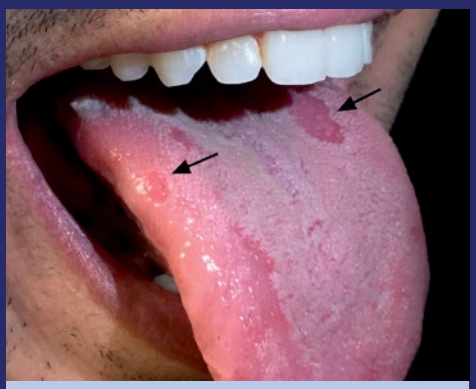
Multiple perianal papules & plaques with serous exudate seen in a patient with secondary syphilis.

Source: New York City Department of Health and Mental Hygiene, Sexual Health Clinicc



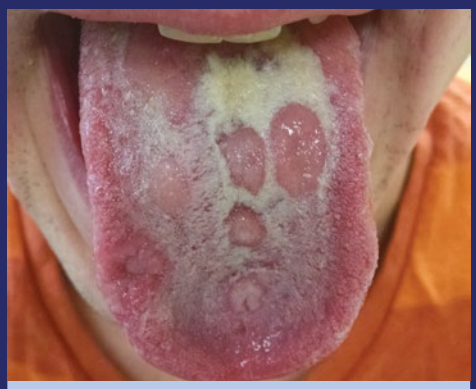
Condyloma lata (firm, slight whitened papules/ plaques with serous exudate) adjacent to the labia of a patient with secondary syphilis.

Source: Dr. Joseph Engelman, San Francisco City Clinic



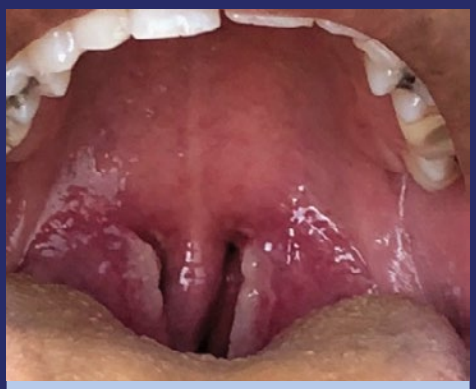
Multiple mucous patches on the tongue of a patient with secondary syphilis.

Source: Negusse Ocbamichael, PA; Public Health—Seattle & King County STD Clinic; National STD Curriculum https://www.std.uw.edu/go/pathogen-based/syphilis/core-concept/all.



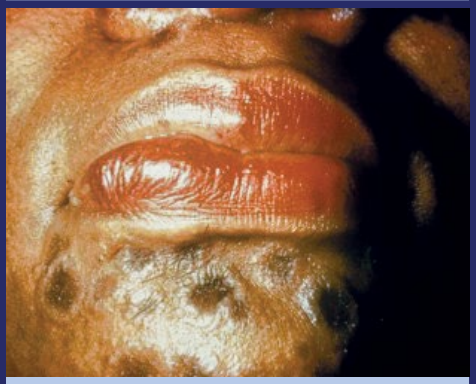
Multiple patches and raised plaques on the tongue of a patient with secondary syphilis.

Source: Division of STD Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention. www.cdc.gov/std/syphilis/images.htm



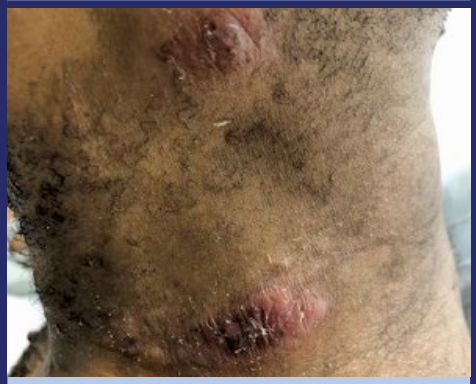
Whitened fleshy plaques seen on the tonsillar pillars in a patient with secondary syphilis.

Dr. Kimberly Workowski, Emory University



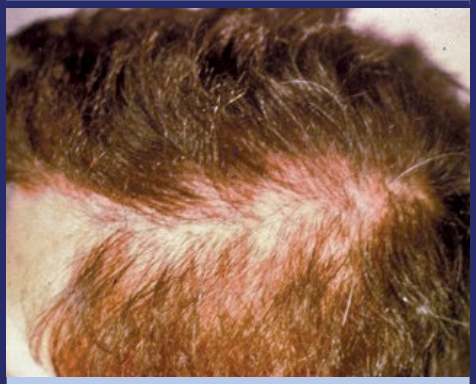
Multiple annular macules and plaques with hyper-pigmented center over the chin and lower cheeks of a patient with secondary syphilis.

Source: CDC/ NCHSTP/ Division of STD Prevention, STD Clinical Slides- Syphilis. https://www.cdc.gov/std/training/clinicalslides/slides-dl.htm



Multiple dry, dusky erythematous plaques seen on the lateral neck of a patient with secondary syphilis.

Source: Dr. Kimberly Workowski, Emory University



Patchy moth-eaten alopecia seen on the scalp of a patient with secondary syphilis.

Source: CDC/ NCHSTP/ Division of STD Prevention, STD Clinical Slides- Syphilis. https://www.cdc.gov/std/training/clinicalslides/slides-dl.htm